**Title:** Examining the relationship between sensory reactivity symptoms and repetitive behavior in Phelan-McDermid syndrome

**Authors:** Francesca Garces1,2, Tess Levy1,2, Hailey A. Silver1,2, Jessica Zweifach1,2, Kate Friedman1,2, Serena Cai1,2, Joseph D. Buxbaum1,2,3,4,5, Alexander Kolevzon1,2,3, Elizabeth Berry-Kravis6, Jon Bernstein7, Siddharth Srivastava8, Mustafa Sahin8, Latha Soorya9, Audrey Thurm10, Paige M. Siper1,2,3, the Developmental Synaptopathies Consortium

**Introduction**: Phelan-McDermid syndrome (PMS) is a genetic disorder commonly associated with autism spectrum disorder (ASD) (Tavassoli et al., 2021). Sensory reactivity, including hyperreactivity, hyporeactivity, and seeking, is a core symptom of autism spectrum disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013). Previous literature describes a theoretical relationship between sensory symptoms and repetitive behaviors with the notion that motor stereotypies, and self-injury may provide sensory stimulation (Boyd et al., 2010). In PMS, high levels of visual, tactile, and auditory hyporeactivity and high tactile seeking behaviors (e.g., mouthing of objects) have been reported (Tavassoli et al., 2021). Increased repetitive motor movements, lower impulsive behaviors, and insistence on sameness have also been reported in PMS related to other neurodevelopmental disorders (Srivastava et al., 2021). This study examines the relationship between sensory symptoms and repetitive behavior in children with PMS.

**Method**: The Sensory Assessment for Neurodevelopmental Disorders (SAND) (Siper et al.,2017) and the Repetitive Behaviors Scale-Revised (RBS-R) (Bodfish et al., 1999) were completed for 52 participants (Mage=9.16 ± 6.35 years) with PMS who visited the Seaver Autism Center at Mount Sinai between 2017 and 2024. The SAND is a clinician-administered observation and corresponding caregiver interview that quantifies sensory Hyperreactivity, Hyporeactivity, and Seeking across Visual, Tactile and Auditory modalities. Higher SAND scores indicate a greater number of sensory symptoms. The RBS-R is a caregiver questionnaire that produces scores in the following domains: Stereotyped Behavior, Self-Injurious Behavior, Compulsive Behavior, Ritualistic Behavior, Sameness Behavior, and Restricted Behavior. Higher scores on the RBS-R indicate more severe behaviors. Simple regression analyses were run in RStudio. The Stereotyped Behavior domain of the RSB-R contains a question about sensory symptoms, and the regressions between SAND domains with the stereotyped behavior domain were re-run with the sensory item of the RSB-R removed to ensure it did not impact the results. To control for mental age, multiple regression analyses were also calculated with mental age as a covariate. Mental age was calculated from a developmentally appropriate cognitive test, including the Mullen Scales of Early Learning (n=44), the Stanford Binet, 5th Edition (n=7), and the Differential Ability Scales-II (n=2).

**Results:** Mean and standard deviations for SAND and RSB-R domains were as follows: SAND: Hyperreactivity (3.90±4.02), Hyporeactivity (16.35±6.87), Seeking (11.48±6.76), Total (31.73±11.55); RBS-R: Stereotyped Behavior (3.44±3.18), Self-injurious Behavior (2.36±2.79), Compulsive Behavior (2.21±2.67), Ritualistic Behavior (1.73±2.29), Sameness Behavior (3.98±3.67), and Restricted Behavior (2.33±2.34). Thirty-eight percent of participants obtained a Hyperreactivity domain score above the clinical threshold, 96% of participants obtained a Hyporeactivity score over the clinical threshold, and 81% of participants obtained a seeking score over the clinical threshold. Total scores on the SAND were significantly positively associated with the RBS-R Stereotyped Behavior domain (df= (1,50), t=.48, p=.0055). SAND Hyporeactivity was negatively associated with the Ritualistic Behavior domain (df= (1,50), t=-3.3, p=.002). No significant relationships between sensory Hyperreactivity and any RSB-R domains were observed. SAND Seeking was positively associated with the Stereotyped Behavior domain (df= (1,50), t=3.17, p=.0026), and the Restricted Interests domain (df= (1.50), t=3.0, p=.0038). When controlling for mental age, SAND Total Score remained significantly associated with RBS-R Stereotyped Behavior (df = (2,49), t=2.76, p=.0081) and SAND Seeking remained significantly associated with both Stereotyped Behavior (df= (2,49), t=2.95, p=0.0048) and Restricted Interests (df= (2,49), t=3.0, p=0.0041). No significant relationships were identified between sensory Hyperreactivity, Hyporeactivity and any RBS-R domains when mental age was included as a covariate. All findings remained significant when corrected for multiple comparisons using the Benjamini-Hochberg adjustment (p<.05 for all) and when the sensory item was removed from the RBS-R stereotyped behavior domain (p<.01).

**Discussion:** Findings reveal a relationship between stereotyped behavior (e.g., hand and finger mannerisms, body rocking) and restricted behavior with sensory seeking, suggesting motor stereotypies may indeed fulfill sensory cravings. To ensure the sensory item from the RBS-R Stereotyped Behavior domain was not driving this result, analyses were run with this single item removed, and results remained consistent, implying stereotyped behaviors are likely a distinct but related construct to sensory reactivity.In contrast, when mental age was controlled for, the relationship betweenhyporeactivity symptoms and ritualistic behaviors (i.e., insistence on performing activities of daily living or communicating in a routinized way) was not maintained and was likely driven by developmental level. Finally, the lack of findings in the hyperreactivity domain may be due to very low scores in this area. Larger samples are needed to further elucidate the relationship between sensory symptoms and repetitive behaviors in both PMS and autism more broadly. Understanding this relationship can inform intervention plans to optimally address each child’s unique sensory and behavioral needs.

**References:**

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Bodfish, J. W., Symons, F. J., Parker, D. E., & Lewis, M. H. (2000). *Repetitive Behavior Scale–Revised (RBS-R)*

Boyd BA, Baranek GT, Sideris J, Poe MD, Watson LR, Patten E, Miller H. Sensory features and repetitive behaviors in children with autism and developmental delays. Autism Res. 2010 Apr;3(2):78-87. doi: 10.1002/aur.124. PMID: 20437603; PMCID: PMC3071028.

Siper PM, Kolevzon A, Wang AT, Buxbaum JD, Tavassoli T. A clinician-administered observation and corresponding caregiver interview capturing DSM-5 sensory reactivity symptoms in children with ASD. Autism Res. 2017 Jun;10(6):1133-1140. doi: 10.1002/aur.1750. Epub 2017 Mar 11. PMID: 28296264; PMCID: PMC8524392.

Srivastava, S., Condy, E., Carmody, E. *et al.* Parent-reported measure of repetitive behavior in Phelan-McDermid syndrome. *J Neurodevelop Disord* **13**, 53 (2021). https://doi.org/10.1186/s11689-021-09398-7

Tavassoli T, Layton C, Levy T, Rowe M, George-Jones J, Zweifach J, Lurie S, Buxbaum JD, Kolevzon A, Siper PM. Sensory Reactivity Phenotype in Phelan-McDermid Syndrome Is Distinct from Idiopathic ASD. Genes (Basel). 2021 Jun 26;12(7):977. doi: 10.3390/genes12070977. PMID: 34206779; PMCID: PMC8306746.

1Seaver Autism Center for Research and Treatment, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

2Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

3The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

4Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

5Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

6Department of Pediatrics, Neurological Sciences, Biochemistry, Rush University Medical Center, Chicago, Illinois 60612, USA

7Department of Pediatrics, Stanford University, Stanford, CA, 94304, USA

8Zander Translational Neuroscience Center, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA

9Department of Psychiatry, Rush University Medical Center, Chicago, Illinois 60612, USA

10Neurodevelopmental and Behavioral Phenotyping Service, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland 20814, USA