CHAPTER SIX

Neurobiology of sensory processing in autism spectrum disorder

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Abstract

Altered sensory processing and perception has been one of the characteristics of autism spectrum disorder (ASD). In this chapter, we review the neural underpinnings of sensory abnormalities of ASD by examining the literature on clinical, behavioral and neurobiological evidence that underlies the main patterns of sensory integration function and dysfunction. Furthermore, neural differences in anatomy, function and connectivity of different regions underlying sensory processing are also discussed. We conclude that sensory integration intervention is built on the premise of neuroplasticity to improve function and behavior for individuals with ASD.

1. Introduction

Autism spectrum disorder (ASD) is defined clinically by impairment in communication, social interaction, and behavioral flexibility.[1] There is strong evidence to support that the "autistic brain" is functionally and

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structurally different from the brain of typically developing (TD) children. Moreover, there exists a wide range of phenotypic variations involving cognitive ability, the pace of language development and the co-morbidity of other diagnoses like epilepsy or attention deficit and hyperactivity disorders.[2]

ASD is a complex neurodevelopmental disorder characterized by heterogeneity of skills and functioning. A variety of models have been developed to describe the disorders which included the temporal binding hypothesis, the intense world theory and the sensory integration theory.[3] One of the most common features to individuals with ASD across the spectrum are the atypical behavioral responses to sensory stimuli. Literature showed that over 96% of children with ASD report hyper and hypo-sensitivities in multiple domains, including the vestibular, somatosensory, visual, auditory, olfactory and gustatory system.[4,5] Atypical sensory processing in ASD is postulated to be one of the cause core features of ASD and can interfere with development and affect the interaction with the environment.[6] However, the neurobiological underpinnings of sensory abnormalities in ASD have been less addressed in the literature. The sensory behavioral differences range from mild to severe and the functional impairment can endure throughout the adulthood.[4,7] Early abnormalities in sensory processing can be compounded over time, creating a maladaptive developmental trajectory of functional impairment.

Sensory integration theory was proposed by Dr. A. Jean Ayres who was an occupational therapist and neuropsychologist. She developed theory and intervention to help and treat children with learning and behavioral challenges.[8,9] In this theory, different sensory system laid an important foundation for adaptive behavior. It involves perceiving, organizing, and interpreting information received through sensory systems which included taste, touch, smell, sight, auditory, vestibular that support movement and development.[8,9] Ayres hypothesized that poor sensory stimulus registration and modulation impairments were commonly seen in individuals with ASD.[8]

This chapter reviews the abnormalities in each affected sensory system of ASD by integrating clinical, behavioral and neurobiological evidence to explore the sensory impairments in ASD. To begin with, we will examine the existing construct of sensory registration and sensory modulation in Ayres Sensory Integration (ASI) hypothesis in ASD. Then we will discuss the possible mechanisms by which atypical sensory processing across the core sensory systems including vestibular, proprioceptive, tactile, visual, auditory, olfactory and gustatory systems. While several primary sensory and

association cortex areas may be involved in sensory processing and integration of related information, we will briefly discuss different neural regions in midbrain and cerebral cortex and address their roles in processing sensory stimuli in individuals with ASD.

2. Atypical sensory processing in ASD

According to the American Psychiatric Association's Diagnostic Manual for Mental Disorders-Fifth Edition (DSM-5), hyper- and hypo-sensory reactivity have been included as diagnostic criteria of ASD.[2] These criteria, however, manifest differently across individuals with ASD. For examples, some individuals seem to be unaware of certain auditory, visual or tactile stimuli (classified as hypo-responsivity), while others may avoid the same stimuli altogether (classified as hyper-responsivity).[1] These modulation deficits can contribute to and/or overlap with the core characteristics of ASD and hinder their participation in everyday activities.

Ayres proposed that children with ASD not only fail to register sensory input properly but also has trouble modulating input that they register. Sensory registration is "the detection of sensory sensations within the central nervous system"[10] (p. 3). For example, children with ASD may not detect the presence of novel stimulus, e.g., the sensation of a puff of air on their necks, the way TD children do. Ayres hypothesized that registration problems are related to poor central nervous system (CNS) registration of sensory stimuli.

Impairments in emotion-related brain regions like limbic system not only has impact on registration, but also on sensory modulation.[8] Limbic system comprised several subcortical nuclei and cortical structures including the insula, hypothalamus, hippocampus, para-hippocampal gyrus, amygdala, fornix, mammillary body, septal nuclei and thalamus.[11,12] Structural abnormalities in the forebrain limbic system were postulated to dysfunction in sensory modulation, which could lead to emotional problems.[13] Studies show that adults with ASD have reduced amygdala and hippocampus volume as compared to typical individuals.[14] A few white matter studies have reported variation in tracts connecting emotion-related brain regions to motor, auditory and cognitive processes.[3,15]

Ayres defined modulation as the "brain's regulation of its own activity"[10] (p. 182). Based on her clinical observation, she suggested that hypo- or hyper-reactivity to vestibular and tactile sensations, may manifest gravitational insecurity (i.e., fear of movement) and tactile defensiveness

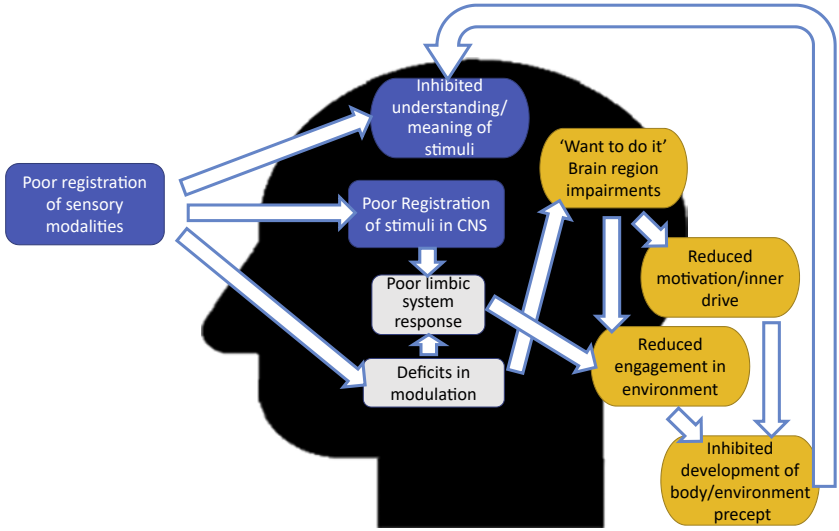

Fig. 1 A proposed figure of Ayres Sensory Integration hypothesis in autism spectrum disorder. *Adapted from Kilroy E, Aziz-Zadeh L, Cermak S. Ayres theories of autism and sensory integration revisited: what contemporary neuroscience has to say.* Brain Sci. *2019;9 (3):68. doi: 10.3390/brainsci9030068.*

(fight, fright or flight reaction to light touch that other children consider normal sensation). Ayres' postulation about abnormal modulation of sensory input in ASD would have implications for therapy. Multisensory experiences are embedded in our daily life and are crucial to our life participation. In TD children, multisensory inputs allow processing and interpretation of sensory events in the environment. However, individual with ASD of poor modulation show weaker evoked potentials to auditory and somatosensory stimuli and atypical auditory-somatosensory integration, which would overwhelm them and may hinder their functioning in their own environment.[11] Fig. 1 summarizes the proposed visualization of sensory integration hypothesis in ASD by Kilroy and her colleagues.[10]

3. Vestibular system

Vestibular system has a significant role on brain and behavior function.[8–10] Research shows that vestibular connection to many brain regions that serve as arousal regulation, static and dynamic postural control, balance and equilibrium responses, bilateral coordination, maintenance of stable visual field and spatial perception of body movement.[11,12]

One example is the rapid or rotary movement of the body through space is associated with increased alertness and autonomic responses that activate the arousal system via the brainstem reticular formation.[12] On the other hand, slow and rhythmic movement, such as gentle rocking, decreased arousal experienced as calming or drowsiness. Vestibular information travels via the vestibulospinal tracts activates neck and trunk muscle to uphold the postural and head control. Vestibular information also carried in the medial longitudinal fasciculus to the cranial nerves control the ocular motor muscles to support coordinated eye and head movements. Furthermore, since vestibular system is a bilateral system that affects muscle activation of left and right sides, it contributes to bilateral motor coordination. With the anatomical connection with vision and proprioception, the vestibular system contributes to anticipatory motor actions and sequences.[3,16] In fact, decreased vestibular response in post-rotary nystagmus test were postulated to deficits in bilateral integration, decreased extension against gravity, poor equilibrium reactions and decreased coordination of eye and head movement.[6]

It is still being controversial whether the vestibular system is affected in ASD. Studies have shown that functions related to the vestibular system, including maintaining balance[17] and responsivity to vestibular stimuli,[18] are found to be significantly different between ASD and TD individuals. While the vestibulo-ocular reflex (vof) of keeping fixation on an object is found in ASD individuals and the accuracy of the reflex is not significantly different from TD, the latency to start saccade was shown to be significantly increased in ASD.[19] Furthermore, the gain (angle of eye movement divided by angle of head movement) and ratio of eye velocity to head velocity of vof were also found to increase in ASD subjects.[20] The difference between ASD and TD subjects was attributed to delayed visual information processing or lack of cerebellar inhibitory input to the vestibular nuclei, rather than a dysfunctional vestibular system.[19] Though vestibular input is usually involved in the sensory-based therapy (e.g., sensory integration therapy) for children affected by ASD, the aim of the therapy is to organize the sensory system via different sensory modalities and not necessarily pinpointing a dysfunction in the vestibular system.[21] As also suggested by an early study, the abnormal responsivity toward vestibular stimuli in ASD may be due to the altered sensory processing, and the signs of hyper-responsivity and hypo-responsivity may not be homogenous in ASD individuals.[18]

Recently, neuroscientists have shown that temporo-parietal junction, anterior parietal lobe, posterior parietal and medial superior temporal cortices, cingulate gyrus and retrosplenial cortex, and hippocampal and

para-hippocampal cortices all receives vestibular information.[22] With the widespread projection to different neural regions, vestibular system may play an important role in learning and behavioral difficulties of children.

4. Somatosensory system

Somatosensory system is consisted of touch and proprioception. Touch is considered one of the most basic ways in which individuals interact with the world around them.[3] Proprioception is the sense in which we perceive the position and movement of our body.[23] Individuals with ASD were reported to have hypo- and hyper-reactivity to tactile stimuli, with these responses varying according to stimuli and context. Specifically, abnormal detection of tactile stimuli and a lack of habituation to tactile stimuli were reported by them. Literature showed that tactile sensations project to the primary sensory cortex and the secondary somatosensory cortex, a region responsible for object manipulation, tactile discrimination and grasp and release.[24] Structural differences were noted in several primary sensory cortical areas,[25] for instance, the planum temporale (PT) and posterior superior temporal gyrus (pSTG) were found to be significantly larger in ASD, which is in contrast to TD individuals. Also, EEG and MEG studies have shown significant differences in response latencies in the auditory, somatosensory and visual cortices.[26,27] Literature also supports that somatosensory-vestibular-visual integration occurs in many central nervous system (CNS) levels including the vestibular nuclei, the thalamus, and the cortex. For example, vestibular activation increases tactile discrimination and may decrease pain. Tactile input project to the posterior parietal cortex would integrate with visual information and motor signals and to the orbitofrontal cortex contributes to affect.[11]

Another study reported the changes in blood oxygenation level-dependent (BOLD) signal of ASD participants exhibited diminished responses in the posterior cingulate cortex and the insula, particularly for pleasant and neutral tactile stimuli, compared to the typical developing group.[28] For the unpleasant tactile stimuli, ASD participants exhibited greater BOLD signal than the control group in affective somatosensory processing area, including the posterior cingulate cortex and the insula. There is evidence to show that dysfunction in touch and tactile perception are closely tied to social dysfunction and core symptoms of ASD. For example, hyper-responsivity to tactile stimuli (i.e., tactile defensiveness) of children with ASD have been found to relate to social impairment (i.e., avoiding unintentional touch and move away from crowd), and tactile hypo-responsivity was associated with

poorer social functioning and non-verbal communication skills.[3] Differences in tactile processing and atypical tactile behaviors in ASD are observed in early infancy. Atypical touch during infancy can develop into critical social deficits in later life, including forming a secure attachment to caregivers. Therefore, dysfunction in tactile processing early in development can have crucial social and interpersonal implications.

5. Visual system

Similar to the somatosensory system, individuals with ASD were reported to have atypical visual behavior that include avoid visual stimuli (e.g., covering eyes at bright light) or seek out intense visual stimuli (e.g., staring at the sunlight). The atypical visual behavior is likely to be caused by atypical visual processing and perception, including contrast sensitivity, boundary detection and color perception.[29–31] The visual perceptual dysfunctions are likely to be found at dynamic situations rather than in static spatial tasks.[32] While the ability of ASD individuals to identify orientation of simple objects might be even superior than TD controls, increase in information in an experimental stimulus, which required much input from other cortical areas to process, would decrease the ability to correctly identify the orientations. The detection of moving stimulus with high contrast to the background was found worse in ASD individuals.[33] Furthermore, individuals with ASD were also found to perform worse than age-matched controls in detection of coherent motion of target stimuli.[34] These different findings converge on a common atypical property of ASD: motion detection of objects at different levels of processing, possibly include both subcortical and cortical visual pathways.

After receiving light signal by photoreceptors (rods and cones) in the retina, the signal will be transduced to the interneurons termed retinal ganglion cells, and subsequently to the lateral geniculate nucleus (LGN) in the thalamus, and further transduced to the cortical regions for visual perception. In the context of perception of moving objects, the visual pathway of primate and human can be classified according to function of detecting static or moving objects, namely, the parvocellular or magnocellular pathways, respectively.[35] Parvocellular pathways represent the visual pathway which involves the parvocellular geniculate subdivisions of the LGN, and the retinal ganglion cells which provide input to this division is called P-type retinal ganglion cells. The other LGN subdivision is the magnocellular division, and the ganglion cells that transduce signals to this subdivision are termed

M-type ganglion cells. Parvocellular pathway transmit information on color, shape of objects and spatial relationship. In contrast, magnocellular pathway transmit information related to motion. In other words, parvocellular pathway is specialized in detecting high contrast, spatial while magnocellular pathway is specialized in low contrast, temporal resolution. With the deficit in detecting moving objects, it is possible that the magnocellular pathway is affected in ASD.[36]

Apart from subcortical detection of moving objects, it is hypothesized that the cortical processing of visual stimuli is also affected in ASD. This is supported by the observation that second-order motion processing is worse in ASD children compared to TD controls.[37] First-order motion processing is the perception of movement of an object, which has relatively high contrast to the background, by changing the contrast between the object and background. Compared to first-order, the second-order motion processing is a more complex process, in which the object stands out from the background according to the texture. The second-order motion processing requires additional neural computation and integration of information. This points out to the possible dysfunction in cortical regions related to visual processing: the "visual streams" which consist of the occipital lobe and particular regions on dorsal and ventral surface of the cerebrum.[38] It is hypothesized that there are two visual streams at the cortical level of human, namely the dorsal and ventral streams. The ventral stream originates from the visual/occipital cortex, extends to the ventral part of cerebrum including temporal lobe and limbic system. This stream receives input from the parvocellular pathway and is believed to be responsible for perceiving shapes of objects. The dorsal stream extends from the visual cortex to the parietal lobe and interconnected to the ventral stream. This stream is associated with visually guided action and manipulation of objects. There are reports support that both streams may be involved in the motion-detection deficit in ASD,[39,40] but there is no conclusive finding whether both systems are involved, and whether the two streams are associated differentially to different etiologies of ASD. Nevertheless the hypothesis of dysfunctional neuro-integration is a plausible explanation of the complex motion detection malfunction in ASD, and emerging studies are providing evidence for this hypothesis.

Poor facial recognition, facial memory, facial discrimination and deficits in facial emotion recognition of ASD have been well documented in the literature and this is another recognized dysfunction related to vision. When being presented with static face drawings, there was hypo-activation in the areas related to face recognition in ASD subjects, including fusiform

gyrus, superior temporal sulcus and occipital face area.[41] Since fusiform cortex is a part of the ventral visual stream and essential for facial processing, the dysfunction may be associated with alteration in activation and function in this region.[42] Thus the visual stream hypothesis may be applicable on interpreting the poor facial processing. Difficulties in processing visual information in a timely manner are seen in ASD, leading to reduced attention to faces. These differences in early life may affect learning and social participation, as perception of social cues drives visual attention, and as a result, impact on social development which built on joint attention and observation.

6. Auditory system

Auditory hypo- (i.e., lack of orientation of auditory stimuli) and hyper-responsivity (i.e., over-sensitivity to sudden loud noise) are commonly seen in individuals with ASD. Atypical auditory processing with enhanced pitch perception, impaired perception of prosody, and diminished auditory stream segregation[22] were reported. One way to measure the flow of auditory information is through traditional auditory brainstem response (ABR) in which the electrical activity evoked from a series of clicks or tones is recorded using surface electrodes. Auditory information from the vestibulocochlear nerve (cranial nerve VIII) project to cochlear nuclei and the superior olivary complex in the brain stem and the inferior colliculus in the midbrain.[2] Literature supported a significantly longer CN III–V interpeak latency in ASD compared to the TD group. There was also a prolonged latency in child and adolescent ASD cohort.[43]

Besides brainstem studies, cortical auditory processing using event-related potentials (ERPs) with electroencephalography (EEG) and magnetoencephalography (MEG) was another area for investigation. Both EEG and MEG studies show atypical latencies in the early peaks that project to the primary auditory cortex located within Heschl's gyrus in the superior temporal cortex and association auditory cortices.[2] Structural imaging studies of adults with ASD reveal increased cortical thickness in Heschl's gyrus.[44] Other studies also found underrating of less emotionally intense stimuli reported by participants of ASD which was associated with the lower signals project to right caudate nucleus compared to TD controls.[45] Although individuals with ASD did not have a basic auditory impairment, they were reported to have difficulty filtering auditory information which interferes with the ability to perceive other information in the presence

of competing auditory input. Thus, atypical auditory processing in ASD occurs early in development including altered auditory perception and lack of preferential attention to auditory stimuli, impacts speech processing, social engagement, and language development.

7. Olfactory and gustatory systems

There are relatively few established hypotheses and theories on the abnormalities of olfaction and gustation in ASD, but it is generally agreed that individuals with ASD have hypo- and hyper-responsiveness (i.e., sensitivity to smell) with chemosensation (the senses which receive environmental chemical signals). The findings of olfactory dysfunction in ASD are heterogeneous, partly due to the complex etiology of ASD, the use of different olfactory tests and plenty of confounding factors like intelligence and age.[46]

Alteration in olfactory perception of individuals with ASD was documented as early as in 1990s,[47] in which the affected children were shown to response much negatively to unpleasant smells than TD controls. The affected individuals even rate pleasant odors (cinnamon, pineapple and clove) to be less pleasant than TD ones.[48] Later it was shown in a study with parental rating Short Sensory Profile that the affect individuals may avoid certain smells or odors from foods.[49] The ability for the affected children to identify odors in Sniffing Stick test was also found to be worsen in correctly identifying the odors and to have a higher than normal detection threshold, though children with high functioning autism may not show worse performance.[50,51] Interestingly, the olfactory function in adults with ASD is similar to healthy individuals.[52]

The availability of animal models of autism provides an appropriate tool for studying the neurobiology of the olfactory deficit in ASD. Due to the fact that ASD pathology is heterogeneous, the types of animal models which simulate the disorders are hugely diverse. Since olfaction is a major form of sensation for rodents to demonstrate social and communicating behaviors, the disrupted olfactory system may subsequently affects the findings from social ability test of the animals, which is considered similar to the social dysfunction of human affected by ASD and usually tested in animal models of ASD. If there is a dysfunction in the olfactory system, both olfaction and social functions are likely to be affected.

In utero exposure to substance known to cause autism in human is a typical way to establish an autistic model. One of the models is created by exposing rat fetus to valproic acid (VPA) in utero, which is comparable

to exposure to VPA in human prenatal stage.[53] In this model with highly similar etiology to human, the affected offspring showed delayed nest-seeking behavior regulated by the olfactory cues. Injection of polyinosinic-polycytidylic acid (Poly l:C) at gestation day 9.5 is another model, in which Poly l:C acts like a double-stranded viral RNA to mimic maternal infection and activate the immune system.[54] The affected offspring demonstrate reduced neurogenesis (generation of new neurons) in the olfactory bulb. As olfactory bulb is the first anatomical region along the olfactory pathway for integration of olfactory signals, the reduction of neuronal proliferation may affect the ability of odor discrimination. The affected offspring showed compromised olfactory discrimination, this suggests that reduction in olfactory bulb neurogenesis may be a possible mechanism underlying the olfactory dysfunction in ASD.

Transgenic animal is another typical form of animal modeling. Collapsing response mediator protein (CRMP) is a family of proteins suggested to involved in neuronal development, dendritic growth and axonal guidance.[55] The mutation of CRMP was reported to be associated with autism.[56] Transgenic mice without Crmp4 expression (i.e., Crmp4-knockout mice) showed impaired olfactory ability and hyperactivity in the olfactory bulb, and this supports the perspective that the altered olfaction in ASD may be attributed to abnormality of the olfactory bulb. Another line of transgenic mice model of autism, point mutations in neuroligin-3 (NL-3), also showed simultaneous dysfunction in olfaction and lack of social novelty preference.[57] Neuroligins are family of postsynaptic proteins which form a trans-synaptic bridge to facilitate development of synapse; mutation of neuroligins was found to associate with autistic phenotype.[58] Since neuroligins are essential for the formation of both excitatory glutamatergic and inhibitory GABAnergic synapses, this family of proteins virtually affect the neurodevelopment of various brain regions including somatosensory cortex, hippocampus and prefrontal cortex. In particular, NL-3 was found to express in all neurons in the olfactory bulb and in olfactory ensheathing cells,[59,60] which suggest the potential involvement of NL-3 in olfactory dysfunction of ASD. Due to the wide expression of neuroligin in the brain, cortical regions which involve olfactory perception including piriform, entorhinal, thalamocortical and orbitofrontal cortex[61] may possibly be involved in the olfactory dysfunction. The altered cytoarchitecture of the primary olfactory cortex (i.e., piriform cortex) was reported in a postmortem morphological study of ASD patients, in which an increased glial cell density in layer II of the piriform cortex was found.[62] No significant differences in neuronal cell densities, including pyramidal

and non-pyramidal cells, were found between ASD and TD subjects. In addition, in layer I of the piriform cortex from ASD subjects, the amount of corpora amylacea (small masses which may plays a role in debris clearance) was significantly higher than TD subjects. The cause and consequences of the increased glial dentistry and corpora amylacea remain to be determined, but it was hypothesized to be caused by neuro-inflammation. Furthermore, the activity of piriform cortex in adults with ASD was found to be decreased by functional imaging.[63] Collectively these suggest the olfactory dysfunction in ASD is associated with morphological and functional alteration, which is supported by evidence from both animal and human studies.

Apart from the perspective of abnormal changes in the olfactory system, the alteration in olfactory function was also suggested to be caused by resistance to change/repetitive behavior in ASD in another animal study, which demonstrated the inability to shift to favorable olfactory cue in BTBR T + *tf*/J mice (an autism animal model showing behavioral profile of low social preference, selective deficit in reversal learning and lacking anxiety-like behavior[64]). While other mice breeds showed flexible adaptation to receive an appetitive outcome in an exploratory hole-board task, the transgenic mice failed to change its preference in hole-picking. In addition to rodent, a drosophila model of Fragile X syndrome, a known leading genetic cause of ASD in human, also demonstrates impaired olfactory behaviors.[65]

However, the disruption in olfaction and the social function may not be ubiquitous in all animal models of ASD: the olfactory function and social preference of novelty were found to be normal in a mice model with oxytocin knockout (National Institute of Mental Health line in Bethesda and the Baylor/Emory line[66]). Shank1 knockout mice, with deletion of SHANK gene which encodes synaptic scaffolding proteins in postsynaptic regions, also showed no alteration in olfactory learning to discriminate social odors.[67] However, optogenetically induced oxytocin expression was shown to enhance social odor differentiation of same sex and olfactory exploration.[68] These findings suggest olfactory dysfunction may not be found in all individuals with ASD, but intervention for ASD may be possible to improve the olfaction.[69]

Though the observation of food selectivity in ASD has been recognized by clinical practitioners for several decades, the first clinical case report on food selectivity in autism was reported relatively recently in 2003.[70] In this single subject design study, a male individual with autism and profound intellectual disabilities showed a consistent refusal to vegetables but not other food types including protein, starch and fruit. The acceptance of vegetable

was increased after simultaneous addition of condiment like ketchup and mustard. The acceptance, however, could not be maintained by classical conditioning after the simultaneous presentation. It was suggested that the flavor and texture of vegetable elicited the refusal. Later, a study on the parental report of sensory reactivity in children with autism found that the affected children had significantly more sensory symptoms, in particular abnormality in responses to taste and smell.[49] Short Sensory Profile was used in the study and the abnormality observed including avoidance to certain tastes/textures of food, specific preference of certain food taste, texture and temperatures. The finding was echoed by self-reported food selectivity by adults and adolescents with high functioning autism, in which the participants reported preference on foods which are familiar (i.e., food neophobia) and avoided foods with particular textures or strong flavors.[71] Worse taste identification was shown in adults with autism, with more frequent mis-identification of a taste as salty or no taste, which led to an inability to correctly identify sour, bitter and sweet tastes.[72] The worsen identification was further supported by electro-gustometry findings.[50] It is suggested that food selectivity or neophobia in ASD individuals is associated with the magnitude of autistic traits, but unlikely to be modulated by olfactory sensitivity.[73]

Similar to olfaction, it remains elusive on the biological causes of the alteration of olfactory and taste sensations in ASD. One of the proposed mechanisms is the altered arginine-vasopressin (AVP, or anti-diuretic hormone) signaling. AVP is a neuropeptide/hormone which has a range of functions, including reducing volume of urine produced, mediation of social behavior, including pair-bond formation and communication.[74] Since deficits in social behavior is a core symptom of ASD, AVP and its receptors (AVPR1a and AVPR1b) have long been the target genes to be studied in related research, and postulated to be the causes of social and behavior deficits in ASD.[75] Specifically, the lengths of two microsatellite regions (RS1 and RS3) in the promotor regions of AVPR1a are associated with altered expression of mRNA of AVPR1a, and altered social behavior in individuals with ASD.[76] Single nucleotide polymorphism in AVPR1b (rs28373064) was linked to sociability and empathy,[77] while cerebrospinal fluid level of AVP is lower in children with ASD. From clinical studies, it is shown that blocking AVPR1a and increasing available AVP may improve social behaviors in ASD individuals.[78,79]

The involvement of AVP in regulating taste can be shown by an ex vivo study using frog gustatory organs[80]: after perfusion of AVP to the basolateral membrane side of taste cells, the sensitivity of taste cells toward salty and sour

was increased. AVP may modulate taste perception via modulating the activity of epithelial sodium ion channels (ENaCs), which are found to selectively permit sodium to get across the cell membrane. With the presence of AVP, the threshold of stimulating the host cells by sodium influx is lowered, which in turns increase the sensitivity to salty or sour tastes.[81] On the other hand, AVP administered in the CNS stimulates salt intake, and the action is likely to be modulated by ENaCs expressed on magnocellular neurons of paraventricular nucleus and suprachiasmatic nucleus.[82] This is coherent with the function of AVP which was discovered early: to retain water from urine production by increasing reabsorption of water from the renal collecting duct through increasing salt content in the blood stream. Combining with the observation that CSF level of AVP is lower in autistic individuals, the sensitivity to salty and sour tastes may be lower than the other tastes, hence prompts the affected individuals to choose salty and sour food. Though the current understanding of AVP on taste may not be able to explain the complex food selectivity variations of ASD individuals, the AVP signaling may still be useful to explain food selectivity from the perspective of altered taste perception.

The preference and avoidance of particular tastes were found to link to the differential expression of taste-related genes. Engrailed-2 (En2) is a transcriptional factor essential for normal neural development, in which transgenic mice lacking En2 was shown to display autistic traits.[83] The knockout mice showed a preference to sodium chloride solution and decreased lick response to fructose solution. Interestingly, the expression of taste receptor genes including Scnn1a, T2R140, T1R3, Trpm5 and Pkd1I3 are altered in the En2 mice, which is likely to induce a different taste perception in the transgenic mice. T2R38, which encodes bitter taste receptor, was also hypothesized to be affected in ASD and causes the hypersensitivity to bitter taste.[84] Genetic association studies showed that polymorphism of EN2 is associated with autism.[85] ASD-associated haplotype of ASD (rs1861972–rs1861973 A–C genotype) was found to be increased in postmortem cerebellar samples of ASD individuals, which further confirms the involvement of EN2 in ASD.[86] It is still elusive in human that whether the SNPs in EN2 is the cause of altered gustation in ASD, and this is a possible research gap for future studies.

Interestingly, some clinical researchers made use of the food selectivity in autism for behavioral modification treatment.[87] In a single case study, a child with autism showed pica (ingestion of objects that are inedible) and food refusal to tapioca pudding. The researchers dipped the inedible objects in the pudding and this significantly reduced the frequency of pica, and the

conditioning was shown to maintain for at least a year. When compared to the first case report, pairing of stimuli may be more effective when a naturally aversive stimulus is used.

Though olfactory and gustation are traditionally thought to be less important than vision and hearing in human being, the manifestations of alteration in the chemosensations may be potential biomarkers of autism.[88] As the chemosensory systems may have potential association with the pathophysiology of neuropsychiatric disorders, the sensory dysfunctions may provide clues to explore the underlying mechanisms of the disorder, including dysfunctional immune system and neurogenesis.[89] A study showed that olfactory bulb dysgenesis which results in reduced vasopressin and oxytocin receptor binding could be one of the neural foundations of ASD.[90] Another study also found functional connectivity of the amygdala with the orbitofrontal cortex which has impact on the socio-emotional recognition and behavioral regulation in individuals with ASD.[91] These findings suggest that future research is needed to further examine the relationship between olfaction and social cognition and behavioral regulation of ASD.

8. Neuroplasticity and sensory integration

Remodeling of the human brain in response to experience has been supported by neuroscience research. Experience-dependent learning is the ongoing process of creation and organization of neuronal connections that occur as a result of experiences. Changing the input by providing novel experiences and enriched learning opportunities leads to brain changes which include increased gray matter density, angiogenesis, glial volume and neurogenesis.[92] Other animal model studies also showed that enriched environment with novel sensory, motor and cognitive stimulation can initiate functional changes in the brain.[93] These investigators concluded that the enriched environment principles are aligned with the premise of sensory integration intervention. The hallmark of sensory integration intervention is based on the concept of neuroplasticity, through individually tailed sensorimotor activities in the context of play in creating changes of function and behavior of individuals with ASD.[6,10]

9. Conclusion

Abnormal sensory registration and sensitivity in ASD have significant clinical and social implications. With the advancement of neuroimaging and other innovative technologies, tremendous gains have been made over the

past few decades to guide our understanding of the neurobiology of sensory processing. It is hoped that these advancements will provide insight and tailor appropriate and effective intervention in sensory integration and sensory processing to improve participation in people with ASD.

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