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BRIEF REPORT

# Brief Report: Sensory Reactivity in Children with Phelan–McDermid Syndrome

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**Abstract** Phelan–McDermid syndrome (PMS), a monogenic form of autism spectrum disorder (ASD), results from deletion or mutation of the *SHANK3* gene. Atypical sensory reactivity is now included in the diagnostic criteria for ASD. Examining the sensory phenotype in monogenic forms of ASD, such as PMS, may help identify underlying mechanisms of sensory reactivity. Using the Short Sensory Profile, the current study compared sensory reactivity in 24 children with PMS to 61 children with idiopathic ASD (iASD). Results suggest that children with PMS show *more* low energy/weak symptoms and *less* sensory sensitivity as compared to children with iASD. This study is the first to demonstrate differences in sensory reactivity between children with PMS and iASD, helping to refine the PMS phenotype.

**Keywords** Phelan–McDermid syndrome · 22q13 deletion syndrome · Autism · Autism spectrum disorder · Sensory reactivity · Sensory profile

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## Introduction

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) created the diagnosis of autism spectrum disorder (ASD) to encompass all the previously defined pervasive developmental disorders, and also combined the social and communication impairment domains into one category. Another important change to the ASD diagnostic criteria in DSM-5 was the addition of atypical sensory reactivity to the restricted and repetitive behavior domain. Sensory reactivity may include hyperreactivity, hyporeactivity, or an unusual interest to sensory stimuli in the environment. Sensory reactivity in children and adults with ASD has been shown to differ from that of typically developing children (Kientz and Dunn 1997; Ben-Sasson et al. 2007; Tomcheck and Dunn 2007; Boyd et al. 2010; Crane et al. 2009; Dunn et al. 2002; Lane et al. 2011; Tavassoli et al. 2014). Difficulties in sensory reactivity have an impact on everyday life and are associated with higher rates of anxiety (Kinnealey and Fuiek 1999; Kinnealey et al. 2011). Sensory reactivity has also been shown to be a heritable trait. A twin study that included over 1000 toddler twin pairs sampled from a state birth registry, found moderate heritability of auditory and tactile reactivity (Goldsmith et al. 2006). Moreover, in a study of 50 mothers of children and adolescents with ASD, 44 % demonstrated atypical sensory reactivity as evidenced by significantly higher scores on the adolescent and adult sensory profile (Uljarevic et al. 2014).

While sensory reactivity has been widely studied in idiopathic ASD (iASD), this is the first known study to examine sensory reactivity within a specific genetically defined subtype of ASD. Phelan–McDermid syndrome (PMS) is one of the most common monogenic forms of ASD. PMS results from deletion or mutation of the

*SHANK3* gene (Durand et al. 2007) on terminal chromosome 22q, which codes for a master scaffolding protein necessary for glutamatergic synapses and their function (Boeckers 2006). *SHANK3* deletion or mutation is found in up to 2 % of cases of ASD and moderate to profound intellectual disability (ID) (Leblond et al. 2014). The clinical phenotype of PMS has been described in several case report series and some prospective analyses and is characterized by global developmental delay, ID, severely delayed or absent speech, motor skill deficits, and often ASD (Soorya et al. 2013). Anecdotal evidence supports the presence of atypical sensory reactivity in PMS, most commonly reflected by decreased sensitivity to pain. However, no study to date has described the sensory reactivity phenotype in this syndrome. The aim of this pilot study is therefore to define the sensory phenotype in children with PMS and determine whether they differ in reactivity to sensory stimuli as compared to children with iASD and low intellectual functioning. Examining children with monogenic forms of ASD may aid in identifying underlying mechanisms of sensory reactivity.

## Methods

### Participants

The study was approved by the Institutional Review Board at the Icahn School of Medicine at Mount Sinai and parents signed informed consent prior to participation. Participants were recruited from ongoing studies in PMS at the Seaver Autism Center for Research and Treatment at the Icahn School of Medicine at Mount Sinai. Twenty-four participants with PMS and low intellectual functioning [37 % female, mean age = 5.4 years (range 2–11; SD = 2.8)] (Table 1) took part. All participants had a diagnosis of PMS with confirmed deletion or mutation of *SHANK3* using chromosomal microarray (CMA) or Sanger sequencing, respectively. Ninety-one percent of participants with PMS met criteria for autism spectrum disorder based on DSM-5 criteria and the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) (Lord et al. 2000). The Autism Treatment Network (ATN) database was used to select a comparison group of 61 children with ASD and low intellectual functioning [18 % female, mean age = 4.6 years (range 2–10; SD = 1.7)]. The comparison group was chosen based on age, intellectual functioning according to the Mullen Scales of Early Learning (MSEL), and completion of the Sensory Profile (SP). All children in the comparison iASD group had a nonverbal developmental quotient (NVDQ) score below 70. NVDQ was derived by dividing the mean age equivalent (AE) on the Visual Reception and Fine Motor scales of the MSEL by a child's chronological age (CA) and then multiplying by 100 ((AE/CA) * 100) as done in previous studies (Akshoomoff 2006; Bishop et al. 2011) (Table 1). The MSEL was chosen to avoid the floor effects that hinder the use of traditional cognitive measures normed for older children. The sex ratio within each group is representative of PMS and iASD, respectively; there is a higher number of females affected by PMS compared to iASD.

**Table 1** Participant characteristics including sample size (n), mean age and nonverbal (NV) quotients

| | PMS (n = 24) | iASD (n = 61) | *p* value |
|---|---|---|---|
| Age [years (M, SD)] | 5.4 (2.8) | 4.6 (1.7) | .09 |
| NV quotient (M, SD) | 29.2 (16.4) | 46.4 (14.6) | .001* |

Standard deviations are shown in brackets. All participants had nonverbal DQ scores below 70 derived from age-equivalent scores on the Mullen Scales of Early Learning assessment. Group differences are highlighted by * $p < .05$

### Measure

The Sensory Profile (SP) is a 125-item parent report questionnaire that measures a child's response to sensory experiences. The SP was standardized in a group of over 1200 children with and without disabilities and has high internal consistency, $\alpha = .47–.91$ (Kientz and Dunn 1997). More than half of the items on the SP are uncommon for typically developing children (Dunn 1994). The short sensory profile (SSP) is a 38-item parent report derived directly from the SP using item reduction. For participants in both groups, SSP scores were derived from the full SP in order to maximize the number of participants with complete scores. Sensory processing subscales on the SSP include tactile sensitivity, taste/smell sensitivity, visual/auditory sensitivity, movement sensitivity, low energy/weak, and under-responsivity/seeks sensation. SSP tactile, smell/taste and visual/auditory sensitivity scores represent a child's ability to respond to respective sensory stimuli in the environment (see Table 2) (Dunn 1999). Parents use a Likert scale to rate how frequently their child demonstrates a particular behavior (ranging from 1 = always to 5 = never). A lower score indicates greater deviation from typically developing children and indicates more sensory reactivity symptoms. The SSP has been used to distinguish typically developing children from children with clinical disorders, such as ASD, and to describe sensory processing abilities (Kientz and Dunn 1997). Differences in sensory reactivity between children with ASD and typically developing children have also been established using the SSP (Brockevelt et al. 2013; Tomcheck and Dunn 2007; Lane et al. 2011).

**Table 2** The short sensory profile (SSP) domains with sample items from each sensory domain (Dunn 1999)

| Short sensory profile domain | Sample item |
|---|---|
| Tactile sensitivity | Withdraws from splashing water |
| Taste/smell sensitivity | Avoids certain tastes or food smells that are typically part of a children's diet |
| Visual/auditory sensitivity | Covers eye or squints to protect eyes from light |
| Movement sensitivity | Dislikes activities when head is upside down |
| Auditory filtering | Is distracted or has trouble focusing if there is a lot of noise around |
| Low energy/weak | Seems to have weak muscles |
| Underresponsive/seeks sensation | Enjoys strange noises/seeks to make noise for noise's sake |

### Data Analysis

SPSS 20 was used to analyze the data. Descriptive statistics were calculated to determine that the data was normally distributed (Kolmogorov–Smirnoff statistic = .06, $p = .20$). For the SSP, Levene's test showed that the variances were equal for both groups [F (1,86) = .02, $p = .90$]. Groups differed on NVDQ ($p = .001$) (see Table 1). Additionally, there was a significant difference between the groups regarding sex (37 % female in the PMS group vs. 18 % female in the iASD group), and a marginal difference in age ($p = .09$). Group comparisons between children with PMS and iASD on the SSP subscales were calculated using MANCOVA with NVDQ, sex and age as covariates.

## Results

Eighty percent of children with PMS and 81 % of children in the iASD group fell into the category of probable and definite differences from what is seen in typically developing children on the SSP overall score; both groups were one or two standard deviations below SSP norms (total scores ranging from 38 to 154); (Dunn 1999). Using NVDQ, gender and age as covariates, results from the MANCOVA indicated significant differences between children with PMS and children with iASD on the SSP [F (7,74) = 3.83, $p = .001$]. Tests of between-subjects effects showed that children with PMS had higher scores, and therefore fewer sensory reactivity symptoms, as compared to the iASD group on taste/smell sensitivity [F (1) = 12.01, $p = .001$], visual/auditory sensitivity [F (1) = 3.79, $p = .05$], and auditory filtering [F (1) = 7.00, $p = .01$]. Children with PMS also showed marginally less tactile sensitivity [F (1) = 2.92, $p = .09$], in comparison to children with iASD (see Fig. 1; Table 3). In contrast, children with PMS showed significantly lower scores, meaning a greater number of low-energy/weak symptoms, as compared to children with iASD [F (1) = 5.70, $p = .01$] (Fig. 1). Children with PMS and iASD did not differ in movement sensitivity [F (1) = .01, $p = .99$] or under-responsivity [F (1) = .94, $p = .33$].

## Discussion

The present study examined, for the first time, the extent to which children with PMS differ in sensory reactivity as compared to children with iASD. Since sensory reactivity has an impact on everyday life and is associated with higher rates of internalizing symptoms (Kinnealey and Fuiek 1999; Kinnealey et al. 2011), it is important to define the sensory phenotype of children with PMS. In our current study, 80 % of children with PMS and 81 % of children with iASD had sensory reactivity abnormalities as evidenced by overall scores on the SSP. Both groups had significant difficulties processing most sensory stimuli in the environment. However, children with PMS showed fewer symptoms on taste/smell sensitivity, visual/auditory sensitivity and auditory filtering. The PMS group fell into the probable difference range for taste/smell sensitivity and auditory filtering on the SSP whereas the iASD group fell into the definite difference range. Regarding visual/auditory sensitivity, the PMS group actually fell into the typical performance range, whereas the iASD group fell into the probable difference range. Children with PMS showed significantly *less* sensory sensitivity (e.g. being less defensive towards and less overwhelmed by sensory stimuli) as compared to children with iASD. Auditory filtering, a child's ability to screen out sounds in the environment, was also less affected in children with PMS compared to iASD. Children with PMS and iASD did not differ in movement sensitivity or underresponsivity; both groups fell into the definite difference range for underresponsivity and in the probable difference range on the movement sensitivity scale of the SSP. On the other hand, children with PMS showed a greater number of weak/low-energy symptoms compared to children with iASD. The PMS group fell into the definite difference range for low energy/weak whereas the iASD group only fell into the probable difference range. The

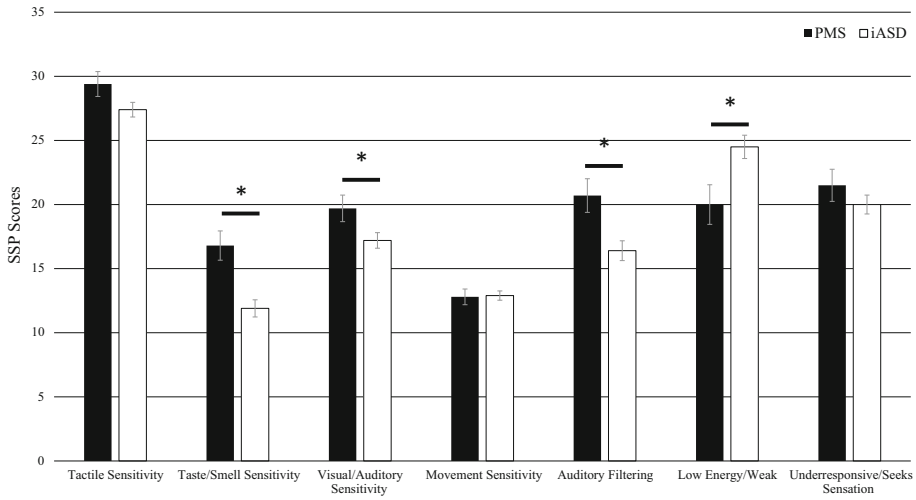


**Fig. 1** *Bars* represent mean scores on the short sensory profile (SSP) subscales in children with Phelan–McDermid syndrome (PMS) as compared to children with idiopathic autism spectrum disorder (iASD). Standard errors are shown as *error bars*. Children with PMS showed significant differences from children with iASD on most SSP subscales; group differences are highlighted by $*p < .05$

**Table 3** Mean scores on the short sensory profile (SSP) subscales and overall total score in children with Phelan–McDermid syndrome (PMS) as compared to idiopathic autism spectrum disorder (iASD)

| Short sensory profile domain | PMS | iASD | *p* value |
|---|---|---|---|
| Tactile sensitivity (M, SD) | 29.4 (5.9) | 27.4 (3.7) | .09 |
| Taste/smell sensitivity (M, SD) | 16.8 (5.6) | 11.9 (5.3) | .001* |
| Visual/auditory sensitivity (M, SD) | 19.7 (2.9) | 17.2 (5.1) | .05* |
| Movement sensitivity (M, SD) | 12.8 (2.7) | 12.9 (2.7) | .99 |
| Auditory filtering (M, SD) | 20.7 (6.2) | 16.4 (5.9) | .01* |
| Low energy/weak (M, SD) | 20.0 (8.8) | 24.5 (6.3) | .01* |
| Underresponsive/seeks sensation (M, SD) | 21.5 (6.7) | 20.0 (5.5) | .33 |
| Total score (M, SD) | 140.9 (5.0) | 130.3 (5.75) | .02* |

Standard deviations are shown in brackets. A MANCOVA with NVDQ sex and age as covariates showed that children with PMS showed significant differences from children with iASD on most SSP subscales; differences are highlighted as * $p < .05$

weak/low energy domain captures the child's ability to use muscles in order to move in daily life (Dunn 1999). Children with PMS showed significantly more difficulties in this weak/low energy domain and indeed, the majority of patients with PMS exhibit hypotonia. Since children with PMS were compared to children with idiopathic ASD and low intellectual functioning, these data suggest that the differences may arise as a function of the genetic condition and underlying biology of PMS.

Results may also be considered in the context of disease pathophysiology and neurotransmitters known to play a key role in *SHANK3*. PMS is caused by a deficiency of the *SHANK3* gene, which plays a critical role in scaffolding postsynaptic glutamate receptors, resulting in impaired glutamatergic regulation. Mice with *SHANK3* deletions have reduced number of GluR1-immunoreactive puncta and reduced glutamatergic transmission (Bozdagi et al. 2010). Our findings may reflect a potential relationship between glutamatergic functioning and sensory reactivity, especially for low energy/weak symptoms. However, low energy/weak symptoms could also result from peripheral nervous system dysfunction and other medical comorbidities associated with PMS. Future studies should examine whether there is a relationship between these sensory reactivity findings and the glutamatergic dysfunction associated with PMS. Previous studies have already identified associations between sensory reactivity and GABAergic processing using mouse models and magnetic resonance spectroscopy (DeLorey et al. 2011; Puts et al. 2011; Tavassoli et al. 2014). Using the excitatory/inhibitory imbalance theory as a framework (Rubenstein and Merzenich 2003), our method of comparing monogenic and idiopathic forms of ASD provides a novel way to address questions about the underlying biology of sensory reactivity in addition to defining the specific sensory phenotype of children with PMS. More work is needed in this area, however, and investigating the potential role of glutamatergic processing in sensory reactivity is relevant to the excitatory/glutamatergic and inhibitory/GABAergic imbalance theory of ASD (Rubenstein and Merzenich 2003). It is also likely that other genetic mutations, in addition to *SHANK3,* contribute to the severity of the PMS

phenotype and further emphasize the need for more studies examining the genetics of sensory phenotypes.

One limitation of the study is the relatively small sample size. However, PMS remains a rare disorder. In addition, groups were not matched on IQ or sex ratio, but both groups had low intellectual functioning evidenced by NVDQ $< 70$, and sex ratio was representative of each population. Future studies should include groups as closely matched as possible, but in this study, NVDQ, age, and sex were taken as covariates in the data analysis. Another limitation is that the SSP relies entirely on parent report, although it is a widely accepted and commonly used measure of sensory reactivity in children with ASD and/or ID. This is the first step in defining a sensory phenotype in PMS. Given that children with PMS fell into the category of definite and probable sensory differences, future studies are needed to replicate these findings using larger sample sizes matched on IQ and incorporating more objective, clinician-administered sensory measures in addition to parent reports.

Understanding the biology of a single-gene form of ASD may help identify mechanisms of sensory reactivity subtypes. The phenotypic differences found between PMS and iASD with regard to sensory sensitivity also highlight the importance of identifying genetically defined subgroups when developing assessment tools and clinical trial outcome measures for individuals with ASD.

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**Compliance with Ethical Standards**

**Conflict of interest** The authors declare no competing financial interests.

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