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Title: Sensory Processing in Sotos Syndrome and Tatton-Brown Rahman Syndrome

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Abstract: Sotos syndrome (Sotos) and Tatton-Brown Rahman Syndrome (TBRS) are two of the most common overgrowth disorders associated with intellectual disability. Individuals with these syndromes tend to have similar cognitive profiles and high likelihood of autism symptomatology. However, whether and how sensory processing is affected is currently unknown. Parents/caregivers of 36 children with Sotos and 20 children with TBRS completed the Child Sensory Profile 2 (CSP-2) and the Sensory Behaviour Questionnaire (SBQ) along with other standardised questionnaires assessing autistic traits (SRS-2), ADHD traits (Conners 3), anxiety (SCAS-P) and adaptive behaviour (VABS-3). Sensory processing differences were clearly evident in both syndromes, though there was significant variation in both cohorts. SBQ data indicated that both the *frequency* and *impact* of sensory behaviour were more severe when compared to neurotypicals, with levels of sensory behaviour impact and frequency being similar to autistic children. CSP-2 data indicated 77% of children with Sotos and 85% children with TBRS displayed clear differences in sensory Registration (missing sensory input). Clear differences relating to Body Position (proprioceptive response to joint and muscle position; 79% Sotos; 90% TBRS) and Touch (somatosensory response to

touch on skin; 56% Sotos; 60% TBRS) were also particularly prevalent. Correlation analyses demonstrated that in both syndromes sensory processing differences tend to be associated with difficulties relating to autistic traits, anxiety and some domains of ADHD. In Sotos, sensory processing differences were also associated with lower adaptive behaviour skills. This first detailed assessment of sensory processing, alongside other clinical features, in relatively large cohorts of children with Sotos and TBRS, demonstrates that sensory processing differences have a profound impact on everyday life.

Keywords: Sensory processing; Sensory profile; Sotos syndrome; Tatton-Brown Rahman Syndrome; Overgrowth; Genetic syndromes

General Scientific Summary: This study found that children with Sotos Syndrome and Tatton-Brown Rahman Syndrome were likely to experience sensory differences, although the level of differences varied. Common differences in both syndromes were missing sensory input and differences in the processing of body position and touch information.

Introduction

Sotos syndrome (Sotos) and Tatton-Brown Rahman syndrome (TBRS) are two of the most common single gene disorders associated with overgrowth (defined as height and/or head circumference at least 2 standard deviations above the population mean) and intellectual disability (Tatton-Brown et al., 2017). Sotos is estimated to affect 1 in 14,000 individuals worldwide (Tatton-Brown & Rahman, 2004) and is caused by haploinsufficiency of the NSD1 (nuclear receptor binding SET domain protein 1) gene on chromosome 5q35.2– 5q35.3 (Kurotaki et al., 2002). Sotos is characterised by distinctive facial features, macrocephaly, and intellectual disability. Other common features are childhood overgrowth, advanced bone age, cardiac and genitourinary anomalies, neonatal jaundice, neonatal hypotonia, seizures, and scoliosis (Tatton-Brown & Rahman, 2004). Individuals with Sotos have demonstrated a consistent cognitive profile of relative strength in verbal ability and visuospatial memory but relative weakness in non-verbal reasoning ability and quantitative reasoning, with mean IQ estimated to be around 61 (range 37 – 101 in a cohort of 52 individuals) (C. Lane, Milne, & Freeth, 2019). TBRS was identified in 2014 and is caused by constitutive variants of the *DNMT3A* gene on chromosome 2p23.3 (Tatton-Brown et al., 2014), the exact prevalence of TBRS is yet to be determined but it is considered to be less common than Sotos (Tatton-Brown et al., 2017). TBRS is characterised by tall stature and/or large head circumference, intellectual disability and distinctive facial appearance. Joint hypermobility, obesity, hypotonia, behavioural/psychiatric issues, kyphoscoliosis and afebrile seizures are also common clinical features (Tatton-Brown et al., 2018). Like Sotos, individuals with TBRS exhibit an uneven cognitive profile characterised by relatively better verbal ability compared to non-verbal reasoning ability and spatial ability (C. Lane, Tatton-Brown, & Freeth, 2020). Overall intellectual ability has been found to be somewhat more impaired in TBRS than

Sotos, with mean IQ estimated to be around 53 (range 39 – 76 in a cohort of 18 individuals) (C. Lane et al., 2020).

Both Sotos and TBRS are associated with autism, with somewhat less severe autism symptomatology reported in adulthood in both Sotos (C. Lane et al., 2017) and TBRS (C. Lane et al., 2020). Analysis of data from a large cohort of individuals with autism has also identified an association between *de novo* mutation in *DNMT3A*, the cause of TBRS, and autism (Sanders et al., 2016). Sensory processing differences are a core feature of autism (American Psychiatric Association, 2013; Baum, Stevenson, & Wallace, 2015; Ben-Sasson et al., 2009; Tomchek & Dunn, 2007). To date, sensory processing has not been systematically investigated in Sotos or TBRS. In light of the emerging link between autism and these two overgrowth disorders, it is possible that sensory processing atypicality constitutes a core aspect of the syndromes.

Sensory processing describes the process by which the central and peripheral nervous systems register, modulate, and discriminate information from the senses (e.g., auditory, visual, touch, taste, smell, vestibular, proprioceptive or interoceptive input). Ayres (1972) first proposed sensory processing to be an integral developmental process and highlighted that impaired sensory processing may result in various functional problems in a child's day-to-day life. Sensory processing differences are highly heterogeneous in presentation and may include hypo-responsivity, hyper-responsivity, and/or sensation seeking behaviour. Sensory processing differences in children have been associated with wide ranging differences in social, emotional, and behavioural function with varied impacts including disruption in learning, leisure activities or eating a balanced diet (Baker, Lane, Angley, & Young, 2008; A. E. Lane, Young, Baker, & Angley, 2010; Schaaf, Toth-Cohen, Johnson, Outten, & Benevides, 2011). Improved understanding of children's sensory processing differences can inform targeted intervention to reduce the negative impact of sensory processing problems.

Studies have identified sensory processing differences in populations of children with Fragile X syndrome (Rogers, Hepburn, & Wehner, 2003), Down syndrome (Bruni, Cameron, Dua, & Noy, 2010), ADHD (Dunn & Bennett, 2002; Ermer & Dunn, 1998), Angelman and Cornelia de Lange syndrome (Heald, Adams & Oliver, 2020), Marshall-Smith syndrome and Malan syndrome (Mulder et al. 2020) and Williams syndrome (John & Mervis, 2010). However, whether this is also the case for Sotos and TBRS is currently unknown. There is some evidence to suggest different neurodevelopmental disorders may manifest as distinct profiles of sensory processing difference. For example, Rogers et al. (2003) found both autistic children and children with Fragile X syndrome to exhibit atypical sensory processing compared to children with developmental disabilities of mixed aetiology and typically developing children. However, autistic children had more atypical responses to taste and smell whereas children with Fragile X syndrome had more atypical responses in regard to low energy/weak muscles. The investigation of sensory processing differences in specific clinical groups can be useful to clearly define the sensory processing patterns unique to each disorder, to improve understanding of the condition and, in turn, guide the most appropriate intervention (Tomchek & Dunn, 2007).

There is high autism prevalence in a very broad range of genetic conditions, hence a diagnosis of autism encapsulates an extremely heterogeneous group of people. The genotype-first approach may support the future classification of autism subtypes which could facilitate understanding of the neurobiological mechanisms of autism (Scerif & Karmiloff-Smith, 2005; Bernier & Eichler, 2014) and lead to more effective diagnosis, intervention, and understanding of autism (Stessman et al., 2014). It is postulated that the study of sensory processing in particular may be key to identifying differences in neural circuitry that underpin multiple levels of autistic features (Baum et al., 2015; Robertson & Baron-Cohen, 2017).

Clinical features that have been associated with sensory difference include autistic traits (Robertson & Simmons, 2013), adaptive behaviour (Dellapiazza et al., 2019), anxiety (Engel-Yeger & Dunn 2011), and ADHD traits (Panagiotidi et al, 2018). Understanding the relationship between sensory processing differences and clinical features can further inform understanding of the conditions of interest and guide supporting strategies for affected individuals.

The primary aim of the present study was to characterise sensory processing in children with Sotos and TBRS and to identify whether there are specific sensory profiles associated with each condition. A secondary aim was to determine whether other clinical features are associated with the level of sensory processing difference in individuals with Sotos or TBRS. We hypothesised that children with Sotos and TBRS would exhibit sensory processing differences but did not have specific hypotheses with regards to particular sensory domains. We also hypothesised that clinical features; autistic traits, anxiety, ADHD traits, and adaptive behaviour, would be related to sensory processing differences in both Sotos and TBRS and were interested to reveal the nature of these relationships in these relatively under researched genetic conditions.

Methods

Participants

The sample comprised 36 parents/primary caregivers of children with a diagnosis of Sotos and 20 parents/primary caregivers of children with a diagnosis of TBRS (see Table 1 for participant characteristics).

<INSERT TABLE 1 ABOUT HERE>

Parents/primary caregivers were recruited via the Sheffield Autism Research Lab (ShARL) genetic syndrome participant database, website and social media; advertisement via

syndrome-specific Facebook support groups; advertisement via partner charities, the Child Growth Foundation (a UK charity that supports families of individuals affected by growth conditions) and Tatton Brown Rahman Syndrome Community (a US patient support organisation that supports families of individuals with TBRS). Eligibility criteria were being a parent/primary caregiver to a child with a diagnosis of Sotos or TBRS where the child was aged between 3 years and 14 years 11 months and being able to read, understand and complete questionnaires written in English.

Measures

Demographic questions and six standardised parent/caregiver questionnaires were administered via two online platforms (over three stages) in accordance with copyright and licensing requirements. Participants were able to complete measures in their own time. Demographics questions, the Sensory Behaviour Questionnaire; Social Responsiveness Scale, Second Edition; Spence Children's Anxiety Scale, Parent Version and Conners 3 ADHD scale, Parent Short were administered in Stage one. The Child Sensory Profile 2 was administered in Stage two. The Vineland Adaptive Behavior Scales, Third Edition was administered in Stage three. If the child's age fell outside of the specified range for the measure, the measure was not administered. Online platforms required responses to all items. As such, there were no missing data among measures administered. A minority of participants did not complete the CSP-2 (Stage two) (n=2 Sotos) or the Vineland (Stage three) (n=7 Sotos; n=1 TBRS) due to attrition. Demographics questions asked about the child's age, sex, country of residence and diagnosis. Answers to the question, "*Has your child been diagnosed with any co-occurring conditions (e.g. ADHD, autism, dyslexia, epilepsy)? Yes/No. If yes, please state the co-occurring conditions*." were used to establish autism diagnosis status.

Sensory Behaviour Questionnaire The Sensory Behaviour Questionnaire (SBQ; Neil et al., 2017) is a 50-item measure of both the frequency and impact of sensory behaviour. The tool was initially designed as a clinical and research tool to assess sensory behaviours in individuals with a moderate-to-severe learning disability or pervasive developmental disorder. Each item is scored on a scale of 1 (all the time/an extreme problem) to 6 (never/not at all) with lower scores indicating greater frequency or impact of sensory behaviours. Scores are summed to generate individual frequency and impact subscale scores. An overall total score is generated by summing the total frequency and impact scales. The SBQ was completed by all eligible participants. The SBQ has demonstrated excellent internal consistency in frequency ($\alpha = .93$), impact ($\alpha = .94$), and overall total ($\alpha = .97$) scales and convergent validity with the Short Sensory Profile (r=.79) (Neil et al., 2017). This study used SBQ frequency, impact, and total raw scores.

Child Sensory Profile 2 The Child Sensory Profile 2 (CSP-2) (Dunn, 1999, 2014) is a parent/caregiver questionnaire measure of children's responses to everyday sensory experiences for use with children aged 3-14 years old. Items are measured on a five-point scale ranging from 5 (when presented with the opportunity my child 'almost always' responds in this manner) to 1 (when presented with the opportunity my child 'almost never' responds in this manner). The measure includes discrete scales for six sensory systems; Auditory (response to things heard), Visual (response to things seen), Oral (response to smells or touch/taste in the mouth), Touch (somatosensory response to touch on skin), Movement (vestibular response to movement), and Body Position (proprioceptive response to joint and muscle position), and three scales for associated behaviours (Conduct, Social-Emotional, Attentional). From the sensory system and associated behaviour items, scores are also generated for Dunn's four patterns of sensory processing (Seeking, Avoiding, Sensitivity and Registration). Example items from each CSP-2 scale are presented in Supplemental

Material Table 1. Raw scores can be calculated for each scale with higher scores indicating more sensory differences. The CSP-2 was normed in a large general population sample of children aged 3 to 14 years, 11 months (N=697 US children, n=348 Male, n=349 Female). An additional classification system outlines an individual's scores according to a bell curved distribution from the normative sample. Scores for each scale can be classified as being 'Much less', 'Less', 'Just like', 'More' and 'Much more' than the majority of others. Comparable to the normative sample, the gender split in the present Sotos sample was even, whereas there was a dominance of males (65%) in the TBRS sample. As well as full-length questionnaire, items from the short version of the measure, the Short Sensory Profile 2 (SSP-2), were extracted which comprises 34 highly discriminatory items enabling the generation of a composite score as an indicator of overall sensory differences. The CSP-2 has demonstrated good to excellent internal consistency (α=.80-.90) in all scales apart from the visual scale (α=.60) which showed questionable internal consistency (Dunn, 2014). The SSP-2 composite score has also demonstrated good internal consistency (α=.86) (Dunn, 2014). This study used raw scores for each CSP-2 scale, classification scores for each CSP-2 scale, and raw scores for the SSP-2 composite score.

Social Responsiveness Scale, Second Edition The Social Responsiveness Scale, Second Edition (SRS- 2) (Constantino & Gruber, 2012) is a 65-item questionnaire measure of behaviour associated with autism. Items are coded on a 4-point scale ranging from 0 (not true) to 3 (almost always true). Raw scores are converted to T-scores which are adjusted for gender with higher scores representing greater severity. The School Age version of the form was administered to participants with children aged 4 to 14 years old and was completed by all eligible participants. The SRS-2 School Age has demonstrated excellent internal consistency (α=.95) and has demonstrated convergent validity with other rating scales of social behaviour and communication (Bruni, 2014). SRS-2 data were not collected for

children aged 3 years old (n=3 Sotos). This study used SRS-2 total T-scores which adjusted for gender.

Spence Children's Anxiety Scale, Parent Version The Spence Children's Anxiety Scale, Parent Version (SCAS-P) (Spence, 1998) is a questionnaire measure of anxiety for children aged 6-18 years old. The 38-item scale provides an overall measure of anxiety and six domain-level scores of separation anxiety, social phobia, generalised anxiety, panic/agoraphobia, panic/agoraphobia, physical injury fears and obsessive compulsive disorder. Parents rate each item on a 4-point scale ranging from 0 (Never) to 3 (Always). Scores from all items are summed to create a total score, ranging from 0 to 114 with higher scores reflecting greater severity of symptoms. The SCAS-P has demonstrated good internal consistency (α=.89) in both anxiety disordered children and normal controls and has demonstrated convergent validity with the parent-reported Child Behaviour Checklist (CBCL; Achenbach, 1991) and the child-report version of the SCAS (Nauta et al., 2004). The SCAS-P was administered to participants with children aged 6 to 18 years old. SCAS-P data were not collected for children aged 3 to 5 years old (n=10 Sotos; n=4 TBRS). This study used SCAS-P total raw scores.

Conners 3 ADHD scale - Parent Short The Conners 3 ADHD scale – Parent Short (Conners, 2008) is a questionnaire measure of Attention Deficit Hyperactivity Disorder and its most common co-occurring problems for children aged 6-18 years old. The 43-item scale provides scores for five content scales: Inattention, Hyperactivity / Impulsivity, Learning Problems, Executive Functioning, Defiance / Aggression and Peer Relations. Parents rate items on a scale ranging from 0 (Not at all true (Never, Seldom)) to 3 (Very much true (Very often, Very frequently)). Raw scores are converted to T-scores which are adjusted for age and gender with higher scores associated with a greater number and/or frequency of reported concerns. T-scores are interpreted as, $\geq$70 very elevated score, 65-69 elevated score, 60-64

high average score, 40-59 average score and <40 low score. The Conners 3 Parent Short content scales demonstrated acceptable to good levels of reliability (α= .72 to .89), except for the Defiance/Aggression scale (α = .47) which showed unacceptable internal consistency, and has shown moderate correlations with scores of self and teacher-reported versions of the scale (Izzo et al., 2019). The Conners 3 was administered to participants with children aged 6 to 14 years old. Conners 3 data were not collected for children aged 3 to 5 years old (n=10 Sotos; n=4 TBRS). This study used Conners T-scores which adjusted for age and gender.

Vineland Adaptive Behaviour Scales, Third Edition (Domain Level Parent/Caregiver Form) The Vineland Adaptive Behaviour Scales, Third Edition (Vineland) (Sparrow, Cicchetti, Balla, & Saulnier, 2016) domain-level parent/caregiver form is a questionnaire measure of adaptive behaviour covering ages from birth to 90 years. The core 120-item scale, provides an overall level of adaptive functioning (ABC) and domain-level scores for communication, daily living skills and socialisation. Parents/caregivers rate each item on a 3-point scale from 0 (never) to 2 (usually or often). Norm-referenced ABC scores are generated, describing the individual's scores compared to others in their age group. Standard scores range from 20 to 140 (M=100, SD=15). Data are reported for all children (aged 3-14 years old). The Vineland domain-level parent /caregiver form has demonstrated excellent internal consistency (α = .97) and moderate convergent validity (*r*=.55-.73) with the Adaptive Behaviour Assessment System (ABAS-3; Harrison & Oakland, 2015; Sparrow et al., 2016). This study used Vineland ABC scores which adjusted for age.

Ethical approval was obtained from The University of Sheffield Psychology department ethics sub-committee. All participants provided written informed consent.

Data Analysis

Descriptive statistics were generated for demographic data and for all questionnaire measures (mean, SD, ranges).

Sensory Behaviour (Frequency and Impact) Scores on the SBQ were analysed to assess the severity of sensory behaviour differences experienced in both Sotos and TBRS groups. In order to contextualise the level of difference experienced, SBQ scores were compared to datasets published by Neil et al. (2017) which provide data from large cohorts of neurotypical children (N=77; Mean age = 9 years, 7 months; SD= 2 years, 7 months; Age range = 6 years – 16 years, 7 months; males = 36; females = 34) and autistic children (N=66; Mean age= 10 years; 3 months; SD= 2 years, 6 months; Age range = 6 years, 9 months – 16 years, 5 months; males = 57; females = 9). Single-sample *t*-tests, using Bonferroni correction for multiple comparisons, compared the scores from our cohort to the mean scores of the Neil et al. (2017) datasets. Welch independent samples *t*-tests (equal variances not assumed) compared the Sotos and TBRS cohorts.

Sensory Profile To establish whether there were particular areas of sensory processing difference associated with Sotos and TBRS, CSP-2 data were analysed to produce descriptive statistics and histograms to demonstrate the distribution of scores. To observe the co-occurrence of differences in sensory patterns, systems, and associated behaviour, CSP-2 classification scores were charted for each individual child. To explore the within-syndrome differences between children with and without an autism diagnosis, the association between autism diagnosis and the proportion of children scored as 'much more' than the majority of others was assessed using Fisher's Exact tests using Bonferroni correction for multiple comparison.

Phenotype cluster analysis of Sotos and TBRS To establish whether the two syndromes had independent sensory profiles, cluster analysis of sensory profile data were conducted using both the CSP-2 sensory systems and SBQ frequency and impact scores.

Prior to running the analysis, all the data were normalised and SBQ scores were reversed in order to achieve consistency with CSP-2; As a result, higher scores in CSP-2 or SBQ indicated higher severity in sensory issues. Missing data (n = 3 for CSP-2) were interpolated with the collapsed group median score of each respective CSP-2 sensory system level). Hierarchical agglomerative cluster analysis was performed in Python using the Scikit-learn library and the AgglomerativeClustering object. Hierarchical cluster analysis was deemed appropriate as it is a widely used technique that is robust and useful for problems requiring the identification of a hierarchy of relatively homogenous groups in the dataset. The Euclidean distance and Ward parameters were selected to compute the linkage distance and cluster merge strategy. The dendrogram and heatmap were created using the Seaborn library and clustermap object. Based on a minimum sample size recommendation of n=20 per subgroup by Dalmaijer et al. (2022), our sample size (n=36 Sotos; n=20 TBRS) was sufficient for this analysis.

Association between clinical features and sensory behaviour To investigate whether the level of sensory behaviour differences were associated with other clinical features in the Sotos and TBRS cohorts, Spearman's correlation analyses were conducted between the main clinical questionnaire summary measures (SRS-2 total T-scores; SCAS-P total; Vineland ABC; Conners 3 subscales T-scores) and the sensory behaviour measures (SSP-2; SBQ total; SBQ frequency; SBQ impact). To understand which relationships explained independent proportions of variance sensory differences multiple regressions were conducted. Due to the limited sample sizes and the Conners 3 not producing an overall summary score value, it was decided to only use the SRS-2 total T-scores, SCAS-P total and Vineland ABC as predictors. All assumptions of regression analysis were met. These were checked using residuals vs fitted plots, scale-location plots and checks for multicollinearity were conducted using the Durbin Watson test.

All of the above described analyses (apart from the cluster analysis) were performed in SPSS v26 (www.ibm.com/analytics/us/en/technology/spss) and RStudio 1.3.1056.

Results

Summary scores for all parent/caregiver questionnaires are outlined in Table 2.

<INSERT TABLE 2 ABOUT HERE>

Sensory Behaviour (Frequency and Impact)

The Sotos cohort exhibited significantly greater levels of sensory behaviours than the neurotypical children from the Neil et al. (2017) cohort, $t(35) = -10.48$, $p<.001$, $d=1.75$, with both the frequency of behaviours, $t(35) = -11.36$, $p<.001$, $d=1.90$, and impact of behaviours, $t(35) = -9.13$, $p<.001$, $d=1.52$, demonstrating this pattern. The Sotos children displayed similar levels of sensory behaviour differences to the autistic children from the Neil et al. (2017) cohort, $t(35) = -0.88$, $p=.34$, $d=0.15$, this was true both in terms of frequency of behaviour, $t(35) = -0.92$, $p=.37$, $d=.15$, and impact of behaviours, $t(35) = -0.81$, $p=.43$, $d=-0.14$ (see Figure 1). Similarly, the TBRS cohort also exhibited significantly greater levels of sensory behaviours than the neurotypical children, $t(19) = -7.28$, $p<.001$, $d=1.63$, with both the frequency of behaviours, $t(19) = -8,26$, $p<.001$, $d=1.85$, and impact of behaviours, $t(19) = -5.89$, $p<.001$, $d=1.32$, demonstrating this pattern. As for the Sotos children, the TBRS children displayed similar levels of sensory behaviour differences to the autistic children, $t(19) = 1.39$, $p=.18$, $d=0.31$, this was true both in terms of frequency of behaviour, $t(19) = 1.00$, $p=.33$, $d=0.22$, and impact of behaviours, $t(19) = 1.75$, $p=.10$, $d=0.39$.

<INSERT FIGURE 1 ABOUT HERE>

When compared to one another, the Sotos and TBRS cohorts did not score differently on SBQ total, $t(46.02)=-1.62$, $p=.11$, $d=-0.42$ or SBQ frequency, $t(45.27)=-1.36$, $p=.18$, $d=-0.36$. There was a trend for SBQ impact scores to indicate greater sensory behaviour differences in the Sotos cohort, though this did not reach significance, $t(46.62)=-1.84$, $p=.07$, $d=-0.48$. Overall, these results indicate that levels of sensory behaviour differences were similar between the two overgrowth conditions.

Sensory Profile

Table 3 includes descriptive statistics for the CSP-2 sensory patterns, systems, and associated behaviours. Supplemental Material Figures 1 , 2, and 3 show the distribution of CSP-2 raw scores. In all CSP-2 domains, responses were highly likely to fall in the 'more' or 'much more' than the majority of others ranges, though for each cohort, and in all but one scale, there were responses in the 'just like' others range. The exception was the Registration scale for the TBRS cohort where all 20 children fell in the 'more' or 'much more' than others ranges. Overall, this indicates significant variability in the sensory differences experienced within Sotos and TBRS cohorts.

<INSERT TABLE 3 ABOUT HERE>

CSP-2 – Sensory Patterns. The profile of sensory processing patterns (Table 3) was similar between Sotos and TBRS groups with children experiencing differences in all sensory patterns and particularly increased differences in sensory Registration. The co-occurrence of differences in CSP-2 sensory patterns is shown in Supplemental Material Figure 4. Overall, in both Sotos and TBRS cohorts, children who scored as 'more' or 'much more' than the

majority of others in one pattern were likely to score as ‘more’ or ‘much more’ in one or more other patterns.

CSP-2 – Sensory Systems. The profile of sensory processing systems (Table 3) was similar between Sotos and TBRS groups. Differences were experienced in most sensory systems and there were particularly increased differences in the processing of Body Position and Touch information. The distribution of scores (Supplemental Material Figure 2) indicated a trend for Sotos children to be more likely to experience difference in the processing of Oral information compared to TBRS children. For both Sotos and TBRS groups, the proportion of children experiencing difference in the processing of Visual information was similar to what would be expected in the general child population. Supplemental Material Figure 5 shows the co-occurrence of differences in CSP-2 sensory systems in Sotos and TBRS cohorts.

CSP-2 – Behavioural Responses Associated with Sensory Processing. The profile of behaviours associated with sensory processing (Table 3 and Supplemental Material Figure 3) was also similar between Sotos and TBRS groups.

A within-condition comparison of the proportion of children with and without an autism diagnosis (as reported by the parent/ caregiver) that scored as ‘much more’ than the majority of others is presented in Supplementary Materials Table 2 (CSP-2 sensory patterns), Supplementary Materials Table 3 (CSP-2 sensory systems), and Supplementary Materials Table 4 (CSP-2 associated behaviours). No significant associations were found between autism diagnosis and sensory difference, indicating that the conclusions drawn in relation to the sensory profile of Sotos and TBRS children were largely relevant both to those with and without an autism diagnosis.

Phenotype cluster analysis of Sotos and TBRS

In line with the above findings, the cluster analysis showed that Sotos and TBRS did not display independent sensory profiles, rather the two syndromes displayed similar sensory processing profiles. The dendrogram heatmap in Figure 2 represents clusters of cases that are similar in their severity of the respective sensory domains, as extracted from the CSP-2 sensory systems and SBQ impact and frequency. Initial iterations of the unsupervised clustering algorithm formed small clusters of highly similar cases. Groups of small clusters eventually formed two final large clusters (Cluster A and Cluster B), which included all cases.

Overall, 'Cluster A' grouped cases (Sotos and TBRS) that presented with higher sensory severity and 'Cluster B' grouped cases (Sotos and TBRS) with lower sensory severity across all the sensory domains. Each syndrome clustered to a similar extent in both clusters: 61% Sotos (n=22) and 50% TBRS (n=10) for Cluster A and 39% Sotos (n=14) and 50% TBRS (n=10) for Cluster B. There was no significant association between syndrome (Sotos and TBRS) and cluster (A and B) groups: $\chi 2\ (1) \chi 2\ (1) = 0.42$, $p = 0.518$.

<INSERT FIGURE 2 ABOUT HERE>

Sensory differences and clinical features

Findings from the Spearman's correlation analyses are shown in Figure 3 (Sotos) & Figure 4 (TBRS). Results from the Sotos cohort found that increased severity of sensory behaviours, as indicated by the SSP-2, was associated with higher autistic traits (SRS-2), lower adaptive behaviour skills (Vineland ABC), increased executive functioning problems (Conners 3 executive functioning), increased hyperactivity (Conners 3 hyperactivity), increased inattention (Conners 3 inattention) and increased learning problems (Conners 3

learning problems). When sensory behaviours were assessed via the SBQ (total) relationships were found with higher autistic traits (SRS-2), anxiety (SCAS-P), lower adaptive behaviour skills (Vineland ABC), higher defiant / aggressive behaviour (Conners 3 defiance/aggression), increased hyperactivity (Conners 3 hyperactivity) and increased inattention (Conners 3 inattention).

<INSERT FIGURE 3 ABOUT HERE>

Results from the TBRS cohort found that increased severity of sensory behaviours, as indicated by the SSP-2, was associated with higher autistic traits (SRS-2), increased executive functioning problems (Conners 3 executive functioning), increased hyperactivity (Conners 3 hyperactivity), increased learning problems (Conners 3 learning problems) and increased peer relation difficulty (Conners 3 peer relations). When sensory behaviours were assessed via the SBQ (total) relationships were found with higher autistic traits (SRS-2), anxiety (SCAS-P), increased executive functioning problems (Conners 3 executive functioning), and increased learning problems (Conners 3 learning problems).

<INSERT FIGURE 4 ABOUT HERE>

Overall, results from the Spearman's correlation analyses demonstrated that sensory processing differences tend to be associated with difficulties relating to other clinical features.

Multiple regression analyses found SRS-2 T-scores, SCAS-P total and Vineland ABC scores explained 71% of the variance in the SSP-2 total scores of the Sotos group, $F(3,17)=13.73$, $p<.001$. Inspection of beta-weights indicated that SRS-2 *t*-total (β =0.51,

p=.03) and Vineland ABC (β =-0.43, p=.03) both explained a significant independent proportion of the variance. For the TBRS data these variables explained 78% of the variance in SSP-2 total, $F(3,11)=13.42$, $p<.001$. Inspection of the beta-weights indicated that SRS-2 *t*-total was the only predictor to explain a significant independent proportion of the variance (β =0.95, $p<.001$).

Discussion

The primary aim of this study was to characterise sensory processing in children with Sotos and TBRS including establishing whether there are distinct sensory processing profiles evident in each syndrome. In line with our hypothesis, this study found sensory processing differences to be common in both children with Sotos and TBRS, though scores revealed significant variation in children with each diagnosis. Overall, sensory behaviour differences were reported as being both high in frequency and impact and at a similar level to those typically observed in autistic children. Sensory pattern data indicated 77% of Sotos and 85% of TBRS children exhibited clear differences in sensory Registration (missing sensory input). In terms of sensory systems, there were particularly increased differences in the processing of Body Position and Touch information. Differences to neurotypical children in Movement, Oral, and Auditory processing were also common. Overall, the sensory differences observed in the two conditions was similar, although there was a trend for Sotos children to present with somewhat increased differences in the processing of Oral information compared to TBRS children. Sensory differences were present regardless of whether the child had a co-occurring diagnosis of autism. For both syndromes, there were comparatively fewer differences in relation to the processing of Visual information. In line with these findings, the cluster analysis demonstrated that Sotos and TBRS cases tended to present with similar sensory processing profiles with individuals within syndromes grouping similarly into two

separate clusters of overall higher sensory severity and overall lower sensory severity. In line with our second hypothesis, in both syndromes, increased sensory processing differences were associated with other clinical features, with fewer adaptive behaviour skills explaining a significant independent proportion of the variance in sensory difference in Sotos syndrome and increased autistic traits explaining a significant independent proportion of the variance in sensory difference in both syndromes.

Behaviour consistent with Sensory Registration (missing sensory input) was particularly prominent in both Sotos and TBRS. Registration behaviours may result in children missing more sensory cues than others. For example, children may be less able to detect the sensation of pain caused by minor injury or may not be able to detect changes in typical body sensations such as temperature or hunger. Registration patterns in proprioception and movement sensory systems may result in children appearing uncoordinated, lethargic or unmotivated. Whilst children with registration patterns may appear more easy-going than others (e.g., they may be less disturbed in busy classroom environments), it may be more difficult to get the child's attention. Furthermore, the child may find it hard to engage in a task and complete it in a timely manner. Compared to other groups, patterns of Sensory Registration have been shown to be more common in autistic children than those with Williams Syndrome (Glod, Rigby, & Rodgers, 2020) and a tendency to engage in emotional eating and eating in relation to external environmental cues was associated with reduced sensory awareness in a neurotypical adult population (Hebert, 2018). Strategies to benefit children with reduced sensory awareness include providing children with more intense and varied sensory experiences in their everyday activities with the view to support and improve the child's ability to detect and respond to changes in sensory input (Dunn, 2007).

It is important to consider that there may be some overlap between overgrowth characteristics (e.g., tall stature, overweight) and certain sensory-related behaviours, hence

syndrome specific management strategies should be in place to support development (Tatton-Brown & Rahman, 2007). For example, the Body Position and Sensory Registration CSP-2 items, "Walks loudly as if feet are heavy" and "Props to support self" could be attributable to overgrowth features. Within the clinical assessment and management of Sotos and TBRS, it is thus important for sensory differences to be interpreted in the context of characteristic overgrowth features, while also acknowledging that the behaviours exhibited in these domains are atypical and likely to cause distress. Sensory avoidance behaviours have been shown to be associated with increased BMI in autistic children (Lawson & Foster, 2016) and although BMI was not assessed in the current study, individuals with TBRS tend to experience obesity (Tatton-Brown et al. 2018). In future, it will be important to investigate whether specific sensory experiences are associated with elevated BMI in TBRS.

The current study observed that, in Sotos and TBRS, differences in sensory Registration were more common than differences in Sensitivity, Avoiding, and Seeking. This pattern profile is different to that reported in an autistic child cohort by Simpson et al. (2019) who reported SSP-2 scores in the 'much more' range as: Seeking (37.1%), Avoiding (62.1%), Sensitivity (65.7%), and Registration (56.5%). Contrastingly, a study by Lyons-Warren et al. (2022) observed pronounced differences in sensory Sensitivity in Phelan-McDermid Syndrome and SYNGAP1-related Intellectual Disability relative to other sensory patterns. Together this indicates that the prominence of difference in Registration in Sotos and TBRS is unusual. In regard to sensory systems, the most common area of difference in Sotos and TBRS was Body Position. Differences in Body Position have also been noted 16p11.2 deletion and duplication (Smith et al. in press). Contrastingly, in Williams Syndrome and Marshall-Smith syndrome differences in auditory processing have been reported as common (John & Mervis, 2010; Mulder et al. 2020; Powell & Van Herwegen, 2021). Interestingly, in their longitudinal study of children with William's syndrome, Powell and Van Herwegen

(2021) reported that CSP-1 pattern and system profiles were not stable over time therefore underlining the importance of longitudinal studies in determining the presence of distinct sensory profiles in different neurodevelopmental conditions. Additionally, it should be noted that these Sensory Profile investigations in other neurodevelopmental conditions used different measures to the CSP-2 (e.g., the CSP-1, the SSP or the SSP-2) and are therefore not directly comparable to the findings of this study. Nevertheless, the present study adds to the increasing evidence in this area. Future research using consistent measures of sensory processing will allow for easier comparison over time and across neurodevelopmental conditions.

There was a trend to suggest that differences in Oral sensory processing may be a distinguishing sensory feature between Sotos and TBRS, with Sotos presenting with a relatively higher severity in this domain. Detailed investigation of craniofacial, dental and oral features in Sotos syndrome, conducted by Hirari et al. (2011), identified a high palate, excessive tooth wear, crowding, hypodontia, deep bite and other features. These dental and oral features may partially explain the higher severity in sensory oral processing in Sotos compared to TBRS. Thus, identifying sensory profiles is useful for management of sensory-related difficulties between similar yet heterogeneous rare genetic syndromes.

In Sotos syndrome, fewer adaptive behaviour skills was found to explain a significant independent proportion of the variance in sensory differences. This fits with a recent systematic review into the association between adaptive behaviour and sensory processing in autistic children which found that there was a clear association, across multiple studies, between increased sensory processing differences and more maladaptive behaviour, though whether the underlying cause of difficulty is sensory processing or adaptive behaviour is currently unclear (Dellapiazza et al., 2018). Similar findings in those with Fragile X syndrome and Angelman syndrome have been observed whereby lower self-help skills were

found to be associated with increased sensory processing differences, though no such association was observed in Cornelia de Lange syndrome (Heald et al., 2020). In Sotos, increased severity of sensory behaviours was also associated with higher autistic traits, lower adaptive behaviour, higher defiant / aggressive behaviour, increased hyperactivity, increased inattention and increased learning problems. In TBRS, increased severity of sensory behaviours was associated with higher autistic traits, increased anxiety, increased executive functioning problems, increased hyperactivity, increased learning problems and increased peer relation difficulty. Autistic traits were found to explain a significant independent proportion of the variance in sensory differences for both Sotos and TBRS. Furthermore, sensory differences in Sotos and TBRS were reported as similar in frequency and impact to autistic children. As such, this study aligns with previous research linking Sotos and TBRS and autism in childhood (C. Lane et al., 2017, 2020; Tatton-Brown et al., 2018) and offers further evidence of this association. This indicates that, where autistic traits are elevated, it will be important for clinicians to consider sensory processing differences as these will be very likely to occur and have a profound impact.

Anxiety was found to correlate with sensory differences in both Sotos and TBRS although it did not explain a significant independent proportion of the variance in sensory difference in either syndrome. In light of the co-occurrence of anxiety and sensory difference in autism, researchers have explored proposed models of the relationship between autism and anxiety and how this may be linked to sensory over-response (SOR), characterised by sensory hypersensitivity. Green and Ben-Sasson (2010) proposed three models. The ‘Primary Anxiety Model’ suggests that autism produces anxiety and associated stress and in turn this results in SOR. The ‘Primary SOR Model’, proposes that autism produces SOR. This causes stress, which in turn results in anxiety. The ‘Alternate Hypothesis’ considers the idea that SOR and anxiety are not directly related but are both influenced by a common risk factor. A general

adult population study conducted by Amos et al. (2019) found the 'Primary SOR model' was best able to explain the variance in the data compared to the other models. This indicates that anxiety symptoms in autism could be reduced by mitigating SOR (e.g., via the introduction of sensory neutral environments). While the causal relationships between autistic traits, anxiety and sensory differences in Sotos and TBRS were not tested in the current study, future investigation of directional effects in these specific populations may provide insight into the underlying mechanisms of symptoms.

The small sample sizes in this study could be argued as a limitation. In particular, when comparing the sensory behaviour of Sotos and TBRS groups the study was underpowered to detect anything other than large effect sizes. The subgroup analysis of within-syndrome autism and non-autism groups has a further reduced sample size and thus should be interpreted with caution. Despite this, given the rarity of these conditions the sample size achieved was fairly large.

Many of the measures used in this study were developed for use with typically developing children. It is likely that the appropriateness of these measures varies across different levels of cognitive ability. For example, some of the items included in the SRS-2, Conners and SCAS-P relate to skills in communication, literacy, or numeracy that cannot be assumed among children with intellectual disability and thus may have lacked relevance for some families. This study was further limited by the lack of measures of anxiety, autistic traits and ADHD for younger children (3-5 years).

Due to the limited socio-demographic information collected in the study, the direct comparability to normative samples is uncertain. The data presented here do not consider the degree of the child's developmental disability. Previous research has found a negative association between mental age and sensory processing differences in children with developmental disability (Baranek et al., 2006) hence, inclusion of a measure of the child's

cognitive ability would have been beneficial in aiding understanding whether the sensory differences observed were underpinned by this factor. Due to data collection taking place at the height of the COVID-19 pandemic it was not possible to collect face-to-face assessment of the child's cognitive ability. It will be important for future sensory processing investigations to control for the degree of cognitive ability to determine whether differences can be attributed specifically to Sotos or TBRS. The inclusion of children with co-occurring diagnoses challenged the ability to clearly delineate syndrome-specific features from those associated with other conditions. However, the significant overlap, and likely shared genetic aetiology, between neurodevelopmental conditions (Stessman, Bernier, & Eichler, 2014), combined the rarity of these genetic diagnoses means that excluding children with additional diagnoses would have been counterintuitive.

Our finding of increased, but variable, sensory processing differences in children with Sotos and TBRS is important for the care of children with these diagnoses. Knowledge that sensory differences are extremely likely, particularly in areas of sensory Registration and Body Position, is important for effective diagnosis and treatment. Addressing individual sensory needs can help to prevent overstimulation or under stimulation, thereby enhancing participation, learning and daily functioning (Engel-Yeger et al. 2011).

In summary, this assessment of sensory processing, alongside other clinical features, in Sotos and TBRS demonstrates that sensory processing differences generally have a profound impact on their lives. Overall, sensory behaviour was found to be similar to autistic children without a genetic diagnosis. It is important for educators and clinicians to be aware of these differences and the impact of sensory processing on other aspects of behaviour in order that individuals with these syndromes can be appropriately supported.

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Tables and Figures

Table 1 Participant Characteristics

	Sotos	TBRS
Age		
Mean (SD)	8y,3m (3y,4m)	8y,8m (3y,0m)
Range	3y,3m – 14y,9m	4y,7m – 14y,2m
Sex		
Males	18 (50%)	13 (65%)
Females	18 (50%)	7 (35%)
Location of Residence		
UK	24 (66.67%)	6 (30%)
Europe	0 (0%)	2 (10%)
North America	6 (16.67%)	11 (55%)
Australasia	6 (16.67%)	1 (5%)
Worldwide other	0 (0%)	0 (0%)
Co-occurring diagnoses		
Autism	17 (47%)	8 (40%)
ADHD	6 (16.67%)	5 (25%)
Dyspraxia	1 (2.78%)	1 (5%)
Epilepsy	6 (16.67%)	4 (20%)
Other reported medical conditions[a]	6 (16.67%)	5 (25%)

a Chiari Malformation, hypotonia, hypermobility, heart defects, kidney defects, neutropenia, ear infections

Table 2. Summary scores for parent/caregiver questionnaires

	Sotos	TBRS
SBQ [a] total		
N	36	20
Mean (SD)	206.06 (46.88)	224.95 (38.67)
Range	103-283	129-277
SSP-2 [b]		
N	34	20
Mean (SD)	43.76 (13.05)	41.95 (10.37)
Range	20-67	24-60
SRS-2 [c]		
N	33	20

Mean (SD)	78.97 (11.40)	74.25 (10.74)
Range	61-99	56-94
SCAS-P [d] total		
N	26	16
Mean (SD)	31.77 (18.30)*	19.50 (12.64)*
Range	5-77	3-50
Vineland 3 ABC [e]		
N	29	19
Mean (SD)	69.72 (14.36)	67.00 (10.46)
Range	35-110	43-84
CON-T[f] Inattention		
N	26	16
Mean (SD)	75.46 (12.90)	81.44 (9.83)
Range	47-90	59-90
CON-T[f] Hyperactivity		
N	26	16
Mean (SD)	73.85 (13.50)	68.94 (14.40)
Range	50-90	51-90
CON-T[f] Learning problems		
N	26	16
Mean (SD)	77.19 (13.53)	84.00 (8.33)
Range	43-90	64-90
CON-T[f] Executive Functioning		
N	26	16
Mean (SD)	78.08 (9.86)	74.75 (14.58)
Range	61-90	53-90
CON-T[f] Defiance / aggression		
N	26	16
Mean (SD)	63.35 (17.67)	59.75 (18.03)
Range	45-90	45-90
CON-T[f] Peer relations		
N	26	16
Mean (SD)	86.08 (8.69)	82.63 (12.45)
Range	58-90	52-90

[a] SBQ = Sensory Behavior Questionnaire (lower scores reflect greater levels of sensory behaviors)
[b] SSP-2 = Short Sensory Profile 2 (lower scores reflect greater levels of sensory behaviors)
c SRS-2 = Social Responsiveness Scale 2 (higher scores reflect higher amount of autistic traits)
[d] SCAS-P = Spence Children's Anxiety Scale (higher scores reflect greater levels of anxiety)
[e] Vineland 3 ABC = Vineland 3 Adaptive Behaviour Composite (higher scores reflect increased adaptive behaviour)
[f] CON-T= Conners 3 T-scores by sub-scale

*indicates a significant difference between groups, $p<.05$

Table 3 CSP-2 sensory processing differences in Sotos and TBRS

		Sotos (n=34)		TBRS (n=20)	
		Mean (SD)	% 'much more'	Mean (SD)	% 'much more'
Pattern	Registration	65.35 (16.52)	77%	67.95 (10.77)	85%
	Seeking	52.29 (20.16)	42%	49.25 (14.22)	20%
	Sensitivity	52.56 (16.09)	44%	46.85 (12.31)	15%
	Avoiding	56.76 (15.70)	38%	48.50 (14.25)	15%
System	Body Position	26.03 (7.35)	79%	26.05 (6.00)	90%
	Touch	29.26 (10.09)	56%	29.60 (8.07)	60%
	Movement	21.68 (9.62)	47%	22.30 (5.26)	35%
	Oral	23.53 (11.24)	29%	18.25 (8.42)	10%
	Auditory	24.15 (6.81)	21%	22.50 (6.32)	10%
	Visual	14.47 (4.32)	3%	13.50 (3.98)	5%
Associated behaviour	Attentional	30.00 (9.68)	47%	28.15 (7.91)	40%
	Social-emotional	41.35 (11.82)	47%	37.30 (11.67)	30%
	Conduct	25.94 (8.85)	38%	23.85 (7.38)	30%

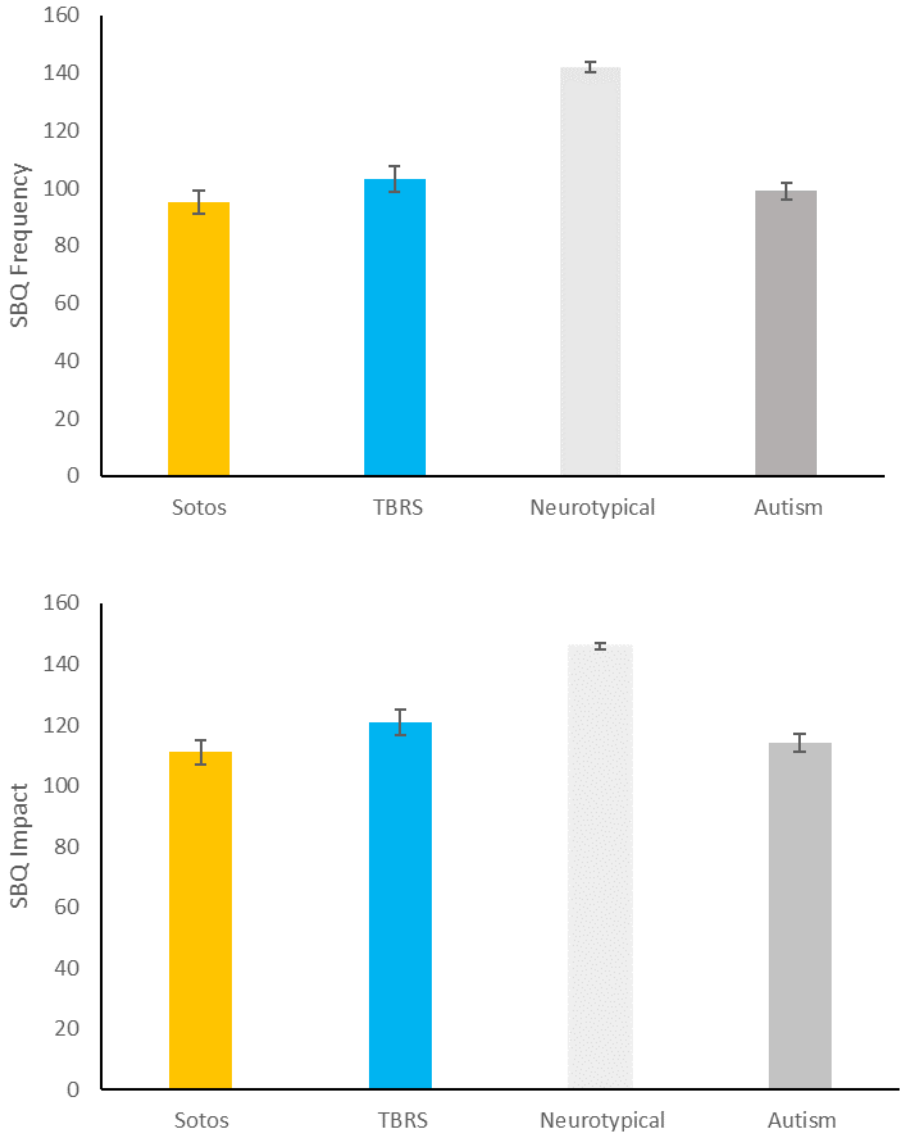


Figure 1. Mean scores of SBQ Frequency (panel A) and SBQ Impact (panel B) by group. Error bars represent +/- 1S.E.. N.b. data for Neurotypical group and Autism taken from Neil et al. (2017), lower scores indicate increased severity.

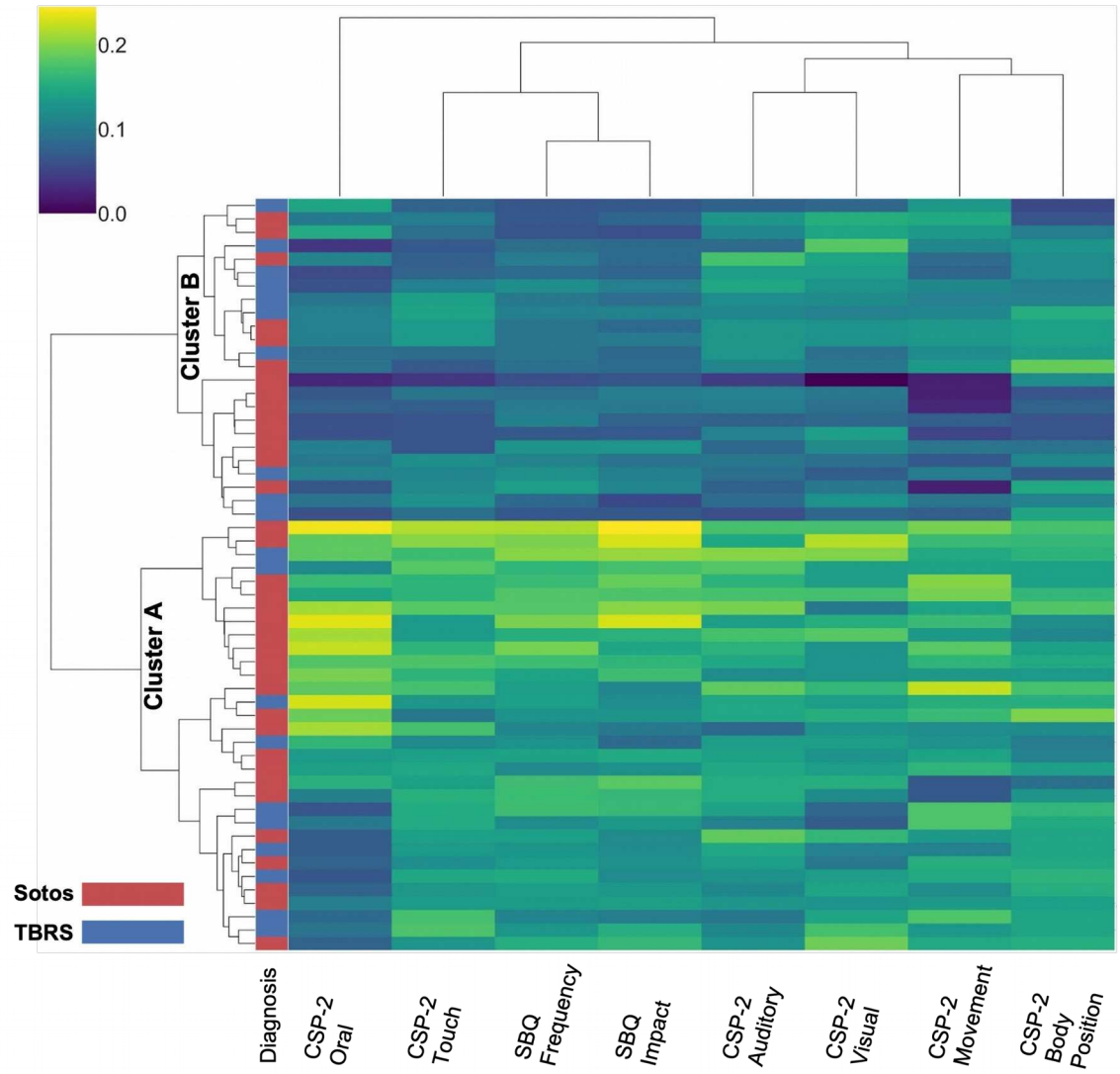


Figure 2. Phenotype cluster analysis of Sotos and TBRS. CSP-2, Child Sensory Profile 2; SBQ, Sensory Behaviour Questionnaire. The colour bar indicates the severity level (yellow=greatest severity) of the respective CSP-2 and SBQ domains in the Sotos and TBRS cohorts.

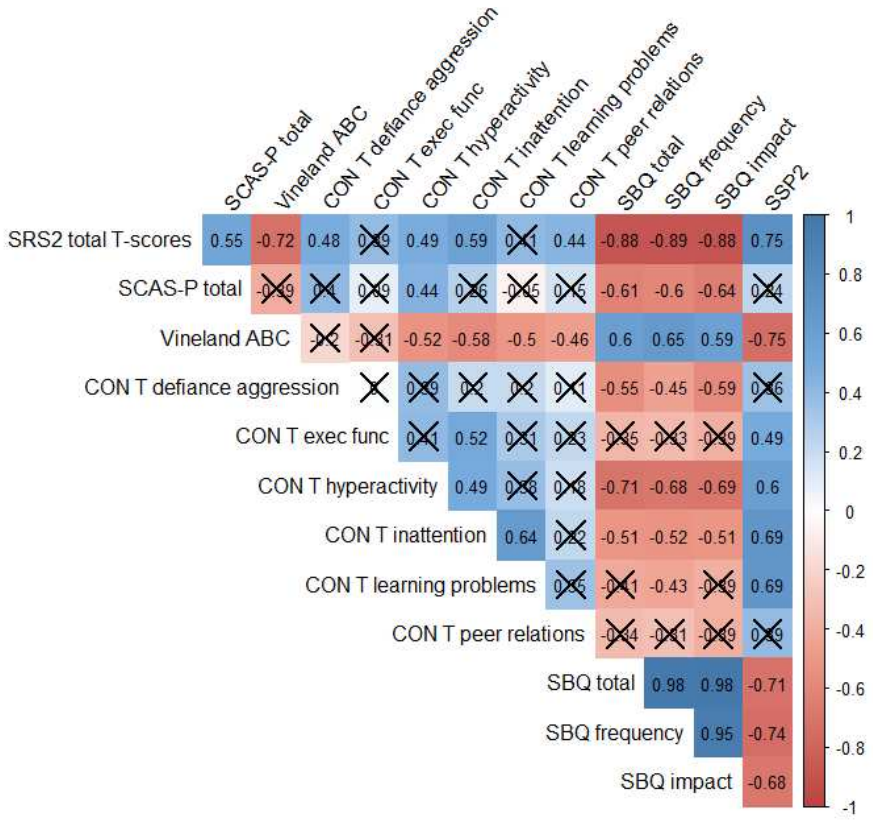

SCAS-P total
Vineland ABC
CON T defiance aggression
CON T exec func
CON T hyperactivity
CON T inattention
CON T learning problems
CON T peer relations
SBQ total
SBQ frequency
SBQ impact
SSP2
SRS2 total T-scores
SCAS-P total
Vineland ABC
CON T defiance aggression
CON T exec func
CON T hyperactivity
CON T inattention
CON T learning problems
CON T peer relations
SBQ total
SBQ frequency
SBQ impact
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

Figure 3. Sotos clinical outcome measure correlation table reporting Spearman's r-values.

n.b. r-values where p>.05 are crossed.

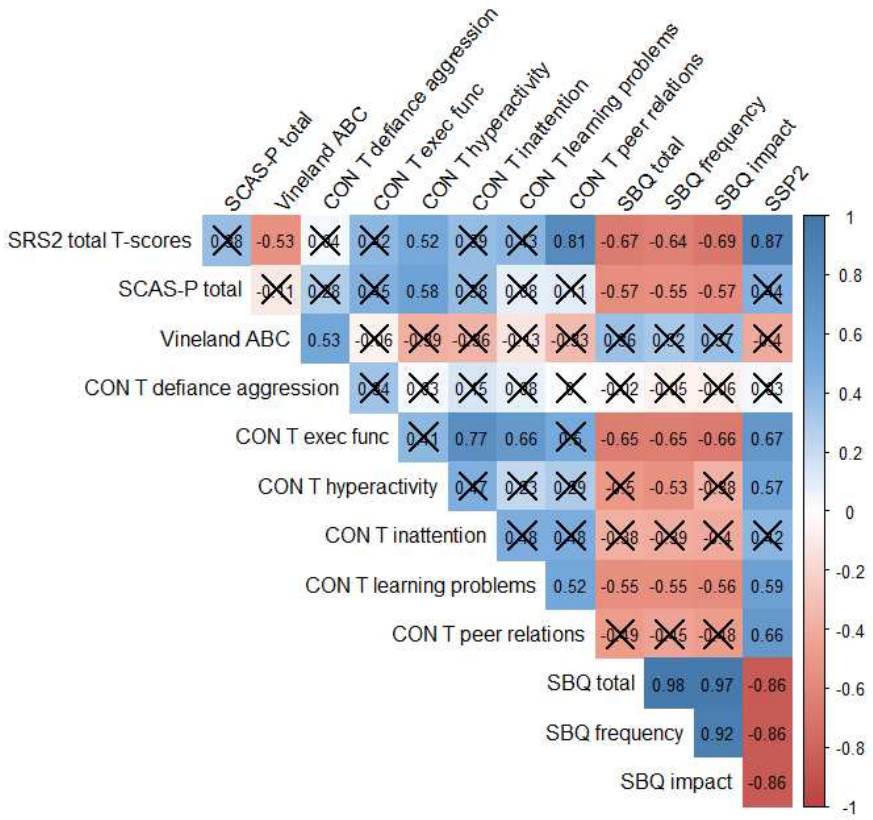


Figure 4. TBRS clinical outcome measure correlation table reporting Spearman's r-values. n.b. r-values where p>.05 are crossed.

Supplemental Material

Supplemental Material Table 1. Child Sensory Profile-2 (CSP-2) scales, descriptions, and items

CSP-2 Scale	Description	Example item
Seeking	Obtaining sensory input	Watches everyone when they move around the room
Avoiding	Being bothered by sensory input	Shows an emotional or aggressive response to being touched
Sensitivity	Detection of sensory input	Is more bothered by bright lights than other same-aged children
Registration	Missing sensory input	Seems unaware of pain
Auditory	Response to things heard	Holds hands over ears to protect them from sound
Visual	Response to things seen	Enjoys looking at visual details in objects
Oral	Response to smells or touch/ taste in the mouth	Rejects certain tastes or food smells that are typically part of children's diets
Touch	Somatosensory response to touch on skin	Shows distress during grooming (for example, Fights or cries during haircutting, face washing, fingernail cutting)
Movement	Vestibular response to movement	Rocks in chair, on floor, or while standing

Body Position	Proprioceptive response to joint and muscle position	Seems to have weak muscles
Conduct	Response to expectations	Rushes through colouring, writing or drawing
Social-emotional	Expressiveness	Has strong emotional outbursts when unable to complete a task
Attentional	Ability to detect important stimuli	Has a hard time finding object in competing environments

Supplemental Material Table 2. Percentage of children with and without a reported diagnosis of autism scoring 'much more' than the majority of others for each of the CSP-2 sensory patterns

	Sotos			TBRS		
	No autism (n=18)	Autism (n=16)	*p*	No autism (n=12)	Autism (n=8)	*p*
Registration	61%	94%	.043	83%	88%	1.000
Seeking	39%	44%	.524	8%	38%	.255
Sensitivity	39%	50%	.730	8%	25%	.537
Avoiding	33%	44%	.725	17%	13%	1.000

Includes results of Fisher's Exact Tests of association between autism diagnosis and number of children scoring 'much more' than others. P value adjusted for multiple comparisons using Bonferroni correction (p=.0125).

Supplemental Material Table 3. Percentage of children with and without a reported diagnosis of autism scoring 'much more' than the majority of others for each of the CSP-2 sensory systems

	Sotos			TBRS		
	No autism (n=18)	Autism (n=16)	*p*	No autism (n=12)	Autism (n=8)	*p*
Body Position	72%	88%	.405	92%	88%	1.000
Touch	44%	69%	.185	50%	75%	.375
Movement	44%	50%	1.000	25%	50%	.356

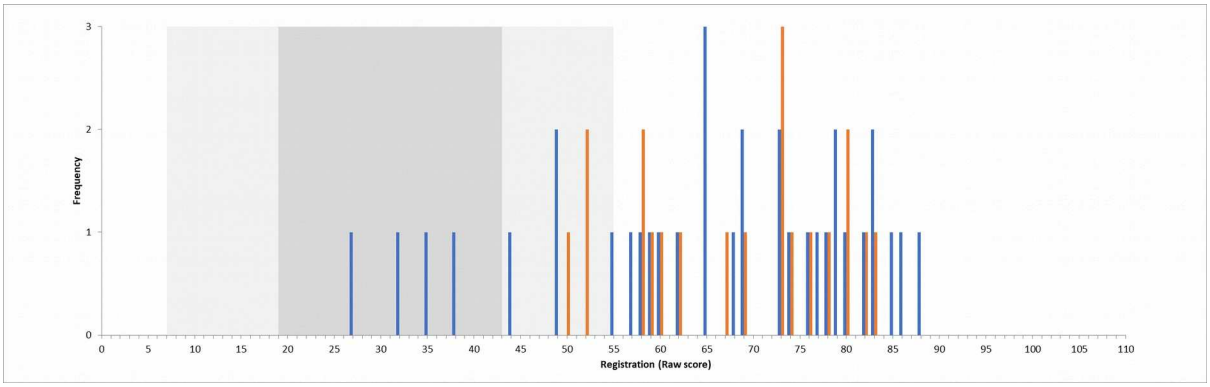
Oral	28%	31%	1.000	0%	25%	.147
Auditory	17%	25%	.681	8%	13%	1.000
Visual	0%	6%	.471	0%	13%	.400

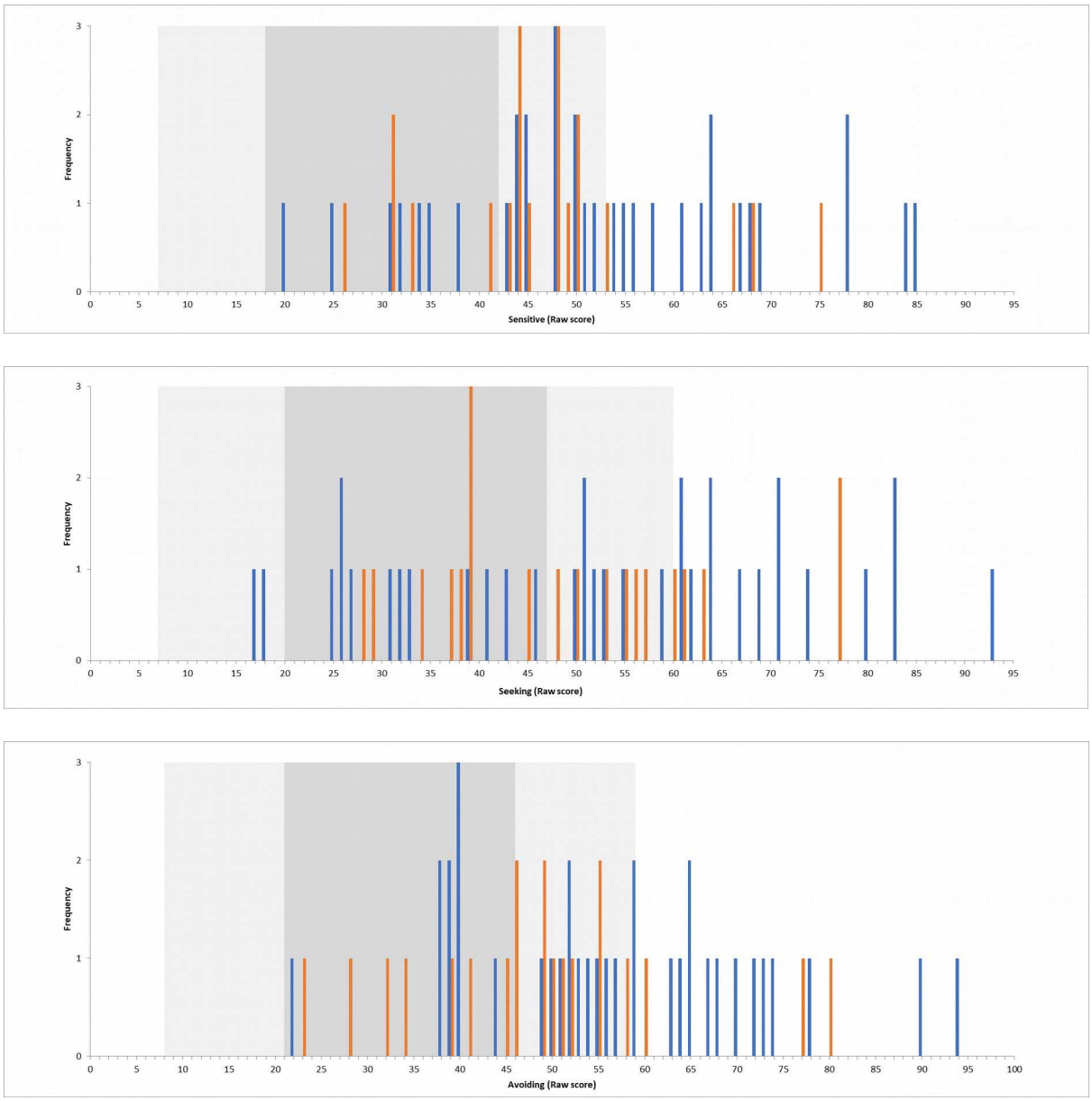
Includes results of Fisher's Exact Tests of association between autism diagnosis and number of children scoring 'much more' than others. P value adjusted for multiple comparisons using Bonferroni correction (p=.008).

Supplemental Material Table 4. Percentage of children with and without a reported diagnosis of autism scoring 'much more' than the majority of others for each of the CSP-2 associated behaviours

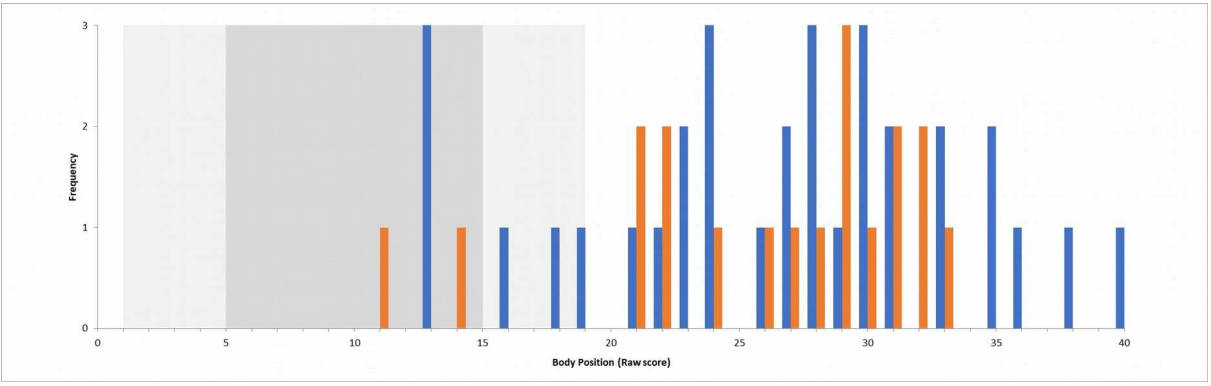
	Sotos			TBRS		
	No autism (n=18)	Autism (n=16)	*p*	No autism (n=12)	Autism (n=8)	*p*
Attentional	39%	56%	.492	25%	63%	.167
Social-emotional	28%	69%	.037	25%	38%	.642
Conduct	33%	44%	.725	17%	50%	.161

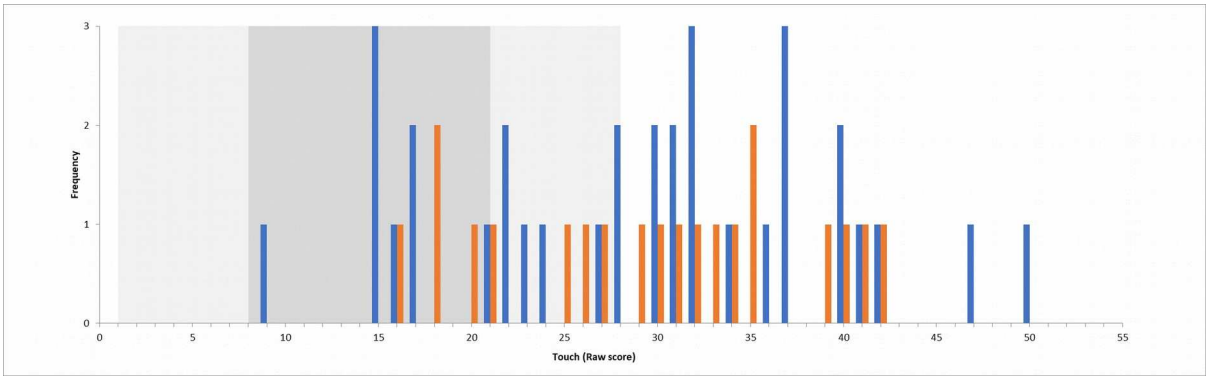
Includes results of Fisher's Exact Tests of association between autism diagnosis and number of children scoring 'much more' than others. P value adjusted for multiple comparisons using Bonferroni correction (p=.017).

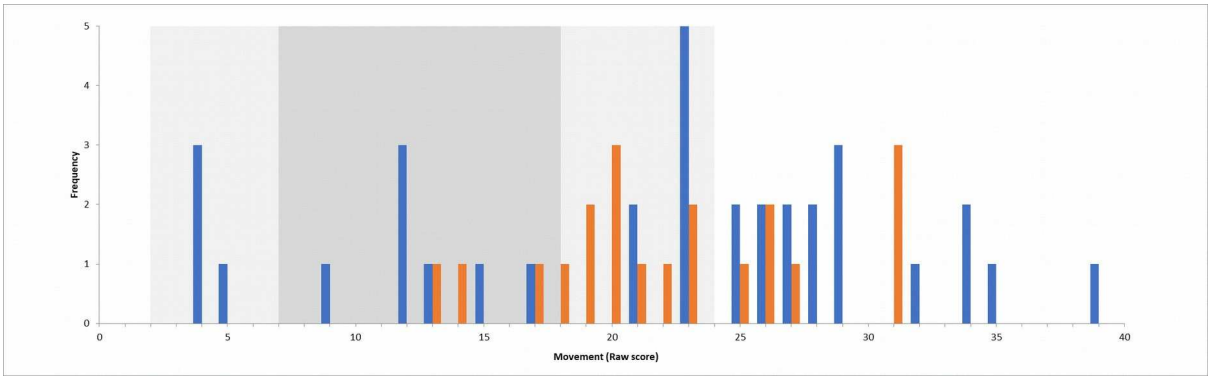


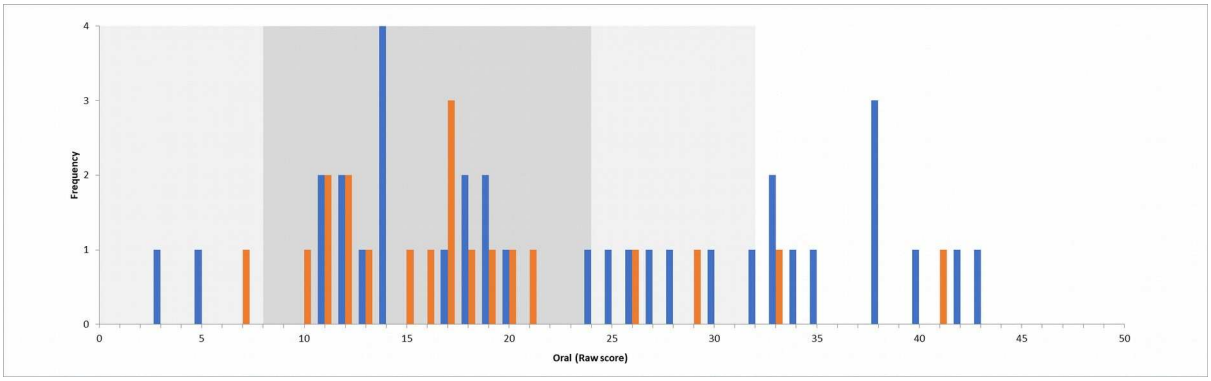


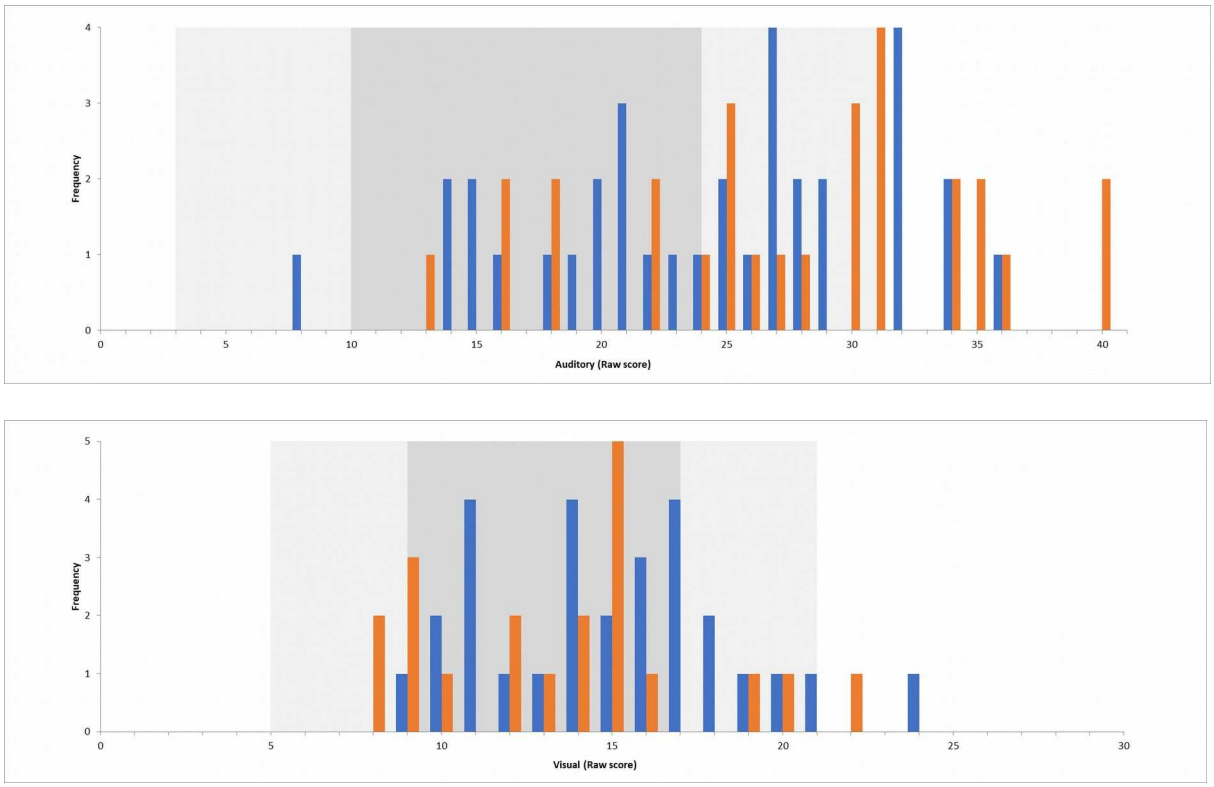
Supplemental Material Figure 1. Distribution of CSP-2 raw scores for each of the sensory patterns (Registration, Sensitivity, Avoiding, Seeking) for Sotos (blue) and TBRS (orange). The dark grey box indicates the range of scores associated with the majority (68%) of the normative sample (Dunn, 2014). The light grey boxes indicate the range of scores whereby the minority of the normative sample exhibit sensory behaviour less (14%) or more (14%) than the majority of others. Ranges outside of these areas (white background) indicate the range of scores whereby the small minority of the normative sample exhibit sensory behaviour much less (2%) or much more (2%) than the majority of others.


Frequency
Body Position (Raw score)

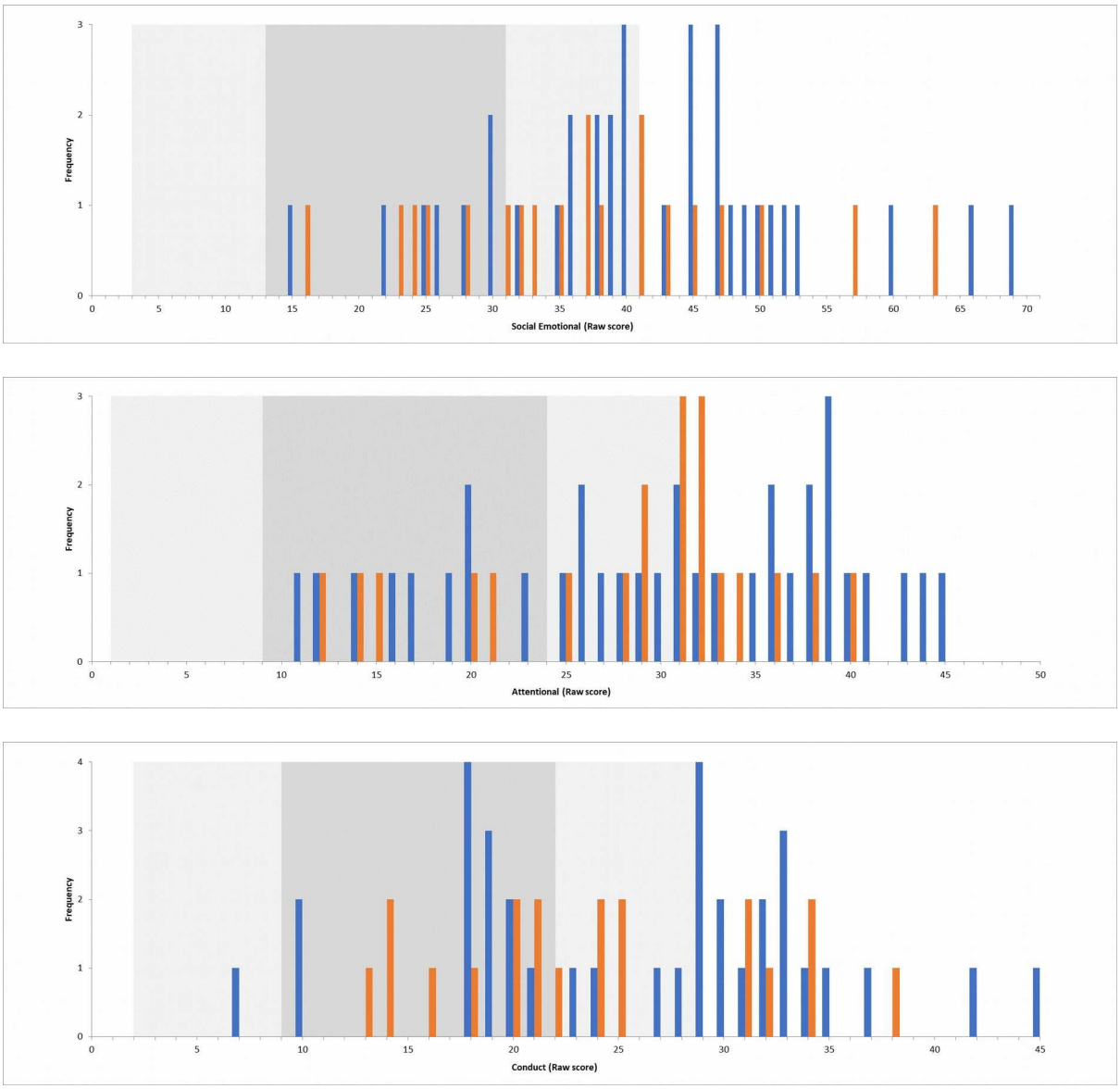

Frequency
Touch (Raw score)


Frequency
Movement (Raw score)


Frequency
Oral (Raw score)



Supplemental Material Figure 2. Distribution of CSP-2 raw scores for each of the sensory systems (Body position, Touch, Movement, Oral, Auditory, Visual) for Sotos (blue) and TBRS (orange). The dark grey box indicates the range of scores associated with the majority (68%) of the normative sample (Dunn, 2014). The light grey boxes indicate the range of scores whereby the minority of the normative sample exhibit sensory behaviour less (14%) or more (14%) than the majority of others. Ranges outside of these areas (white background) indicate the range of scores whereby the small minority of the normative sample exhibit sensory behaviour much less (2%) or much more (2%) than the majority of others.



Supplemental Material Figure 3. Distribution of CSP-2 raw scores for each of the associated behaviours (Conduct, Social Emotional, Attentional) for Sotos (blue) and TBRS (orange). The dark grey box indicates the range of scores associated with the majority (68%) of the normative sample (Dunn, 2014).The light grey boxes indicate the range of scores whereby the minority of the normative sample exhibit sensory behaviour less (14%) or more (14%) than the majority of others. Ranges outside of these areas (white background) indicate the range of scores whereby the small minority of the normative sample exhibit sensory behaviour much less (2%) or much more (2%) than the majority of others.

A

Ppt no.	Seeking	Avoiding	Sensitivity	Registration
1	5	5	5	5
4*	5	5	5	5
5	5	5	5	5
10*	5	5	5	5
11	5	5	5	5
12	5	5	5	5
35*	5	5	5	5
7	4	5	5	5
13*	4	5	5	5
27	3	5	5	5
16*	5	4	5	5
19	5	4	5	5
23	5	4	5	5
21*	5	3	5	5
33*	5	3	5	5
2*	4	5	4	5
3	4	5	4	5
34*	3	5	4	5
17*	5	4	4	5
36	5	4	4	5
25*	4	4	4	5
26*	4	4	4	5
28*	3	4	4	5
32	3	4	4	5
6	3	3	4	5
9*	3	4	3	5
29*	3	4	4	4
14	4	3	4	4
22	3	4	3	4
18	3	3	3	4
15	3	3	3	3
24	3	3	3	3
8	2	3	3	3
20	2	3	3	3

B

Ppt no.	Seeking	Avoiding	Sensitivity	Registration
20*	5	5	5	5
8	4	5	5	5
10*	5	4	5	5
12	3	5	4	5
7*	5	4	4	5
13	5	4	4	5
2*	4	4	4	5
3	4	4	4	5
14*	4	4	4	5
4*	4	3	4	5
5*	4	3	4	5
1	3	3	4	5
9	3	3	4	5
17	3	3	4	5
6	3	4	3	5
18	3	3	3	5
19	3	3	3	5
11	3	4	4	4
16*	4	3	3	4
15	3	3	3	4

** indicates autism diagnosis*

Supplemental Material Figure 4. Co-occurrence of CSP-2 sensory patterns in Sotos (panel A) and TBRS (panel B) children. Each row indicates a child included in the study. Coloured cells include CSP-2 classification scores (1= 'Much Less' 2 = 'Less', 3='Just like', 4='More', 5='Much more' than the majority of others) for each of the sensory patterns (Seeking, Avoiding, Sensitivity, Registration).

A

Ppt no.	Visual	Auditory	Oral	Movement	Touch	Body

						Position
1	4	5	5	5	5	5
4*	4	5	5	5	5	5
7	3	5	5	5	5	5
10	5	4	5	5	5	5
12	3	4	5	5	5	5
33*	3	4	5	5	5	5
35*	4	5	4	5	5	5
5	3	4	4	5	5	5
11	3	4	4	5	5	5
36	3	4	4	5	5	5
2*	3	4	3	5	5	5
25*	4	3	3	5	5	5
19	4	5	5	4	5	5
21*	3	3	5	4	5	5
23	3	3	5	4	5	5
27*	4	5	3	4	5	5
26*	3	3	3	4	5	5
34*	3	4	3	3	5	5
16*	3	4	5	5	4	5
17*	3	4	3	5	4	5
22	3	3	2	5	4	5
6	3	3	3	3	4	5
9*	3	3	3	2	4	5
14	3	3	4	4	3	5
32	3	3	3	4	3	5
28*	3	5	3	3	3	5
8	1	2	2	2	3	5
13*	3	4	4	3	5	4
29*	3	3	3	3	3	4
24	3	3	3	2	3	4
3	3	3	3	5	4	3
20	3	3	3	2	4	3
15	3	3	3	3	3	3
18	3	3	3	3	3	3

B

Ppt no.	Visual	Auditory	Oral	Movement	Touch	Body Position
20*	5	5	5	5	5	5
10*	3	4	5	5	5	5
8	3	5	3	5	5	5
13	3	4	3	5	5	5
5*	3	3	3	5	5	5
17	3	3	3	5	5	5

14*	2	3	3	5	5	5
1	3	4	3	4	5	5
2*	4	3	3	4	5	5
3	3	3	3	4	5	5
4*	3	3	3	4	5	5
18	3	3	3	3	5	5
7*	3	4	4	4	4	5
12	3	4	3	4	4	5
9	3	3	3	4	3	5
6	4	3	2	4	3	5
11	3	4	3	3	3	5
19	3	3	3	3	3	5
16*	2	3	3	3	4	3
15	3	3	4	4	3	3

** indicates autism diagnosis*

Supplemental Material Figure 5. Co-occurrence of CSP-2 sensory systerms in Sotos (panel A) and TBRS (panel B) children. Each row indicates a child included in the study. Coloured cells include CSP-2 classification scores (1= 'Much Less' 2 = 'Less', 3='Just like', 4='More', 5='Much more' than the majority of others) for each of the sensory patterns (Seeking, Avoiding, Sensitivity, Registration).