**Title**: Early childhood sensory hyperresponsivity and brain structure predicts later emergence of specific phobia in autistic youth with and without intellectual disability.

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**Introduction**: Autistic individuals often experience clinically significant anxiety (Kerns & Kendall, 2012; South & Rodgers, 2017). Specific phobia is among the most predominant anxieties in autistic youth, especially autistic youth with intellectual disability (ID) (Kerns et al., 2021). Theoretical models of specific phobia suggest that the heightened sensory responsivity often experienced by autistic individuals leads to maladaptive learning and ultimately extreme fear of something that poses no true danger (Green & Ben-Sasson, 2010). While many brain structures contribute to heightened sensory responsivity and sensory-based learning in autism, the striatum may be particularly important for the development of specific phobia given its role in integrating sensory information with cognitive and affective information to drive learning (Parkinson et al., 2009). This study sought to 1) determine if early differences in sensory hyperresponsivity and striatal structure can predict the emergence of later childhood specific phobia and 2) determine if these associations are similar or different in autistic youth with ID.

**Method**: Early childhood sensory hyperresponsivity and striatal volume (2.0 - 4.5 years) as well as middle childhood specific phobia and intellectual ability (9.1 - 13.7 years) were collected from 67 autistic individuals (15 female). Sensory hyperresponsivity was assessed with the Short Sensory Profile (McIntosh et al., 1999). Striatal volume was parcellated into substructures associated with different aspects of sensory (putamen), cognitive (caudate nucleus), and affective (nucleus accumbens) processing using a multi-atlas approach (Mori et al., 2016). Clinical specific phobia was assessed using the ADIS-ASA (Kerns et al., 2017) and intellectual ability was assessed using the Differential Ability Scales-II. ID was operationally defined as IQ<70. Logistic regression determined if early childhood striatal volumes differently predicted later childhood specific phobia in autistic individuals with and without ID. Similar analyses tested these relationships within structures commonly affiliated with anxiety (amygdala) and in autistic children with other forms of anxiety.

**Results**: 61% of autistic participants had specific phobia and 28% had ID. 57% of the participants with ID had specific phobia. Across all autistic participants, more sensory hyperresponsivity during early childhood (2-4 years) predicted a greater likelihood of specific phobia during later childhood (9-13 years) (b= -0.24, *p*=.03). Additionally, across autistic children with and without ID, the likelihood of later childhood specific phobia was associated with larger early childhood volumes of the putamen, a striatal structure associated with sensory processing (Left: b=0.008, *p*=.04, Right: b=0.002, *p*=.03), even after controlling for differences in early sensory hyperresponsivity. Significant ID status-by-volume interaction effects predicted later childhood specific phobia for the bilateral caudate nucleus (Left: b=-0.005, *p*=.04, Right: b=-0.007, *p*=.02) and right nucleus accumbens (b=-0.02, *p*=.04), striatal structures associated with cognitive and affective processing, respectively. Specifically, for autistic individuals with ID, larger early childhood striatal volumes were predictive of later specific phobia but for autistic individuals without ID, there were no significant associations. No significant relationships between early differences in sensory hyperresponsivity nor brain structure and later anxiety were observed across autistic individuals with all other forms of anxiety (i.e., across generalized, separation, social, autism-specific) or in the amygdala, a brain structure commonly associated with anxiety.

**Discussion:** Results suggest that while behavioral predictors of specific phobia are similar across autistic youth, unique brain mechanisms related to different aspects of sensory integration and learning may drive these associations in autistic children with and without ID. Early differences in both sensory behavior and sensory-associated striatal structures were similarly related to specific phobia across autistic individuals; however early differences in striatal structures associated with cognitive and emotional integration additionally contributed to specific phobia in autistic individuals with ID. These structural brain predictors of specific phobia were not present in the amygdala or across other forms of anxiety, further supporting theoretical models of altered sensory integration as a key driver of specific phobia in autistic youth. These distinct associations suggest that early patterns of striatal differences may eventually be viable markers of adolescent specific phobia in subgroups of autistic youth.

**References:**

Green, S. A., & Ben-Sasson, A. (2010). Anxiety Disorders and Sensory Over-Responsivity in Children with Autism Spectrum Disorders: Is There a Causal Relationship? *Journal of Autism and Developmental Disorders*, *40*(12), 1495–1504. https://doi.org/10.1007/s10803-010-1007-x

Kerns, C. M., & Kendall, P. C. (2012). The presentation and classification of anxiety in autism spectrum disorder. *Clinical Psychology: Science and Practice*, *19*(4), 323–347. https://doi.org/10.1111/cpsp.12009

Kerns, C. M., Renno, P., Kendall, P. C., Wood, J. J., & Storch, E. A. (2017). Anxiety Disorders Interview Schedule–Autism Addendum: Reliability and Validity in Children With Autism Spectrum Disorder. *Journal of Clinical Child & Adolescent Psychology*, *46*(1), 88–100. https://doi.org/10.1080/15374416.2016.1233501

Kerns, C. M., Winder-Patel, B., Iosif, A. M., Nordahl, C. W., Heath, B., Solomon, M., & Amaral, D. G. (2021). Clinically Significant Anxiety in Children with Autism Spectrum Disorder and Varied Intellectual Functioning. *Journal of Clinical Child & Adolescent Psychology*, *50*(6), 780–795. https://doi.org/10.1080/15374416.2019.1703712

Mori, S., Wu, D., Ceritoglu, C., Li, Y., Kolasny, A., Vaillant, M. A., Faria, A. V., Oishi, K., & Miller, M. I. (2016). MRICloud: Delivering High-Throughput MRI Neuroinformatics as Cloud-Based Software as a Service. *Computing in Science & Engineering*, *18*(5), 21–35. https://doi.org/10.1109/MCSE.2016.93

South, M., & Rodgers, J. (2017). Sensory, Emotional and Cognitive Contributions to Anxiety in Autism Spectrum Disorders. *Frontiers in Human Neuroscience*, *11*. https://doi.org/10.3389/fnhum.2017.00020

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