Overreactive Brain Responses to Sensory Stimuli in Youth With Autism Spectrum Disorders

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Objectives: Sensory over-responsivity (SOR), defined as a negative response to or avoidance of sensory stimuli, is both highly prevalent and extremely impairing in youth with autism spectrum disorders (ASD), yet little is known about the neurological bases of SOR. This study aimed to examine the functional neural correlates of SOR by comparing brain responses to sensory stimuli in youth with and without ASD. **Method:** A total of 25 high-functioning youth with ASD and 25 age- and IQ-equivalent typically developing (TD) youth were presented with mildly aversive auditory and visual stimuli during a functional magnetic resonance imaging (fMRI) scan. Parents provided ratings of children's SOR and anxiety symptom severity. **Results:** Compared to TD participants, ASD participants displayed greater activation in primary sensory cortical areas as well as amygdala, hippocampus, and orbital-frontal cortex. In both groups, the level of activity in these areas was positively correlated with level of SOR severity as rated by parents, over and above behavioral ratings of anxiety. **Conclusions:** This study demonstrates that youth with ASD show neural hyper-responsivity to sensory stimuli, and that behavioral symptoms of SOR may be related to both heightened responsivity in primary sensory regions as well as areas related to emotion processing and regulation. J. Am. Acad. Child Adolesc. Psychiatry, 2013;52(11):1158–1172. **Key Words:** amygdala, anxiety, autism spectrum disorders, functional magnetic resonance imaging (fMRI), sensory over-responsivity

Children with autism spectrum disorders (ASD) often display impairments in responding to sensory stimuli, in addition to the core symptoms of ASD, which include impairments in language and reciprocal social behavior. Sensory over-responsivity (SOR) is characterized by an extreme negative response to, or avoidance of, sensory stimuli such as noisy or visually stimulating environments, sudden loud noises, seams in clothing, or being touched unexpectedly.[1] About 56% to 70% of children with ASD meet criteria for SOR[2,3] compared to 10% to 17% of typically developing (TD) children.[3,4] SOR is associated with increased functional impairment in children with ASD, including lower levels of social and adaptive skills,[1,5] negative emotionality,[6] and anxiety.[5,6]

Despite the prevalence of and considerable impairment caused by SOR in children with ASD, there is a paucity of research on the neurobiological bases of SOR. Research in this area is critical to help explain heterogeneity within ASD, and can inform intervention targeted at specific subgroups of children with ASD. In one of the few functional MRI (fMRI) studies of response to nonsocial sensory stimuli in children with ASD, Gomot *et al.*[7] found that early adolescents with ASD responded faster to novel sounds than did TD controls, and had higher activation in prefrontal and inferior parietal regions but no differences in activation of auditory cortex. The authors theorized that novel auditory stimuli are initially processed normally but receive differential attention from the novelty detection circuit. Similarly, Hadjikani *et al.*[8] presented expanding circles of color to adults with and without ASD, and found no between-group differences in visual cortex retinotopic maps. However, some electroencephalography (EEG) studies have found group differences in event-related potentials (ERPs) in response to tones, which may suggest an atypical response to sound in the primary auditory cortex.[9]

The thalamus, which is considered the "gateway" that relays sensory information entering the brain to the cortex, could also be involved in SOR. For example, deficient thalamic gating could overload the sensory cortices; alternatively, thalamic dysfunction might result in a failure to integrate the sensory information appropriately. In support of this hypothesis, abnormally decreased metabolite (glutamate and glutamine) levels were found in the thalamus of individuals with ASD,[10] and these abnormalities related to sensory sensitivity. Although the thalamus has also been found to be smaller in high-functioning individuals with ASD compared to TD controls,[11] functional connectivity between the thalamus and cortex has been shown to be greater in ASD.[12] Mizuno *et al.* further suggest that thalamic hyperactivity during brain development may drive functional specialization in the cortex and could lead to cortical abnormalities such as reduced pruning and thalamo-cortical overconnectivity, which may ultimately place individuals at risk for SOR.

Other hypotheses on the neural basis of SOR posit heightened limbic responses to sensory stimuli, including in the amygdala and hippocampus.[13–15] A number of correlational studies have shown that children with ASD and SOR also have high rates of anxiety symptoms.[6,13,16] Because SOR co-occurs frequently with anxiety symptoms, theories related to abnormal amygdala and hippocampus functioning are particularly relevant, given the role of these structures in anxiety. Functional magnetic resonance imaging (fMRI) studies have consistently highlighted the amygdala's central role in detection and response to threat and fear conditioning.[17–20] Similarly, the hippocampus is thought to be associated with anxiety through its role in context conditioning, memory of threat-related events, and orienting to situations that could be threatening.[21,22] As discussed in a review of fMRI studies on the amygdala by Zald,[19] the magnitude of amygdala activation in response to sensory input from the thalamus is found to correlate with the extent to which a stimulus is perceived as threatening or unpleasant. The amygdala can then trigger a response to these stimuli upon future exposure, including an enhanced sensory response that correlates with amygdala activation.

Limbic system abnormalities may increase the risk of SOR in children with ASD by decreasing the ability to regulate in response to sensory input. There is evidence for functional amygdala abnormalities in ASD, although the evidence is mixed in terms of the direction of effect: early studies showed decreased amygdala activity in ASD[23]; however, Pierce *et al.*[24] found no group differences in amygdala response to faces when stimuli were salient (e.g., family members). Furthermore, more recent studies have found that individuals with ASD show amygdala hyperactivity compared to TD controls during a face processing task,[25–27] and that the extent of activation was correlated with the amount of time ASD participants spent gazing at the eyes.[25,26] Therefore, there is some evidence for abnormal amygdala function and possibly hyperactivity, but this has not been studied in the context of sensory sensitivity.

Few physiological or biological studies of sensory abnormalities in ASD have taken into account within-group heterogeneity in sensory symptoms, which may lead to null findings. For example, physiological studies examining a general hyperarousal in individuals with ASD have yielded few consistent findings,[28] but the majority of these studies used a small sample size and did not examine subgroups. Evidence from behavioral studies[1,6] suggests the presence of SOR only in some children with ASD, whereas other children with ASD are actually underresponsive to sensory stimuli. Consistent with this, a recent study of electrodermal activity in children with ASD found 2 subgroups: 1 with high arousal and slow habituation, and 1 with low arousal and fast habituation.[29] Furthermore, higher baseline arousal in children with ASD is related to greater physiological response to sensory stimuli and higher anxiety levels.[30] Similarly, the evidence for structural abnormalities in the amygdala and hippocampus in autism is mixed, with some studies finding smaller volumes[31] and others finding larger volumes[32,33] than in TD individuals. This inconsistency could again be due to the heterogeneity of the ASD phenotype, and indeed amygdala volume in children with ASD has been found to be positively correlated with anxiety.[34] Therefore, it is important to account for within-group sensory characteristics when examining the neural bases of SOR; however, as of yet there are no functional neuroimaging studies of response to sensory information in children who have both ASD and SOR.

It should be noted that, although physiological hyperarousal appears to be characteristic of both