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SENSORY MODULATION (C LAI, SECTION EDITOR)

Possible Neural Mechanisms Underlying Sensory Over-Responsivity in Individuals with ASD

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Abstract

Purpose of Review Sensory over-responsivity (SOR) is an excessively unpleasant response to or avoidance of sensory stimuli, e.g., sound and light, which is prevalent among individuals with autism spectrum disorder (ASD). Despite its negative impacts on personal and social lives, knowledge about the occurrence of and mechanisms underlying SOR is inadequate. This review of studies on SOR in ASD summarizes the evidence on the close relationship of SOR with prenatal and genetic factors and presents information on neural mechanisms underlying SOR.

Recent Findings Emerging studies have reported that SOR symptoms are related to abnormal structural connectivity in the brain, particularly decreased inter-hemispheric connectivity in subcortical regions (the thalamus and basal ganglia) and increased intra-hemispheric connectivity in the basal ganglia, especially in the right cerebral hemisphere, and with an enlarged amygdala. In the resting state, functional connectivity between the pulvinar and primary sensory regions, the basal ganglia, the limbic system (the amygdala and hippocampus), the temporal cortex, the prefrontal cortex, and sensorimotor regions is enhanced, while structural and functional connectivity between the thalamus and cortex is diminished.

Summary These findings indicate that the functional abnormalities associated with SOR are probably due to reduced top-down regulation, which inhibits the reorientation of attention from external stimuli, thereby causing difficulty in filtering out and/or integrating sensory information and then lowering inhibition in generating excessive responses to the incoming sensory stimuli.

Keywords Sensory over-responsivity · Autism spectrum disorder · Neural mechanism

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Background

Autism spectrum disorder (ASD) is a widespread neurodevelopmental disorder marked by stereotyped and repetitive patterns of behavior and impairments in social communication and interaction [1]. Sensory abnormalities have been reported in as high as 90–95% of individuals with ASD [2–4] and in approximately 16% of the general population [5] and only 8% of the subjects in a sample of 8-year-old children without ASD [6]. Despite the high prevalence of sensory abnormalities in ASD, their occurrence and underlying mechanisms are not yet fully understood. The extent of sensory abnormalities has been found to be associated with the severity of autistic traits, such as repetitive behavior [7, 8] and stereotyped behavior [8–11].

Sensory features of ASD have received growing attention over the past two decades from specialists in a wide range of fields [12, 13]. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, already acknowledges the abnormal preoccupation with sensory aspects of the environment manifested by individuals with ASD (DSM-IV). As per the DSM-V published in 2013 [1], sensory reactivity is now included among the diagnostic criteria for ASD. There are three types of sensory response patterns: sensory over-responsivity (SOR, or sensory hyper-reactivity), sensory under-responsivity (SUR, or sensory hypo-reactivity), and sensation seeking (unusual sensory interests) [14]. Unusual interest shown by individuals with ASD in sensory aspects of the environment is already acknowledged in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). In 2013, the DSM-V added sensory reactivity to the diagnostic criteria for ASD Sensory features can be classified into three sensory response patterns: sensory over-responsivity (SOR, refers to sensory hyper-reactivity), sensory under-responsivity (SUR, refers to sensory hypo-reactivity), and sensation seeking (unusual sensory interests) SUR refers to the lack of awareness of certain stimuli or slow response to sensory inputs such as sounds or spoken language [15, 16]. Conversely, SOR refers to the subjective experience of and hyper-reactivity to sensory overload that would typically not be regarded as troublesome to individuals without SOR [11, 16, 17]. In individuals with ASD, SOR has been reported to be more common than SUR, with prevalence ranging from 56 to 79% [18–20], and to affect almost all sensory modalities [2, 12, 21]. In fact, numerous individuals with ASD have more than one sensory response pattern.

Researchers have proposed theoretical frameworks such as the "weak central coherence" theory [22••], the "temporal binding deficit" hypothesis [23••], and the "excitatory/inhibitory imbalance" model [24••] to account for the SOR phenomenon. A common theme across these frameworks is that SOR is related to abnormal development of neuroanatomical structures crucial for processing visual, auditory, or tactile information [25, 26]. SOR is a form of sensory modulation disorder that falls within the sensory processing disorder umbrella[14]. SOR is a low-neurological-threshold-passive self-regulation method used in response to sensory stimuli, according to Dunn's model of sensory processing [27•]. Because of their heightened sensitivity to their surroundings (caused by a lower-than-average neurological threshold), people with SOR often adopt a passive self-regulation strategy, choosing instead to remain in the current situation and respond to it as it unfolds. In some cases, they may aggravate responses to sensory input. Children with SOR to sounds may, for instance, cover their ears or request silence.

The specificity of and mechanisms underlying SOR in ASD are still under investigation. In this paper, we present a review of behavioral and clinical studies that have reported plausible neural mechanisms underlying SOR in individuals with ASD.

Prenatal and Genetic Influences on SOR

Studies have revealed that prenatal and genetic factors play a role in SOR-related symptoms. A study found that infants and toddlers who were small for gestational age manifested SOR-related behaviors more frequently than their typically developed counterparts [28]. Another study reported that subnormal neuroplasticity of premature babies [29] was associated with SOR. However, Keuler et al. (2011) did not find a wide spectrum of prenatal factors that significantly contributed to SOR symptoms in toddlers [30].

Changes in the internal environment during the prenatal period, such as intake of medication or alcohol, increase hormone production due to excessive stress [31, 32]. Increased secretion of testosterone in pregnant women [33] has been consistently shown to negatively affect neurodevelopmental outcomes in typically developed children without ASD. In children with ASD, mutations in genes encoding neuroligin-3 [34] and gamma-aminobutyric acid receptor subunit beta-3 [35] have been proven to be substantially linked to SOR-related symptoms, as these mutations disturbed the balance of gamma-aminobutyric acid (GABA) [36, 37] and glutamate [38, 39] in the brain. Imbalanced synthesis of GABA and glutamate, particularly the latter, results in excessive inhibitory or excitatory responses to sensory stimuli [24]. A recent magnetic resonance (MR) spectroscopy study reported close relationships between the GABA concentration in the cerebral cortex and visual perceptual functions of children with ASD. Compared with typically developed children, ASD children were found to have lower GABA

concentrations in the visual cortices, which were associated with a stronger sensitivity to visual stimuli [40]. The mechanisms underlying the possible influences of GABA and glutamate imbalance, changes in brain structures, and modulations in neural functions on SOR in ASD are discussed below.

Possible Neural Mechanisms Underlying SOR

(1) Sensory, emotion, and motor processing

Neurophysiological abnormalities may explain the problems encountered by children with SOR when exposed to sensory inputs [41]. To understand the neural mechanism underlying SOR in ASD, it is important to understand normal sensory to motor processing (the process from receiving sensory input to executing the motor and emotional response) in the brain. Wickens and Carswell (2012) suggested that sensorimotor processing includes three components: sensory, emotion, and motor processing (Fig. 1) [42••]. During sensory processing, sensory inputs first reach the short-term sensory store for temporary storage [43]. Selective attention allocates attentional resources to decode, discriminate, and organize the sensory input captured in sensory processing [44], and then to motor processing to select and generate an appropriate response to the sensory signal (Fig. 1) [45]. Emotion processing involves the awareness and appraisal of the experiences associated with incoming sensory information [46]. One study suggested that experiences arouse the emotion attached to related prior events stored in long-term memory [47]. In general, the generation of motor responses to the sensory input involves four steps: response selection [48, 49], response preparation [48, 50], response initiation [50], and response execution [49].

There are many neural substrates associated with sensory, emotion, and motor processing. Sensory inputs arrive in the sensory organs, such as eyes and ears, and are converted into electrical signals that are further propagated to the thalamus and sensory cortices via the midbrain for sensory processing (Fig. 2) [51]. The electrical signals also travel to the amygdala and anterior insula, which are parts of the salience network (SN) for emotion processing [52]. Both the anterior insula (AI) and dorsal anterior cingulate cortex (dACC) within the SN contribute to the emotional processing of sensory stimuli [53]. Depending on the purpose of processing, sensory inputs may or may not be consolidated into long-term memory, which is subserved by the hippocampus and amygdala [54]. In addition, the SN has been shown to be implicated in motor responses [55]. The prefrontal cortex plays a crucial role in subserving working memory for maintaining the sensory input for further processing [56]. The thalamus, pre-supplementary, supplementary and primary motor cortex, and cerebellum mediate the different stages of motor processing [57, 58]. Abnormalities in any of these brain regions, such as abnormal activation or connection, are likely to cause SOR.

(2) Neural abnormalities associated with SOR in ASD

SOR in ASD is related to increased activation in the thalamus and brain areas subserving primary sensory processing (e.g., auditory, visual, and somatosensory cortices) as well as salience detection and attention (e.g., the insula and amygdala) (Fig. 3) [59•, 60•]. In addition to attention

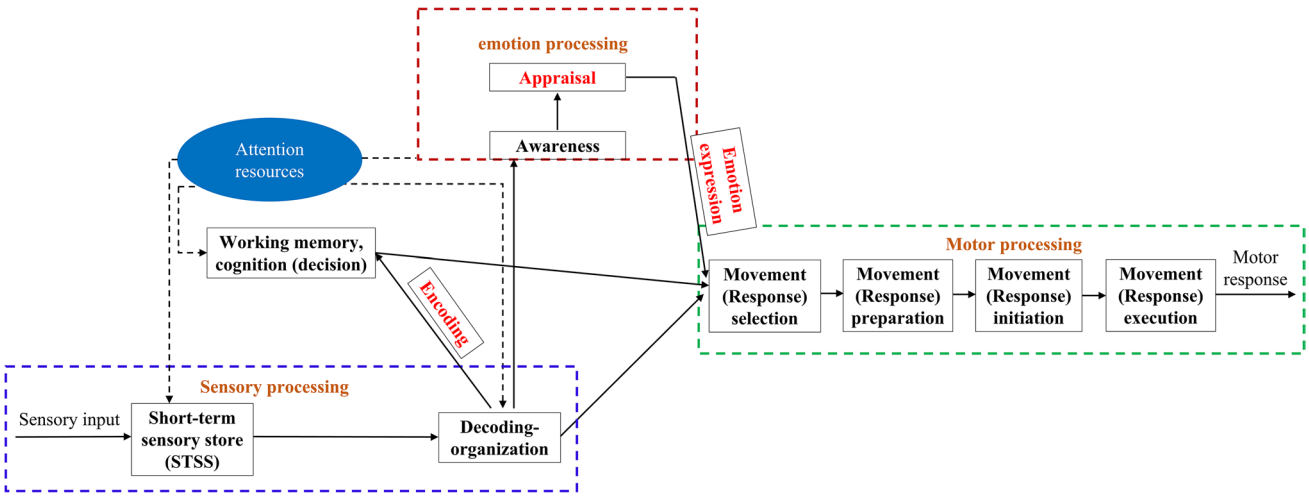

Fig. 1 Summary of sensory-motor processing which has sensory, emotion, and motor components from the detection of the sensory input to make a response

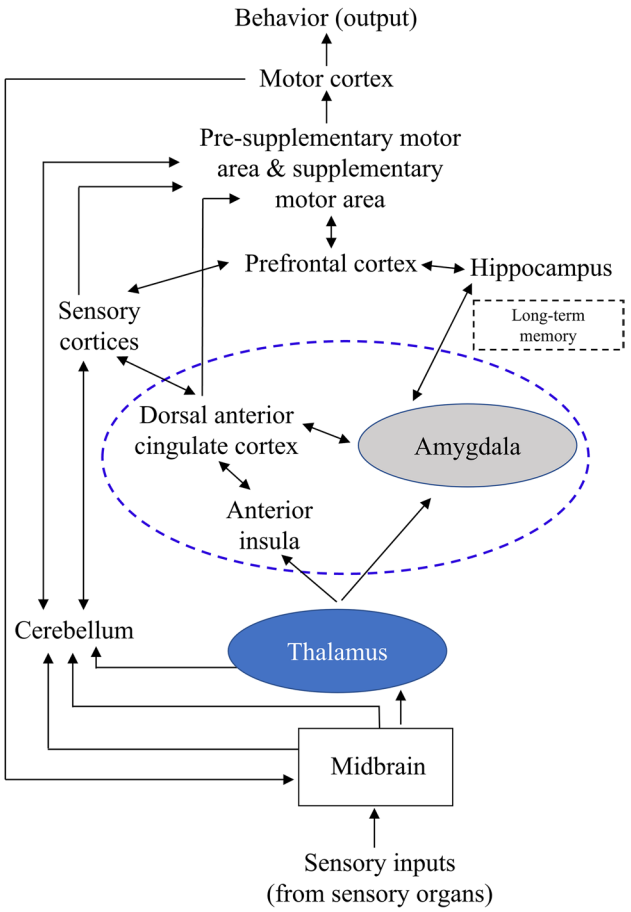

Fig. 2 Summary of neural substrates and their connectivity subserving sensory-motor processing. Neural substrates of the salience network are grouped within the blue dotted-line circle. The thalamus (shaded in blue) plays a prime role in sensory processing, while the amygdala (shaded in grey) plays a prime role in emotion processing and behavior selection

and sensory processing, three studies have found that the core facets of SOR in normal individuals are associated with deep sensory integration (e.g., in the prefrontal cortex, precuneus and inferior frontal gyrus), enhanced empathy and emotionality (e.g., involving the claustrum, anterior insula, amygdala, and cingulate cortex), and preparation for action (i.e., involving the premotor region as well as dorsolateral and medial prefrontal cortices) [61–63].

(3) Functional connectivity abnormalities — the thalamus and amygdala

The thalamus is a subcortical neural substrate functionally connected to the insula and somatosensory, motor, and premotor areas of the cortices [64]. It is essential for the transmission and integration of sensory information in the brain [65]. Children with sensory processing disorders, including SOR, have been found to have reduced structural connections between the cortex and thalamus, and decreased functional connections among the primary sensory regions and thalamus, compared with typically developed children [66, 67]. These findings are consistent with the aberrant intrinsic thalamus connection observed in ASD participants. [68]. In contrast, Cerliani et al. (2015), based on resting-state functional magnetic resonance imaging (fMRI), reported increased functional connections among primary sensory regions and the thalamus as well as basal ganglia. These differences in the results of the three studies may be due to the use of different sample populations (all individuals with sensory disorders vs. individuals with ASD) and/or the different age ranges of the participants. It is also possible that the brain itself can do its best to control and reinforce the functional connection when it needs to function, even though the fundamental structural connection is weakened.

Functional connectivity between the thalamus and sensorimotor regions is reduced in children and adolescents with ASD, while it is strengthened between the thalamus and the right temporal cortex [69]. During sensory processing (when exposed to slightly unpleasant tactile and auditory stimuli), adolescents with ASD and SOR showed reduced functional connection between the thalamus and cortex, according to a fMRI research [70•]. Reduced thalamocortical connectivity has been hypothesized to reflect impaired top-down regulation in ASDs with SOR [71], making it more challenging for those with the disorder to ignore irrelevant sensory data, integrate sensory data, and exercise selective inhibition and focus on relevant information [70•]. Individuals with ASD are more likely to feel overwhelmed by irrelevant stimuli or while receiving several stimuli simultaneously, which is consistent with sensory gating hypotheses showing abnormalities in sensory gating and selective attention of sensory stimuli [4].

Among the thalamic nuclei, the pulvinar appears to play a unique role in regulating and integrating sensory information [72, 73] and selective attention [74]. Individuals with ASD have been shown to have increased connection between the pulvinar and the temporal cortices, prefrontal cortex, and sensorimotor regions [75]. Compared with healthy controls, adolescent with ASD demonstrated increased activation in the pulvinar in response to slightly unpleasant tactile and auditory stimuli [59•, 60•]. In particular, individuals with ASD and SOR showed increased connectivity between the pulvinar and the putamen, hippocampus, and right amygdala [70•]. Another study found that individuals with ASD had larger right amygdala volumes than left amygdala volumes [76•]. The increased connection between the amygdala and pulvinar has been proposed to be responsible for the negative emotion associated

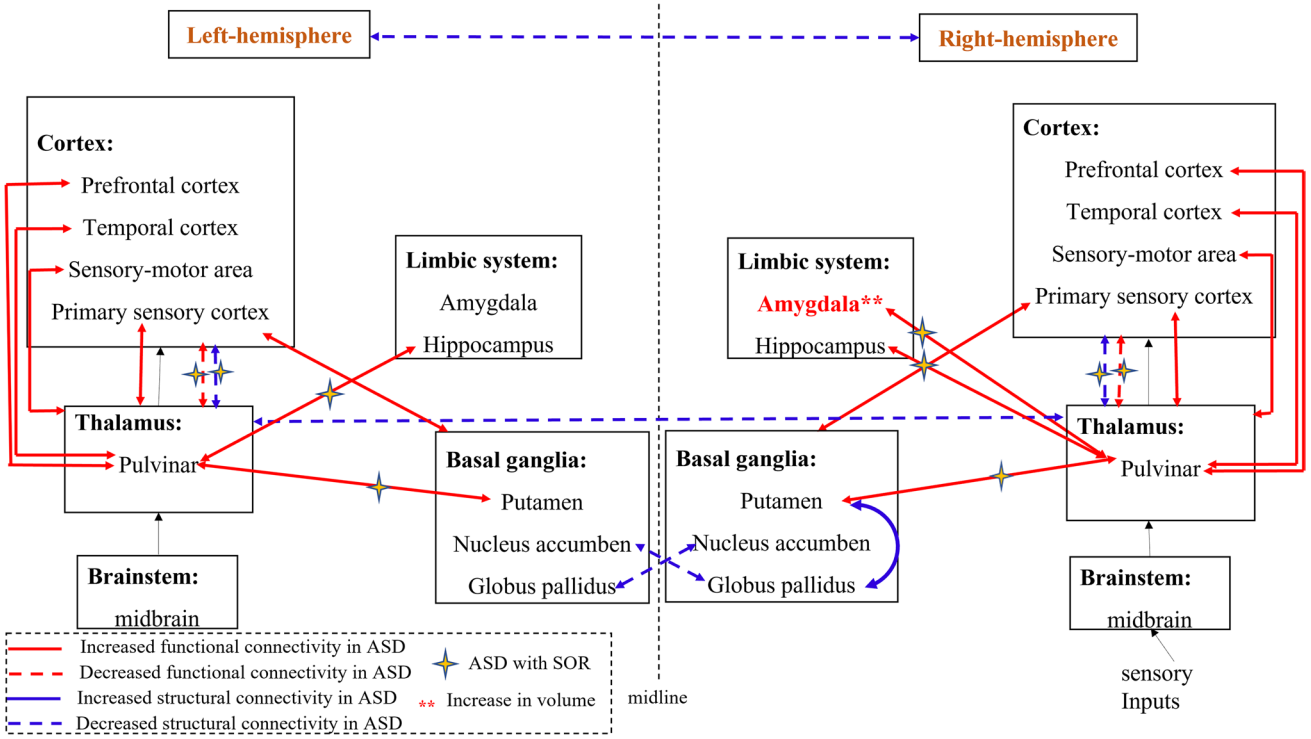

Fig. 3 Abnormal neural substrates and specific functional and structural networks related to sensory over-responsiveness in individuals with ASD

with SOR. Taken together, the increased thalamocortical and pulvinar–amygdala connectivity in ASD offers plausible explanations for why excessive attention to distracting sensory stimuli is likely to be associated with negative emotion when processing the stimuli.

(4) Structural connectivity abnormalities

Duan et al. (2020) and Cardon et al. (2017) reported that children with ASD showed reduced structural connectivity between the right and left hemispheres through the thalamus compared to typically developing children [76•, 77•]. Within the subcortical regions of individuals with ASD, Duan et al. (2020) found decreased connectivity between left nucleus accumbent and the right globus pallidus and between the right nucleus accumbent and left globus pallidus, whereas an increased structural covariance among the adjacent regions in the right globus pallidus. These abnormalities in connectivity may contribute to SOR symptoms, as these neural substrates play important roles in transmitting incoming information received from the sensory organs. For instance, the weakened connectivity between the two hemispheres suggests that sensory cortices do not communicate as well as required, leading to failure in integrating the sensory inputs for initiating adaptive responses. Reduced white matter integrity has been reported to lead to problems with the synchronization of action potential transmission, which is crucial for sensory processing and multisensory integration [67].

(5) Summary of possible neural mechanisms underlying SOR in ASD

Our review of studies on attention and emotion regulation in ASD revealed an association between attention, neural substrates, and SOR, providing a plausible explanation of SOR from the perspective of connectivity among neural substrates. The specific findings are listed below. First, in individuals with ASD and SOR, resting-state functional connections are enhanced between the thalamus, sensory cortex, and amygdala. Involvement of these neural substrates in ASD with SOR suggests that SOR is associated with increased attention and emotional response to sensory stimuli. Second, abnormalities in structural connectivity leading to weaker connections between the left and right hemispheres and stronger connections within the respective hemispheres (between the ipsilateral thalamus and amygdala) lead to excessive attention to emotion stimuli and lack of timely communication and cooperation between the hemispheres. This prevents adequate regulation and integration of sensory

information in the brain, leading to the output of excessive emotional responses and, consequently, more severe SOR symptoms in ASD. Thus, the possible neural mechanism underlying SOR in ASD can be summarized as follows: the abnormalities of functional and structural connectivity in the brain of individuals with ASD inhibits proper top-down regulation and integration of sensory inputs, leading to increased attention to extraneous sensory stimuli during sensory processing and, as a result, the output of excessive emotional response to these stimuli.

Conclusion

Our review revealed that SOR in ASD is associated with the following abnormalities in brain connectivity: (i) reduced inter-hemispheric structural covariance connection across subcortical areas and enhanced intra-hemispheric structural covariance connection, which is thought to cause symptoms of weak central coherence [77•]; (ii) increased structural covariance in the right cerebral hemisphere, which is associated with the theory of hemispheric functional lateralization [78]; and (iii) increased functional connection between the thalamus, sensory cortex, and amygdala and decreased functional connection between the thalamus and cortex, leading to reduced top-down regulation from the cortex to thalamus; this causes difficulty in filtering out and/or integrating sensory information and failure in selective inhibition and attention to external stimuli, causing lowered inhibition in generating excessive responses to the incoming sensory stimuli [70•]. The implications of these findings for the future of intervention research and development for children with ASD and SOR are substantial. Instead of working to restore normal sensory processing, effective interventions should instead train individuals to better manage their attention and emotional responses to outside stimuli [59•, 60•]. There are already effective interventions that teach coping strategies to individuals with ASD in order to decrease their anxiety [79, 80]. Due to the high prevalence of co-occurrence of anxiety and SOR in these individuals, it may be useful to adjust these therapies to focus on SOR [81]. More investigation into SOR's mechanistic underpinnings is needed to inform the development of more efficient therapies and treatment strategies for ASD.

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Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article contains no human or animal subjects studies conducted by any of the authors

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