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RESEARCH ARTICLE

Sensory processing in 16p11.2 deletion and 16p11.2 duplication

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Abstract

Deletions and duplications at the chromosomal region of 16p11.2 have a broad range of phenotypic effects including increased likelihood of intellectual disability, autism, attention deficit hyperactivity disorder (ADHD), epilepsy, and language and motor delays. However, whether and how sensory processing is affected has not yet been considered in detail. Parents/caregivers of 38 children with a 16p11.2 deletion and 31 children with a 16p11.2 duplication completed the Sensory Behavior Questionnaire (SBQ) and the Child Sensory Profile 2 (CSP-2) along with other standardized questionnaires assessing autistic traits (SRS-2), ADHD traits (Conners 3), anxiety (SCAS-P) and adaptive behavior (VABS-3). SBQ and CSP-2 responses found that sensory processing differences were clearly evident in both 16p11.2 deletion and 16p11.2 duplication, though there was significant variation in both cohorts. SBQ data indicated the *frequency* and *impact* of sensory behavior were more severe when compared to neurotypical children, with levels being similar to autistic children. CSP-2 data indicated over 70% of children displayed clear differences in sensory registration (missing sensory input). Seventy-one percent with 16p11.2 duplications were also unusually sensitive to sensory information and 57% with 16p11.2 duplications were unusually avoidant of sensory stimuli. This first detailed assessment of sensory processing, alongside other clinical features, in relatively large cohorts of children with a 16p11.2 deletion and 16p11.2 duplication demonstrates that sensory processing differences have a profound impact on their lives.

Lay Summary

Responses to everyday sensory experiences in 38 16p11.2 deletion children and 31 16p11.2 duplication children were assessed. The frequency and impact of sensory behaviour differences was profound, though there was significant variation in both groups. Overall, sensory behaviour was found to be similar to autistic children. In both groups, over 70% failed to effectively register sensory information. 71% of 16p11.2 duplication children were very sensitive to sensory information and 57% of 16p11.2 duplication children were very avoidant of sensory stimuli.

KEYWORDS
ADHD, anxiety, autistic, sensory processing, sensory systems

INTRODUCTION

Loss or gain of material from the human genetic locus 16p11.2 (BP4–BP5 region) is increasingly recognized as the cause for one of the most common structural chromosome disorders. Prevalence of 16p11.2 deletion and duplication have been estimated to be approximately 1 in 2000 and 1 in 1100 respectively based on analysis of a general population cohort (Männik et al., 2015). The 16p11.2 (500–600 kb) region includes 27–29 genes. 16p11.2 deletions and duplications have a broad range of phenotypic effects including increased likelihood of intellectual disability, autism, attention deficit hyperactivity disorder (ADHD), epilepsy, and language and motor delays

(D'Angelo et al., 2016; Green Snyder et al., 2016; Hanson et al., 2015; Niarchou et al., 2019; Rein & Yan, 2020; Steinman et al., 2016; Weiss et al., 2008). Noted phenotypic differences between the two conditions include large head size and a tendency to be overweight in individuals with a 16p11.2 deletion compared to small head size and a tendency to be underweight in 16p11.2 duplication (Bochukova et al., 2010; D'Angelo et al., 2016; Rein & Yan, 2020; Shinawi et al., 2010; Steinman et al., 2016; Walters et al., 2010). 16p11.2 deletions and duplications have been consistently associated with autism symptomatology (D'Angelo et al., 2016; Green Snyder et al., 2016; Hanson et al., 2015; Niarchou et al., 2019; Rein & Yan, 2020) and identified in screenings of populations of autistic individuals (Marshall et al., 2008; Walsh & Bracken, 2011; Weiss et al., 2008). Rein and Yan (2020) reviewed multiple studies of individuals with a 16p11.2 deletion or duplication and observed autism symptomatology, or a formal autism diagnosis, to be reported in 16.1%–25.6% of individuals with a 16p11.2 deletion and in 20.0%–33.9% of individuals with a 16p11.2 duplication.

Sensory processing differences are a core feature of autism (American Psychiatric Association, 2013; Baum et al., 2015; Ben-Sasson et al., 2009; Tomchek & Dunn, 2007) and have been reported to be experienced by as many as 95% of children and adults with a diagnosis of autism (Crane et al., 2009; Tomchek & Dunn, 2007). In children, impaired sensory processing can result in profound effects on day-to-day life, for example, difficulties relating to social, emotional or behavioral function, learning in a classroom environment, engagement in leisure or travel activities, or eating a balanced diet (Baker et al., 2008; Lane et al., 2010; Schaaf et al., 2011). Differences may manifest as hyporesponsivity, hyper-responsivity, and/or sensation seeking behavior (O'Neill & Jones, 1997).

While many of the medical, anthropometric, cognitive, and behavioral phenotypes associated with a 16p11.2 deletion and 16p11.2 duplication have been investigated, to date, no studies have reported on sensory processing phenotypes in children with a 16p11.2 duplication and only one study has investigated these features in children with a 16p11.2 deletion. Osório, Rodríguez-Herreros, Romascano, et al. (2021) studied groups of children with a 16p11.2 deletion ($n = 17$), children with an autism diagnosis ($n = 121$), and typically developing children ($n = 45$), aged 2–12 years old. Using the parent-reported Sensory Processing Measure (SPM; Parham & Ecker, 2007), they found that, compared to typically developing children, children with a 16p11.2 deletion exhibited differences in domains of vision, hearing, body awareness, and balance and motion but no differences in the touch domain or the taste and smell domain. Additionally, the absence of differences in the touch domain and taste and smell domain differentiated 16p11.2 deletion children from autistic children, who showed elevated scores across all sensory domains assessed. The study also administered the Tactile Defensiveness and Discrimination. Test-Revised (TDDT-R; Baranek et al., 1997), a laboratory-based behavioral assessment of tactile processing, and found, contrary to the SPM data, 16p11.2 deletion children had significantly higher levels of tactile defensiveness than children with an autism diagnosis, with both groups scoring significantly higher compared to typically developing children. The discrepancy between these findings relating to touch processing in 16p11.2 deletion suggests a need for further research.

Understanding of sensory processing differences in 16p11.2 deletion and duplication may inform the provision of appropriate care, such as targeted intervention to reduce the negative impact of sensory processing problems (Tomchek & Dunn, 2007). A recent study by Kleinendorst et al. (2020) explored the experiences of family members involved in the care of children with the 16p11.2 deletion. Family members reported challenges associated with the lack of awareness of the symptoms and characteristics of the condition among health professionals, teachers, and education professionals. To our knowledge, the experiences of family members of children with a 16p11.2 duplication have not been investigated. However, Kleinendorst et al. (2020) speculated that their findings on carers of children with the 16p11.2 deletion were likely to have relevance to microdeletion/duplication susceptibility syndromes in general. Further understanding of the sensory phenotype of 16p11.2 deletion and duplication, the relationship between sensory processing and other clinical features and effective dissemination of information to families and professionals, may help to address this information gap.

The primary aim of the present study was to characterize sensory processing in 16p11.2 deletion and 16p11.2 duplication children and to identify whether there are specific sensory profiles associated with each diagnosis. A secondary aim was to determine whether other clinical features predict the level of sensory processing differences in individuals with a 16p11.2 deletion or duplication.

METHODS

Participants

The sample comprised 38 parents/primary caregivers of children with a diagnosis of 16p11.2 deletion and 31 parents/primary caregivers of children with a diagnosis of 16p11.2 duplication (see Table 1 for participant characteristics).

Parents/caregivers of children with a 16p11.2 deletion or duplication were recruited predominantly via the Simons Searchlight registry, a research registry for genetic conditions associated with autism and neurodevelopmental disorders, funded by the Simons Foundation Autism Research Initiative (SFARI). Parents/primary

TABLE 1 Participant characteristics

Characteristics	16p11.2 deletion	16p11.2 duplication
Age		
Mean (SD)	8 y, 5 m (3 y, 1 m)	8 y, 5 m (3 y, 5 m)
Range	3 y, 6 m–14 y, 5 m	3 y, 9 m–14 y, 9 m
Sex		
Males	27 (71.05%)	16 (51.61%)
Females	11 (28.95%)	15 (48.39%)
Location of Residence		
UK	25 (65.79%)	8 (25.81%)
Europe	2 (5.26%)	3 (9.68%)
North America	10 (26.32%)	19 (61.29%)
Australasia	1 (2.63%)	1 (3.23%)
Co-occurring diagnoses		
Autism	15 (39.47%)	17 (54.83%)
ADHD	5 (13.16%)	10 (32.26%)
Dyspraxia	5 (13.16%)	4 (12.90%)
Epilepsy	9 (23.68%)	5 (16.13%)
Other reported medical conditions[a]	11 (28.95%)	12 (38.71%)

Note: a. Includes mental health disorder, speech, language, and communication difficulties, Chiari Malformation, hypermobility, heart defects, kyphosis, spina bifida, extra rib, cleft epiglottis, cerebral palsy, asthma.

caregivers were also 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 Unique (a UK charity that supports families of individuals affected by rare chromosome and gene disorders). Eligibility criteria were being a parent/primary caregiver to a child with a diagnosis of 16p11.2 deletion or 16p11.2 duplication where the child was aged between 3 years and 14 years 11 months.

Measures

Six standardized parent/caregiver questionnaires were administered via two online platforms (over three stages) in accordance with copyright and licensing requirements and participants were able to complete measures in their own time. The Sensory Behavior 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) ($n = 1$ 16p11.2 deletion; $n = 3$ 16p11.2 duplication) or the Vineland (Stage three) ($n = 4$ 16p11.2 deletion; $n = 8$ 16p11.2 duplication) due to attrition.

Sensory behavior questionnaire

The Sensory Behavior Questionnaire (SBQ; Neil et al., 2017) is a 50-item measure of both the frequency and impact of sensory behavior. The tool was initially designed as a clinical and research tool to assess sensory behaviors 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 behaviors. 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 participants.

Child sensory profile 2/ Short sensory profile 2

The Child Sensory Profile 2 (CSP-2) (Dunn, 1999, 2014) is an 86-item 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 behaviors (Conduct, Social–Emotional, and Attentional). From the sensory system and associated behavior 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 Supporting Information Table 1. The CSP-2 was normed in a large general population sample of children aged 3–14 years, 11 months ($N = 697$). Raw scores can be calculated for each scale with higher scores indicating more sensory differences. In addition, a 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.

As well as the 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.

Social responsiveness scale, second edition

The Social Responsiveness Scale, Second Edition (SRS-2) (Constantino & Gruber, 2012) is a 65-item questionnaire measure of behavior associated with autism. The 65-item scale provides a total score reflecting the severity of social difficulties associated with autism. Items are coded on a 4-point scale ranging from 0 (not true) to 3 (almost always true). Higher scores represent greater severity. The School Age version of the form was administered to participants with children aged 4 to 14 years old. SRS-2 data were not collected for children aged 3 years old ($n = 4$ 16p11.2 deletion; $n = 1$ 16p11.2 duplication)

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, generalized 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 was administered to participants with children aged 6–18 years old. SCAS-P data were not collected for children aged 3 to 5 years old ($n = 10$ 16p11.2 deletion; $n = 11$ 16p11.2 duplication).

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-morbid 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 standard scores with higher scores associated with a greater number and/or frequency of reported concerns. Standard scores are calculated for each content scale and are interpreted as, ≥70 very elevated score, 65–69 elevated score,

TABLE 2 Summary scores for parent-report clinical questionnaire measures

	16p11.2 deletion	16p11.2 duplication
SBQ[a] total		
n	38	31
Mean (SD)	199.47 (55.04)	191.94 (58.65)
Range	65–290	57–285
SSP-2[b]		
n	37	28
Mean (SD)	42.14 (11.45)	42.89 (12.29)
Range	19–65	19–70
SRS-2[c]		
n	34	30
Mean (SD)	77.97 (15.40)	82.07 (12.42)
Range	42–104	62–105
SCAS-P[d] total		
n	28	20
Mean (SD)	25.93 (18.29)*	36.75 (22.04)*
Range	1–61	6-88
CON-T[e] Inattention		
n	28	20
Mean (SD)	73.54 (15.49)*	81.50 (8.21)*
Range	43–90	63-90
CON-T[e] Hyperactivity		
n	28	20
Mean (SD)	66.50 (15.68)*	79.30 (10.90)*
Range	40–90	57-90
CON-T[e] Learning problems		
n	28	20
Mean (SD)	75.61 (11.38)	75.30 (14.60)
Range	50–90	50–90
CON-T[e] Executive Functioning		
n	28	20
Mean (SD)	70.04 (14.42)	73.40 (11.45)
Range	40–90	43–90
CON-T[e] Defiance/aggression		
N	28	20
Mean (SD)	54.33 (12.26)	63.55 (17.42)
Range	44–90	45–90
CON-T[e] Peer relations		
n	28	20
Mean (SD)	83.52 (11.21)	82.15 (11.86)
Range	53–90	52–90
Vineland 3 ABC[f]		
n	34	23
Mean (SD)	69.00 (10.75)	69.39 (9.12)
Range	50–103	49–91

[a]Sensory Behavior Questionnaire (lower scores reflect greater levels of sensory behaviors).
[b]Short Sensory Profile 2 (summary scores from CSP-2) (lower scores reflect greater levels of sensory behaviors).
[c]Social Responsiveness Scale 2 (higher scores reflect higher amount of autistic traits).
[d]Spence Children's Anxiety Scale (higher scores reflect greater levels of anxiety).
[e]Connor's *t*-scores by sub-scale.
[f]Vineland 3 Adaptive Behavior Composite (higher scores reflect better functioning).
*Indicates a significant difference between groups, $p < 0.05$.

60–64 high average score, 40–59 average score, and <40 low score. The Conners 3 was administered to participants with children aged 6–14 years old. Conners 3 data were not collected for children aged 3 to 5 years old ($n = 10$ 16p11.2 deletion; $n = 11$ 16p11.2 duplication).

Vineland adaptive behavior scales, third edition (domain level parent/caregiver form)

The Vineland Adaptive Behavior Scales, Third Edition (Vineland) (Sparrow et al., 2016) domain-level parent/caregiver form is a questionnaire measure of adaptive behavior 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 socialization. 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).

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

RESULTS

Summary scores of the parent-report clinical questionnaire measures are outlined in Table 2.

Age and sensory differences

To investigate the relationship between age and sensory differences, Spearman's correlation analyses were conducted between age and the SBQ total score. A non-significant relationship was found in both 16p11.2 deletion, $r_s(36) = 0.16$, $p = 0.33$, and 16p11.2 duplication, $r_s(29) = -0.04$, $p = 0.84$, groups indicating that sensory behavioral difficulties did not increase nor decrease with age in either cohort.

Sensory behavior (frequency and impact)

Total scores on the SBQ were analyzed to assess the severity of sensory behavior differences experienced in both 16p11.2 deletion and 16p11.2 duplication groups. In order to contextualize 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) and autistic children ($N = 66$; Mean age = 10 years; 3 months; SD = 2 years, 6 months).

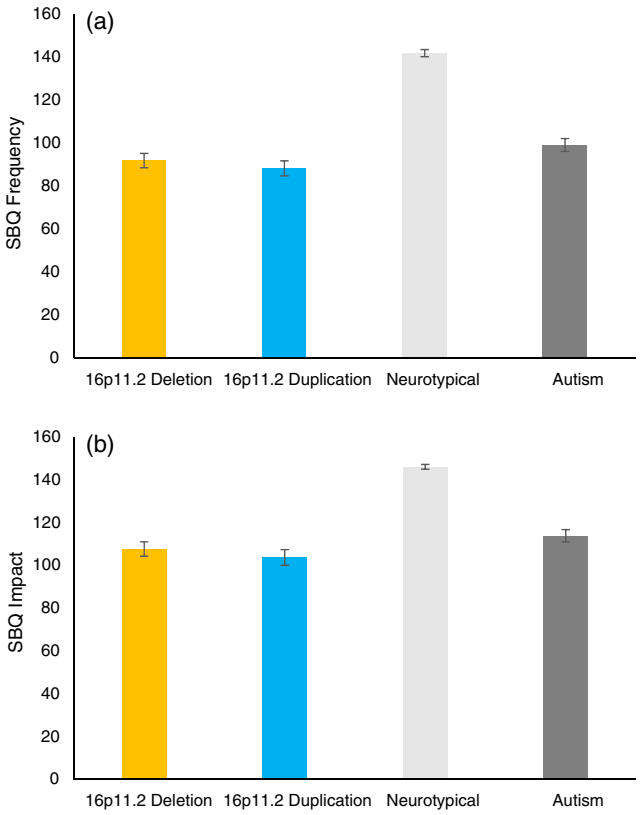

FIGURE 1 Mean scores of SBQ frequency (panel a) and SBQ impact (panel b) by group. Error bars represent ± 1S.E. N.b. data for Neurotypical group and autism taken from Neil et al. (2017), lower scores indicate increased severity

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. The 16p11.2 deletion cohort exhibited significantly greater levels of sensory behaviors than the neurotypical children, $t(37) = -9.90$, $p < 0.001$, $d = 1.60$, with both the frequency of behaviors, $t(37) = -11.10$, $p < 0.001$, $d = 1.80$, and impact of behaviors, $t(37) = -8.47$, $p < 0.001$, $d = 1.38$, demonstrating this pattern. Sixty-three percent of 16p11.2 deletion children had SBQ impact scores more than three standard deviations below the mean SBQ impact score of the neurotypical children (lower scores indicate greater impact) demonstrating that the impact of sensory behavior in this cohort was often profound. The 16p11.2 deletion cohort displayed similar levels of sensory behavior differences to the autistic children, $t(37) = -1.51$, $p = 0.14$, $d = 0.25$, this was true both in terms of frequency of behavior, $t(37) = -1.61$, $p = 0.12$, $d = 0.26$, and impact of behavior, $t(37) = -1.19$, $p = 0.24$, $d = 0.19$ (see Figure 1). Similarly, the 16p11.2 duplication cohort also exhibited significantly greater levels of sensory behaviors than the neurotypical children, $t(30) = -9.11$, $p < 0.001$, $d = 1.63$, with

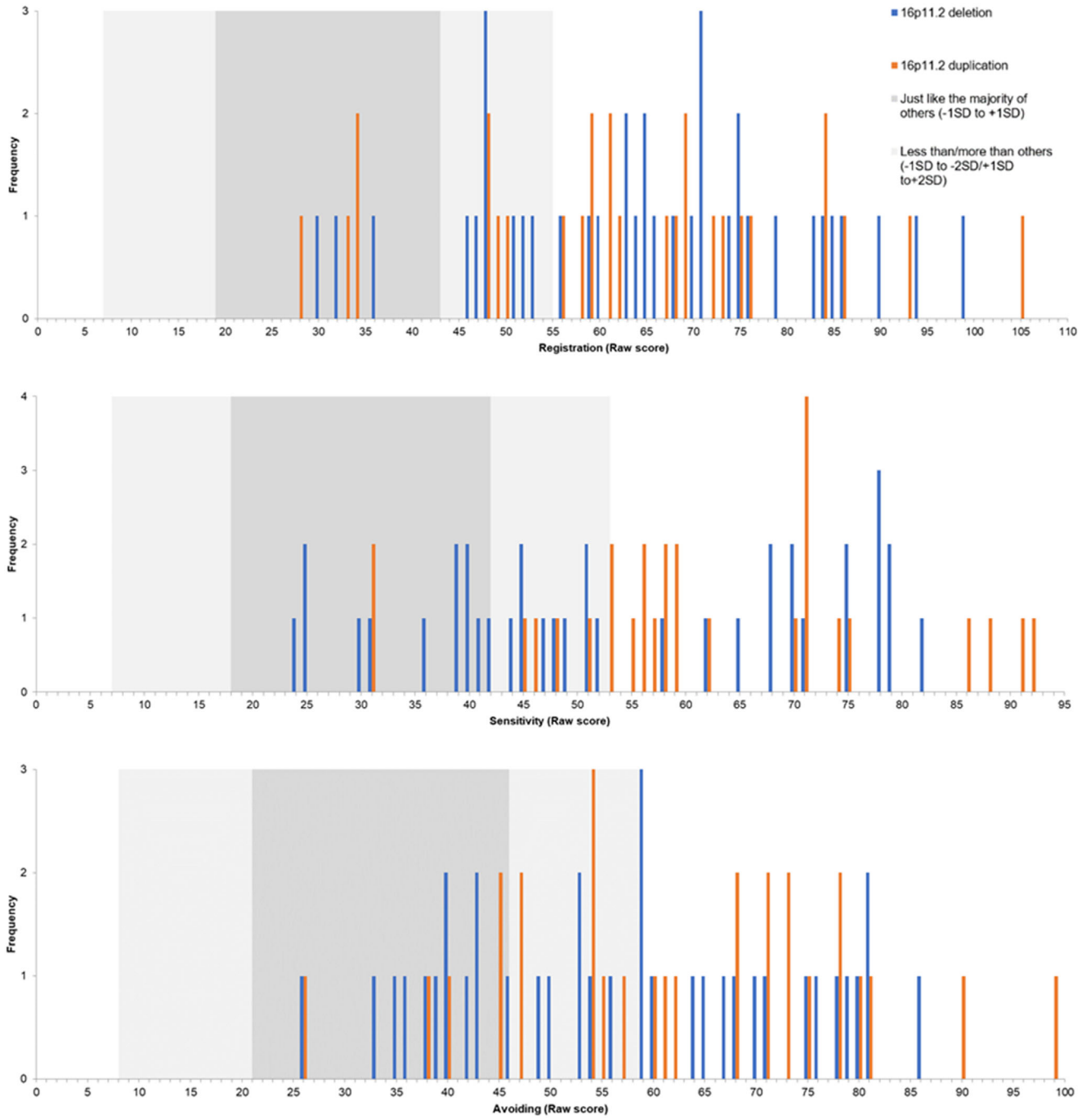

FIGURE 2 Distribution of CSP-2 raw scores for each of the sensory patterns (registration, sensitivity, avoiding, seeking) for 16p11.2 deletion (blue) and 16p11.2 duplication (orange). The dark gray box indicates the range of scores associated with the majority (68%) of the normative sample (Dunn, 2014). The light gray boxes indicate the range of scores whereby the minority of the normative sample exhibit sensory behavior 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 behavior much less (2%) or much more (2%) than the majority of others

both the frequency of behaviors, $t(30) = -10.25$, $p < 0.001$, $d = 1.84$, and impact of behaviors, $t(30) = -7.74$, $p < 0.001$, $d = 1.39$, demonstrating this pattern. Sixty-five percent of 16p11.2 duplication children had SBQ impact scores more than three standard deviations below the mean SBQ impact score of the neurotypical children, demonstrating that the impact of sensory behavior in this cohort was often profound. There was a trend for the 16p11.2 duplication children to display even more sensory behavior differences compared to the autistic children, though this did not reach significance, $t(30) = -1.99$, $p = 0.06$, $d = 0.36$. Additionally, there was a trend for the frequency of behavior differences to be higher in the 16p11.2 duplication children

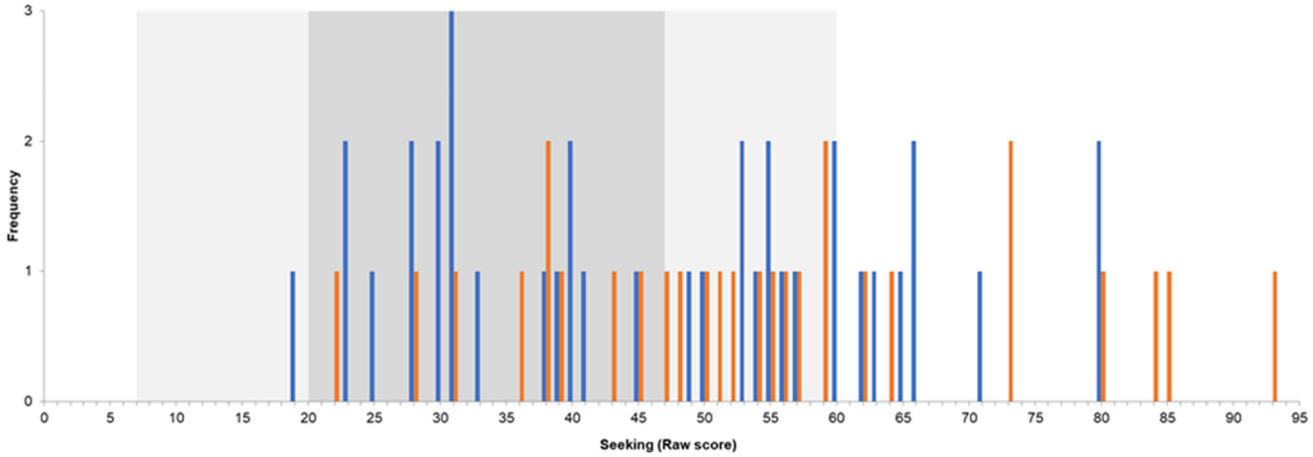

FIGURE 2 (Continued)

compared to the autistic children, $t(30) = -2.08$, $p < 0.05$, $d = 0.37$, though this was not sufficiently robust to withstand Bonferroni correction for multiple comparisons. The impact of behaviors followed a similar trend but did not statistically differ between groups, $t(30) = -1.71$, $p = 0.10$, $d = 0.31$. Overall, results indicate that the impact and frequency of sensory behaviors in the 16p11.2 duplication children was at least as problematic as for the comparison cohort of autistic children.

When compared to one another using Welch independent samples *t*-tests (equal variances not assumed), the 16p11.2 deletion and 16p11.2 duplication cohorts did not score differently on SBQ total, $t(62.46) = 0.55$, $p = 0.59$, $d = 0.13$, SBQ frequency, $t(62.93) = 0.52$, $p = 0.60$, $d = 0.13$ or SBQ impact, $t(61.75) = 0.55$, $p = 0.58$, $d = 0.15$. Overall, these results indicate clear evidence of sensory behavior differences in 16p11.2 deletion and duplication children. The frequency and impact of sensory behavior were more severe when compared to neurotypical children, with levels being similar to autistic children. The level of sensory behavior differences was similar between the two conditions.

Sensory profile

To establish whether there were particular areas of sensory processing difference associated with 16p11.2 deletion and 16p11.2 duplication, scores from the CSP-2 were calculated and compared as outlined below.

CSP-2—sensory patterns

The distribution of raw scores for each sensory pattern are shown in Figure 2. For each of the four sensory patterns, responses were highly likely to fall in the "much more" than the majority of others range, though for each cohort and each pattern there were responses in the "just like" others range, indicating the variability of responses in each cohort. The proportion of children scoring "much more" than others in Registration was 70% in 16p11.2 deletion and 71% in 16p11.2 duplication, Sensitivity: 43% in 16p11.2 deletion and 71% in 16p11.2 duplication, Avoiding: 41% in 16p11.2 deletion and 57% in 16p11.2 duplication, and Seeking: 22% in 16p11.2 deletion and 29% in 16p11.2 duplication. Overall, this indicates that the profile of processing patterns was similar between 16p11.2 deletion and duplication groups. However, 16p11.2 duplication children were more likely to exhibit differences in sensory Sensitivity compared to 16p11.2 deletion children.

The co-occurrence of differences in sensory patterns was explored by observing the classification score of each child on each of the CSP-2 sensory patterns (Figure 3). As can be seen in Figures 2 and 3, in both 16p11.2 deletion and 16p11.2 duplication cohorts, children who scored as "more" or "much more" than the majority of others in one pattern were likely to also be scored as "more" or "much more" in one or more other patterns. Of note, if a child did not score as "much more" in sensory Registration, it was less likely that they would exhibit differences in Sensitivity, Avoiding, or Seeking.

To explore whether sensory patterns were different in 16p11.2 deletion and duplication children with and without an autism diagnosis (as reported by the parent/caregiver), Fisher's Exact tests, using Bonferroni correction for multiple comparisons, assessed the association between autism diagnosis and the proportion of children who scored as "much more" than the majority of others in the each of the CSP-2 sensory patterns (Table 3, see also Figure 3). Scores in the "much more" than others range were more frequent in the Avoiding pattern in the 16p11.2 duplication cohort who had an autism diagnosis compared to those without an autism diagnosis. However, no other statistical differences between those with

(a)

Ppt no.	Seeking	Avoiding	Sensitivity	Registration
4*	5	5	5	5
9*	5	5	5	5
12	5	5	5	5
19*	5	5	5	5
8	4	5	5	5
10	4	5	5	5
17	4	5	5	5
22	4	5	5	5
33*	4	5	5	5
3*	3	5	5	5
20*	3	5	5	5
26*	3	5	5	5
30*	3	5	5	5
21*	5	4	5	5
36*	5	4	5	5
11	4	4	5	5
27	5	5	4	5
16	3	5	4	5
5*	4	4	4	5
23	4	4	4	5
2*	3	4	4	5
6	3	4	4	5
1	5	3	4	5
37	4	4	3	5
31	3	4	3	5
15	4	3	3	5
24*	3	3	4	4
35	3	3	4	4
18	4	4	3	4
13*	3	3	3	4
14	3	3	3	4
29	3	3	3	4
32	3	3	3	4
25	2	3	3	4
7	3	3	3	3
28	3	3	3	3
34*	3	3	3	3

* indicates ASD diagnosis

FIGURE 3 Co-occurrence of CSP-2 sensory patterns in 16p11.2 deletion (panel a) and 16p11.2 duplication (panel B) children. Each row indicates a child included in the study. Colored 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). * indicates ASD diagnosis.

and without an autism diagnosis were observed indicating that the conclusions drawn in relation to the sensory patterns of 16p11.2 deletion and 16p11.2 duplication children were largely relevant both to those with and without an autism diagnosis.

CSP-2—sensory systems

The distribution of raw scores for each sensory system are shown in Figure 4. Body position was the sensory system most frequently scored in the "much more" than the

(b)

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

* indicates ASD diagnosis

FIGURE 3 (Continued)

majority of others range with 65% of 16p11.2 children and 57% of 16p11.2 duplication children scoring in this range. The proportion of children scoring "much more" than others in Touch was 54% in 16p11.2 deletion and 46% in 16p11.2 duplication, Movement: 32% in 16p11.2 deletion and 43% in 16p11.2 duplication, Oral: 38% in 16p11.2 deletion and 39% in 16p11.2 duplication, Auditory: 22% in 16p11.2 deletion and 25% in 16p11.2 duplication, and Visual: 11% in 16p11.2 deletion and 18% in 16p11.2 duplication. Overall, the profile of sensory processing systems was similar between 16p11.2 deletion and duplication groups. The co-occurrence of differences in sensory systems for each child is presented in Supporting Information Figure S1.

To explore whether sensory systems were different in 16p11.2 deletion and duplication children with and without an autism diagnosis (as reported by the parent/caregiver), Fisher's Exact tests, using Bonferroni correction for multiple comparisons, assessed the association between autism diagnosis and the number of children who scored as "much more" than the majority of others in the each of the CSP-2 sensory systems (Table 4, see also Supporting Information Figure S1). No statistical differences were observed between those with and without an autism diagnosis.

CSP-2—behavioral responses associated with sensory processing

The proportion of children scoring "much more" than others in social emotional behavior was 46% in 16p11.2 deletion and 64% in 16p11.2 duplication, Conduct: 35% in 16p11.2 deletion and 50% in 16p11.2 duplication, and Attentional: 30% in 16p11.2 deletion and 43%

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 patterns

	16p11.2 deletion			16p11.2 duplication		
	No autism ($n = 22$)	Autism ($n = 15$)	p	No autism ($n = 12$)	Autism ($n = 16$)	p
Registration	64%	80%	0.466	50%	88%	0.044
Sensitivity	27%	67%	0.023	58%	81%	0.231
Avoiding	32%	53%	0.307	25%	81%	0.006
Seeking	14%	33%	0.228	17%	38%	0.401

Note: 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 ($p = 0.0125$).

in 16p11.2 duplication. The distribution of raw scores in the different behaviors associated with sensory processing are shown in Supporting Information Figure S2.

Sensory differences and clinical features

It was notable that there was considerable variation in scores on the CSP-2 in 16p11.2 deletion and duplication groups (Figures 2 and 4). This variation was also clear in the range of SBQ scores reported (Table 2), particularly when compared with the smaller SBQ ranges reported in neurotypical and autistic comparator groups (Neil et al., 2017, see article for ranges). To investigate whether any of the variability in sensory differences was associated with other clinical features in the 16p11.2 deletion and 16p11.2 duplication 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) and the sensory behavior measures (SSP-2; SBQ total; SBQ frequency; SBQ impact). Results can be seen in Figure 5 (16p11.2 deletion) & Figure 6 (16p11.2 duplication). Results from the 16p11.2 deletion cohort found that increased severity of sensory behaviors, as indicated by the SSP-2, was associated with higher autistic traits (SRS-2 total T-scores), increased anxiety (SCAS-P total scores), lower adaptive behavior skills (Vineland adaptive behavior composite), increased difficulty with executive functioning (Conners 3 T-scores for executive functioning), increased hyperactivity (Conners 3 T-scores for hyperactivity) and increased inattention (Conners 3 T-scores for inattention). A similar profile of relationships was also present when sensory behaviors were assessed via the SBQ, though scores on this scale were also associated with higher defiant/ aggressive behavior (Conners3 T-scores for defiance/aggression), increased learning problems (Conners 3 T-scores for learning problems), and higher peer relations (Conners 3 T-scores for peer relations).

Results from the 16p11.2 duplication cohort found that increased severity of sensory behaviors, as indicated by the SBQ, was associated with higher autistic traits (SRS-2 total T-scores).

Overall, results from the Spearman's correlation analyses demonstrated that, in both 16p11.2 deletion and duplication, sensory processing differences tend to be associated with autistic traits. Sensory processing differences were also associated with other clinical features in 16p11.2 deletion. However, from these analyses it is not clear which relationships explain independent proportions of variance in sensory processing. To determine this, multiple regressions were conducted on both the 16p11.2 deletion and 16p11.2 duplication datasets. For this analysis the SBQ total scores were used to indicate sensory differences as this measure was specifically designed for use with individuals with intellectual disability and therefore may be a more reliable indicator of sensory processing differences than the SSP-2. 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 in the multiple regressions. For the 16p11.2 deletion dataset these clinical questionnaire scores explained 68% of the variance in SBQ total scores, $F(3, 24) = 17.27$, $p < 0.001$. Inspection of beta-weights indicated the SRS-2 T-total ($\beta = -0.59$, $p = 0.012$) and SCAS-P total ($\beta = -0.33$, $p = 0.027$) both explained significant independent proportions of the variance in SBQ total scores. For the 16p11.2 duplication dataset these variables explained 74% of the variance in SSP-2 total, $F(3, 16) = 15.46$, $p < 0.001$. Inspection of the beta-weights indicated that the SRS-2 T-total ($\beta = -0.83$, $p = 0.001$) was the only predictor to explain a significant independent proportion of the variance (see Figure 7). While the SCAS-P total did not explain a significant independent proportion of the variance in SBQ total scores in 16p11.2 duplication, a relationship between these variables was evident upon inspection of the scatterplot (Supporting Information Figure S3). It is noteworthy that the 16p11.2 duplication regression analysis had reduced power to identify independent predictors compared to the 16p11.2 deletion analysis due the cohort being of smaller sample size.

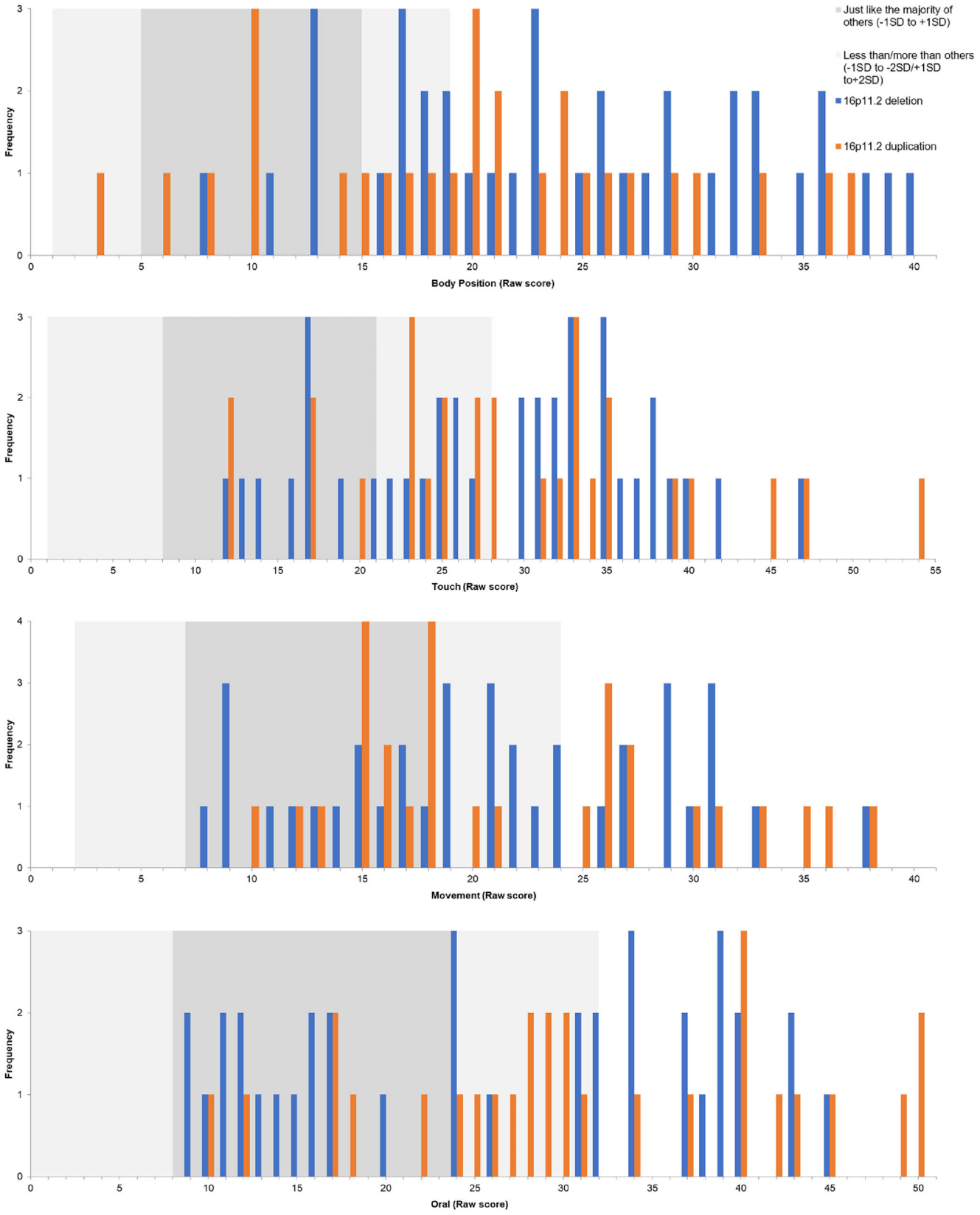

FIGURE 4 Distribution of CSP-2 raw scores for each of the sensory systems (body position, touch, movement, Oral, auditory, visual) for 16p11.2 deletion (blue) and 16p11.2 duplication (orange). The dark gray box indicates the range of scores associated with the majority (68%) of the normative sample (Dunn, 2014). The light gray boxes indicate the range of scores whereby the minority of the normative sample exhibit sensory behavior 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 behavior much less (2%) or much more (2%) than the majority of others

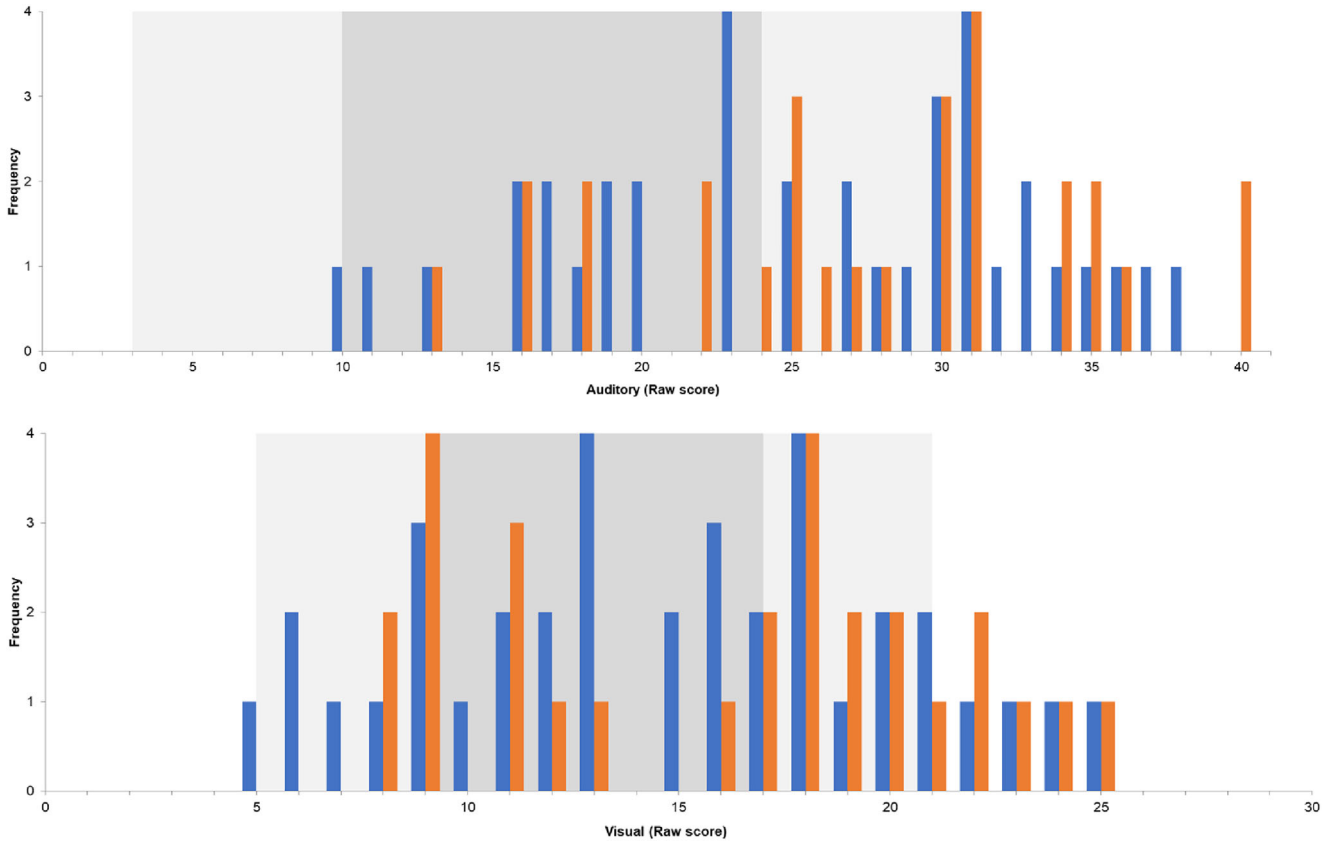

FIGURE 4 (Continued)

DISCUSSION

This study aimed to characterize sensory processing in 16p11.2 deletion and 16p11.2 duplication children. Sensory processing differences were clearly evident in both conditions, though scores revealed significant variation in individuals with each diagnosis. In all sensory domains, the scores of 16p11.2 deletion and duplication children ranged from those that are consistent with those expected in typically developing children, to scores that suggest profound differences. In both groups, the overall severity of sensory behaviors was increased compared to a comparison cohort of neurotypical children and similar to a comparison cohort of autistic children (Neil et al., 2017). Analysis of sensory pattern data indicated over 70% of 16p11.2 deletion and duplication children exhibited clear differences in sensory Registration (missing sensory input). In addition, 71% of 16p11.2 duplication children exhibited clear differences in sensory Sensitivity and 57% of 16p11.2 duplication children exhibited clear differences in sensory Avoidance. Analysis of sensory system data indicated 65% of 16p11.2 children and 57% of 16p11.2 duplication children exhibited clear differences in response to Body Position information. Differences in response to Touch, Movement, Oral, and Auditory information were also common. Sensory differences were present regardless of whether a child had a co-occurring diagnosis of autism and a significant association between autism diagnosis and differences in sensory Avoidance was observed in 16p11.2 duplication children. In 16p11.2 deletion, the level of both autistic traits and anxiety were predictive of sensory processing differences. In 16p11.2 duplication, the level of autistic traits was predictive of sensory processing differences.

Overall, our findings in relation to 16p.11.2 deletion are broadly in alignment with those reported on a smaller 16p11.2 deletion cohort by Osório, Rodríguez-Herreros, Romascano, et al. (2021). However, a key difference from the findings reported by Osório, Rodríguez-Herreros, Romascano, et al. (2021) was that the current study found children with a 16p11.2 deletion exhibited differences in the processing of touch or oral (response to smells or touch/taste in the mouth) sensory information. Clear differences in touch and oral systems were present in both autistic and non-autistic 16p11.2 children (although were somewhat less common in non-autistic children). This casts doubt upon the idea that differences in touch and taste/smell sensory processing differentiate autism from 16p11.2 deletion, as speculated by Osório and colleagues.

Aligned with the current study, studies of human brain activity have also indicated sensory differences in 16p11.2 deletion and duplication. Leblanc and Nelson (2016) recorded visual evoked potentials in 16p11.2

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 sensory systems

	16p11.2 deletion			16p11.2 duplication		
	No autism ($n = 22$)	Autism ($n = 15$)	p	No autism ($n = 12$)	Autism ($n = 16$)	p
Body position	64%	67%	1.000	50%	63%	0.702
Touch	45%	67%	0.315	25%	63%	0.067
Movement	32%	33%	1.000	25%	56%	0.136
Oral	23%	60%	0.038	33%	44%	0.705
Auditory	18%	27%	0.690	16%	31%	0.662
Visual	5%	20%	0.283	0%	31%	0.053

Note: 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 ($p = 0.008$).

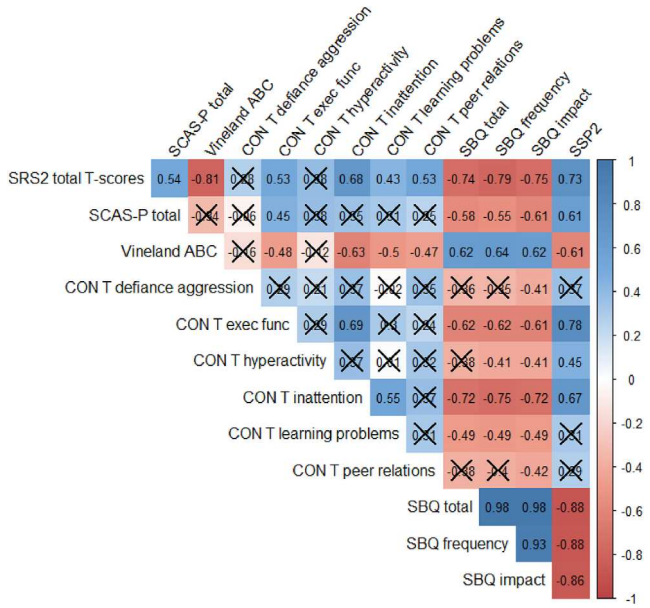

FIGURE 5 16p11.2 deletion clinical outcome measure correlation table reporting Spearman's r_s-values. N.b. r_s-values where $p > 0.05$ are crossed

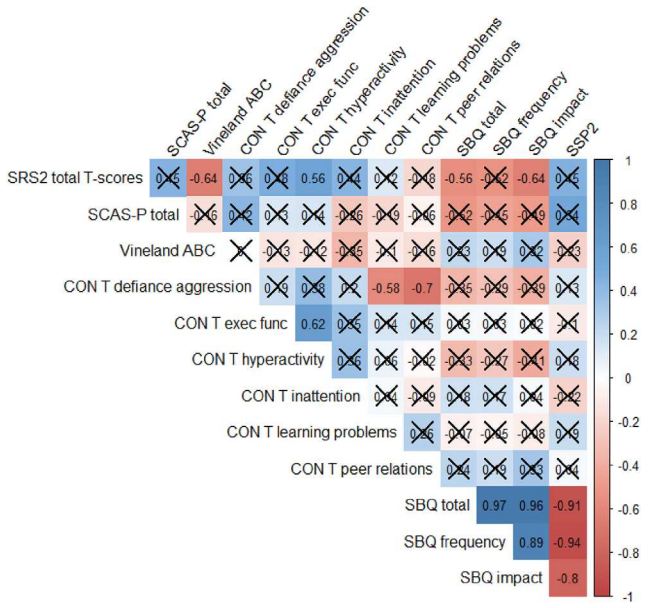

FIGURE 6 16p11.2 duplication clinical outcome measure correlation table reporting Spearman's r_s-values. N.b. r_s-values where $p > 0.05$ are crossed

deletion and duplication children. Relative to controls, visual evoked potentials showed increased amplitude in 16p11.2 deletion children and decreased amplitude in 16p11.2 duplication children. Jenkins et al. (2016) used magnetoencephalography to measure auditory evoked responses in in 16p11.2 deletion and duplication children. Relative to controls, prolonged latency of auditory response was observed in 16p11.2 deletion children but not in 16p11.2 duplication children. These findings suggest that sensory differences in 16p11.2 deletion and duplication may be underpinned by different neural mechanisms that could be gene dosage-dependent. Sensory differences in 16p11.2 deletion have also been indicated in an animal study that reported deafness and increased pain threshold in 16p11.2 heterozygous deletion mice (Yang et al., 2015). These findings could be seen to align with the high levels of sensory Registration and differences in Auditory and Touch processing observed in the 16p11.2 deletion cohort in the present study. However, Yang et al. (2015) noted that their observation of deafness in 16p11.2 deletion mice inconsistent with findings in another known line of 16p11.2 mice that appeared to display normal hearing. It is clear from our data that auditory differences are not universally experienced in 16p11.2 deletion.

It is recognized that differential sensory profiles may present across different neurodevelopmental conditions. The current study observed that, in 16p11.2 deletion, differences in sensory Registration were more common than differences in Sensitivity, Avoiding, and Seeking. While Registration differences were also common in 16p11.2 duplication, differences in Sensitivity and Avoiding were also frequent. The pattern profile observed in 16p11.2 duplication is similar to that reported by Simpson et al. (2019) in an autistic child cohort. Contrastingly, a study by Lyons-Warren et al. (2022) observed pronounced

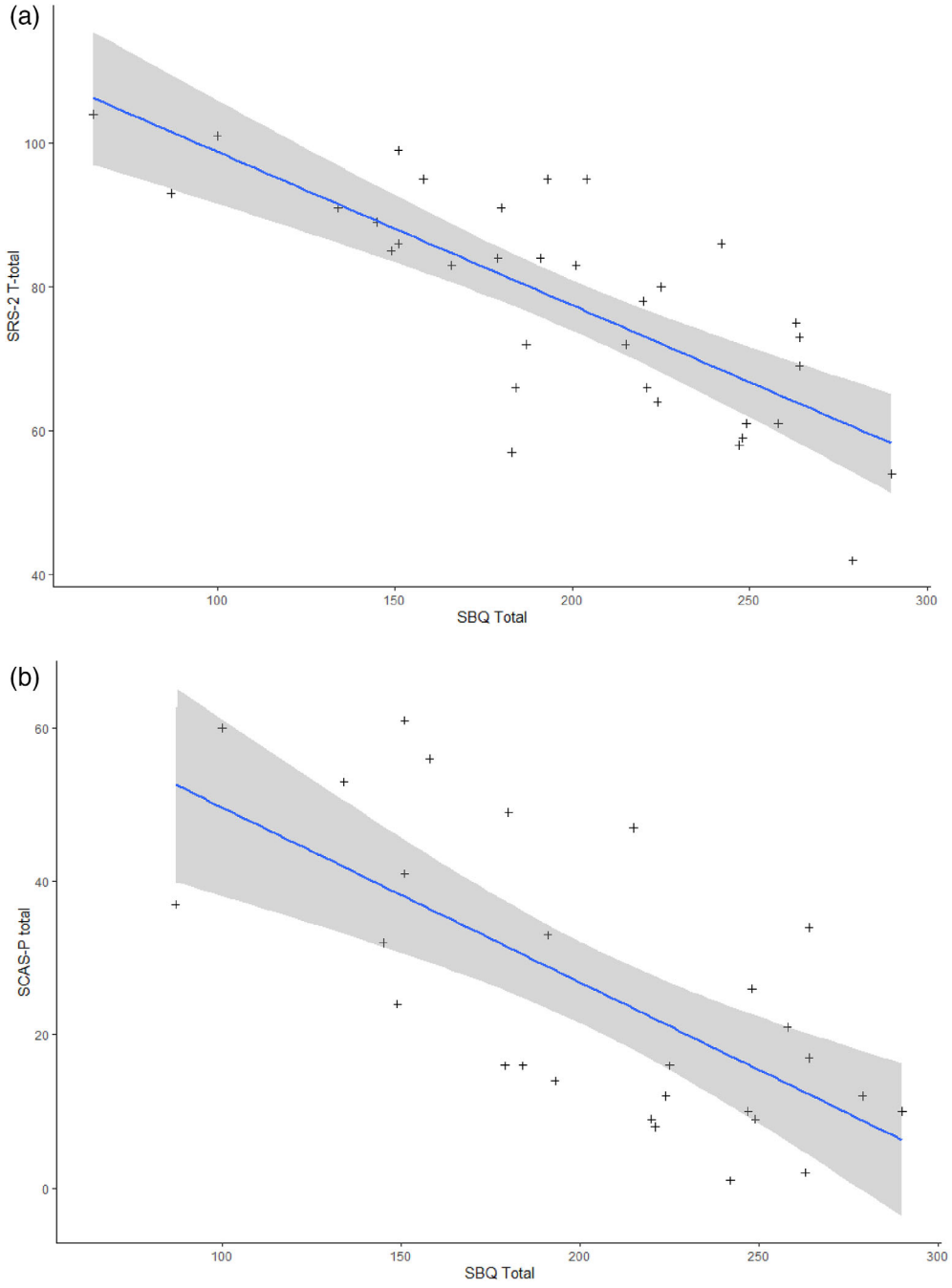

FIGURE 7 Scatter plots with regression line of 16p11.2 deletion (panels a & b) and 16p11.2 duplication (panel c) data indicating the significant predictors of SBQ total scores. Shaded area represents 95% confidence region

differences in sensory Sensitivity in Phelan-McDermid Syndrome and SYNGAP1-related Intellectual Disability relative to other sensory patterns. In regard to sensory systems, the most common area of difference in 16p11.2 deletion and duplication was Body Position. Differences in Body Position have also been noted in overgrowth syndromes; Sotos syndrome and Tatton-Brown Rahman syndrome (Smith et al., under review). Contrastingly, in Williams Syndrome and Marshall-Smith syndrome differences in auditory processing have been reported as common (John & Mervis, 2010; Mulder et al., 2020). It should be noted that these Sensory Profile investigations in other neurodevelopmental conditions used different measures to the CSP-2 (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 across neurodevelopmental conditions.

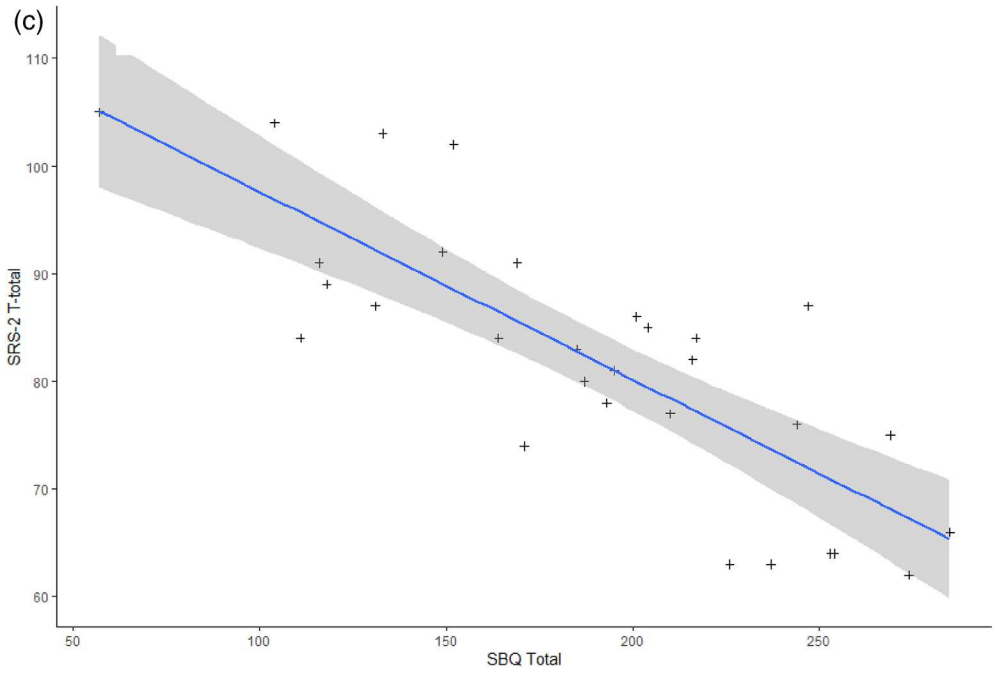

FIGURE 7 (Continued)

The relationship observed between autistic symptomatology and sensory differences indicates that children with a 16p11.2 deletion and duplication who experience autistic symptomatology are also likely to experience sensory differences. The observed relationship in 16p11.2 deletion is also consistent with findings reported by Osório, Rodríguez-Herreros, Romascano, et al. (2021). They reported that ADOS-2 Total Scores and Social Affect (SA) scores, but not Restricted and Repetitive Behavior (RRB) scores, were associated with sensory differences in 16p11.2 deletion children. Contrastingly, in autistic children, the authors only found a relationship between ADOS-2 SA scores and sensory differences, not Total or RRB scores. Further investigation of 16p11.2 deletion, 16p11.2 duplication, and idiopathic autism groups should establish whether distinct relationships between autism symptomatology and sensory differences exist. This could provide insight into the mechanisms that contribute to these clinical phenotypes.

The relationship observed between anxiety and sensory differences (although a non-significant relationship in 16p11.2 duplication children) suggests that sensory differences and anxiety symptoms are likely to co-occur in children with a 16p11.2 diagnosis. Anxiety disorders have been found to be prevalent in 16p11.2 deletion (Hanson et al., 2015) and, while not part of the major diagnostic criteria for autism, anxiety has been identified as an associated feature (American Psychiatric Association, 2013). While the causal relationships between autistic traits, anxiety and sensory differences in 16p11.2 deletion and duplication were not tested in the current study, future investigation of directional effects in this specific population may provide insight into the underlying mechanisms of symptoms and could also inform intervention strategy.

While the use of online parent-reported measures of sensory processing facilitated the global recruitment of these rare clinical samples, it can be argued that these measures are limited to the assessment of observable behavior, subject to bias, and thus less reliable compared to clinical assessment or laboratory-based testing of sensory processing. Furthermore, while sex was relatively balanced in the 16p11.2 duplication child cohort, there was a dominance of males in the 16p11.2 deletion cohort (71%). It has been suggested sex differences play a role in sensory processing differences in neurodevelopmental disorder (Osório, Rodríguez-Herreros, Richetin, et al., 2021). As such, this imbalance may have influenced the results of this study. The small sample sizes in this study could be argued as a limitation although they were relatively large given rarity of these conditions. Subgroup analysis of within-syndrome autism and non-autism groups has a further reduced sample size and thus should be interpreted with caution. While not feasible within this online study design, the inclusion of a measure of the child's cognitive ability may have been informative. Although a relationship between age and sensory processing differences was not found in this study, previous research has found a negative association between mental age and sensory processing differences in children with developmental disability (Baranek et al., 2006).

The present study's finding of increased, but variable, sensory processing differences in 16p11.2 deletion and duplication children is important for the care of children

with these diagnoses. Clinicians, parents/caregivers, and educators should be aware that sensory differences can occur, particularly differences in sensory Registration and response to Body Position information, which appear to be common in both 16p11.2 groups, and differences in sensory Sensitivity and Avoidance which appear to be common in 16p11.2 duplication. Nonetheless, the substantial heterogeneity in sensory differences/ profiles demonstrates the importance of using an individualized approach when assessing a child's sensory needs, from which insights can be used to inform personalized strategies and targeted intervention to minimize associated difficulty and enhance participation and day-to-day functioning (Engel-Yeger & Dunn, 2011).

In summary, this first detailed assessment of sensory processing, alongside other clinical features, in relatively large cohorts of children with a 16p11.2 deletion and 16p11.2 duplication demonstrates that sensory processing differences generally have a profound impact on their lives. Overall, sensory behavior was found to be similar to autistic children without a genetic diagnosis. When considering how to effectively support children with a 16p11.2 deletion or duplication it is clear that clinicians, parents and educators should take sensory processing into account.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Open Science Framework at https://osf.io/w5fud/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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