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Sensory abnormalities in autism spectrum disorder and their in vitro modeling

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Autism Spectrum Disorder (ASD) is characterized by deficits in social interaction, alongside abnormal sensory reactivity that often manifests as avoidance or repetitive behaviors. This review proposes that these core features may stem from somatosensory system dysfunction responsible for processing sensory information driven by an underlying excitatory-inhibitory (E/I) imbalance, a common finding in ASD models, which could drive such sensory impairments and ultimately contribute to the core social and behavioral deficits. We explore how recent advancements in hiPSC-derived assembloid models, which integrate multiple components of the human somatosensory pathway, provide a powerful platform to investigate these mechanisms. Crucially, this review not only highlights the promise of these models but also provides a critical evaluation of their inherent limitations, including cellular immaturity and the absence of key non-neuronal components. By examining the ongoing strategies to overcome these challenges, such as advanced co-culture systems, xenotransplantation, and bioengineering, this review offers a comprehensive outlook on the future of assembloid technology in elucidating ASD pathophysiology and developing novel therapeutic strategies.

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INTRODUCTION

Every organism, including humans, constantly interacts with its environment from birth, and the somatosensory system serves as the gateway for these interactions. External stimuli trigger internal responses that shape our perceptions, emotions, and behaviors, influencing survival, development, learning, and self-actualization. Thus, the interplay between individuals and their surroundings critically impacts cognitive, emotional, and physical growth, ultimately defining human identity. When infants perceive a parent's affectionate gaze or gentle voice, they develop a sense of security and comfort, encouraging them to explore further and engage in complex behaviors. As children grow, interactions with peers teach them linguistic and non-linguistic communication, aiding in understanding social roles, rules, and the development of social skills.

External stimuli are equally important for emotional development. Positive interactions, such as comfort, support, and praise from family and peers, help children express emotions healthily and develop empathy, cooperation, and conflict resolution skills. Proper interaction with the environment also significantly influences physical and neurological development in infancy and childhood. The somatosensory system continuously matures and refines itself through exposure to external stimuli. For instance, tactile feedback from grasping objects helps infants enhance hand-eye coordination, strengthening neural connections involved in motor control [1]. Similarly, visual stimuli aid in establishing and refining neuronal pathways between the eyes and brain, improving visual processing. Auditory stimuli from the environment support the development of hearing and language abilities [2–4].

Overall, interactions with external stimuli, especially in early childhood, lay the foundation for individual growth. These early experiences shape cognitive, emotional, and physical development, profoundly influencing who we become.

SOMATOSENSORY ABNORMALITIES IN AUTISM SPECTRUM DISORDER PATIENTS

According to diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM-5-TR) and the International Classification of Diseases, 11th Revision (ICD-11), autism spectrum disorder (ASD) is identified based on the following core deficits: impairments in social communication and interaction, restricted and repetitive behaviors/interests/activities [5, 6]. One of the representative characteristics of ASD is the atypical response to external stimuli, manifesting as heightened or diminished sensitivity, which significantly impairs social interaction [7]. For instance, a person with auditory hypersensitivity might avoid noisy outdoor activities. Similarly, tactile sensitivities can lead to an insistence on wearing specific clothing, while discomfort with certain tastes or textures may result in the refusal of unfamiliar foods. From this perspective, many of the deficits observed in individuals with ASD may stem from problems in sensory integration.

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Sensory integration, a concept first introduced in the 1970s by American educational psychologist and occupational therapist Dr. Jean Ayres, refers to the process by which the brain integrates sensory information received from various sensory organs and orchestrates appropriate physical responses [8]. Abnormal sensory integration in ASD has been reported in numerous studies. For example, children with ASD demonstrated significantly longer reaction times and lower stimulus recognition than typically developing controls when exposed to multimodal sensory stimuli, including auditory and visual inputs [9]. Such abnormalities in sensory integration make it difficult to respond appropriately to sensory inputs, ultimately complicating social communication and interaction. Since the concept of sensory integration became appreciated and widely accepted, studies have revealed that 90–96% of individuals diagnosed with ASD experience sensory abnormalities, which are now considered part of the diagnostic criteria for ASD [10–12].

Among the sensory abnormalities experienced by individuals with ASD, approximately 60% are known to be related to changes in tactile sensitivity [13]. The somatosensory system delivers diverse types of tactile information, including mechanical signals such as pressure, vibration, and texture from the peripheral nervous system (PNS) to the central nervous system (CNS) via an ascending pathway. In turn, the brain processes this sensory input and sends appropriate signals back to the PNS through the descending pathway to elicit corresponding responses. Tactile sensation is likely the first sensory modality to emerge, shaping early brain development, bonding with family members, and forming social relationships [14–16]. Thus, abnormalities in tactile sensitivity can significantly impact the formation of social relationships. For example, if abnormalities occur in sensory reception or in the organizational processes within the CNS, individuals may avoid physical contact or external stimuli, refrain from outdoor activities, and exhibit obsessive behavior toward stimuli that provide stability. Conversely, individuals with hyporesponsiveness to tactile stimuli may repetitively touch objects, seek more substantial pressure, and demonstrate insensitivity to injuries to their bodies or objects. Impaired tactile discrimination can result in difficulties in tool use, recognizing physical properties, and performing simple but organized tasks such as dressing. These behavioral abnormalities are frequently observed in individuals with ASD.

Accordingly, this review will center on the tactile system to enhance our understanding of how altered sensory integration and processing contribute to the social and functional challenges experienced by individuals with ASD.

THE SENSORY INTEGRATION THERAPY IN ASD PATIENTS

Sensory Integration Therapy (SIT) is an intervention method designed to alleviate sensory abnormality symptoms by promoting effective interactions between children and their environments through various sensory stimuli. This therapeutic approach was first developed by Dr. Jean Ayres, who proposed the theory of sensory integration as mentioned, and is based on the premise that the brain maintains synaptic plasticity even beyond critical developmental periods [17]. Synaptic plasticity refers to the brain's ability to strengthen or weaken synaptic connections as neural activity changes in response to a range of sensory experiences, including visual, auditory, and tactile stimuli [18–21].

The goal of SIT is to improve the sensory integration systems in children with sensory processing disorders, enabling them to adapt to sensory stimuli. The therapy is designed in a personalized manner by licensed occupational therapists, ensuring that children can actively participate, and incorporates methods that address various senses, including visual, auditory, tactile, proprioceptive, and vestibular modalities [22, 23]. Typically, the therapy is conducted in indoor play environments equipped with trampolines, ball pits, and ladders, and employs play-based programs to encourage active participation and a wide range of sensory-motor experiences for children with ASD [24]. During these interventions, the occupational therapist gradually increases the difficulty of activities to support the improvement of the child's performance abilities [25]. For example, in children with hypersensitivity, the therapy may initially begin with gentle stimulation of the skin using soft objects like feathers to reduce anxiety and aversion, and gradually increasing intensity within the child's tolerance using media such as sand and fabrics. Ultimately, the intervention aims to generalize improvements to daily adaptive activities, such as playing in sand or dressing.

SIT is widely applied to children with ASD. Results from parent surveys indicate that SIT is among the most highly preferred and frequently used therapeutic approaches for children with ASD [26, 27], and more than 95% of pediatric occupational therapists report implementing SIT in practice [28, 29]. The therapeutic efficacy of SIT has been demonstrated in numerous previous studies. For example, a study conducted at Nagasaki University administered SIT for 8-10 months to 8 children with high-functioning ASD (mean age: 56.8 ± 9.0 months) diagnosed according to DSM-4 criteria [30]. Comparison of scores on the Japanese version of the Miller Assessment for Preschoolers [31, 32] before and after therapy showed significant improvements in total score as well as in foundation, coordination, non-verbal, and complex subdomains. Similarly, a study from a clinic in Jakarta included 72 children aged 2-5 years diagnosed with ASD according to DSM-5 criteria [33]. These children participated in SIT sessions twice a week for 12 weeks, and as a result, showed significant improvements relative to the control group in communication, daily living skills, and receptive and expressive domains. Nevertheless, the paucity of preceding studies with long-term follow-up of more than 6 months constitutes a limitation to determining whether SIT possesses consistent long-term efficacy. Furthermore, negative findings regarding the efficacy of SIT have been reported as being attributable to interventions that focus solely on the provision of sensory stimuli without sufficiently incorporating standardized principles of SIT (e.g., therapist-child relationship, just-right challenge) [25, 34].

In conclusion, while the efficacy of SIT in children with ASD remains a subject of debate, the evidence suggests that the controversy stems from inconsistent application rather than a lack of inherent effectiveness. Studies reporting negative outcomes often point to interventions that fail to incorporate the standardized principles of SIT. This implies that when properly implemented, SIT can be a powerful therapeutic tool. Therefore, future research is crucial for establishing clear guidelines for SIT delivery and for building a bridge between its foundational neurobiological mechanisms and clinical outcomes. This will allow us to fully realize the therapeutic potential of SIT.

STRUCTURE OF THE SOMATOSENSORY SYSTEM

To understand the sensory abnormalities observed in individuals with ASD, it is essential first to grasp the nature and developmental process of the somatosensory system. The human somatosensory system facilitates the perception of three major sensory domains: exteroception, interoception, and proprioception. Exteroception encompasses sensations such as touch, temperature, pain, and itch. Interoception refers to the perception of internal states of the body, including heartbeat and gastrointestinal activity. Proprioception involves the awareness of the position and movement of body parts [35]. Given that atypical tactile processing is a prominent feature in individuals with ASD, this review will focus specifically on the tactile modality, which falls within the domain of exteroception.

The flow of information within the somatosensory system is bidirectional, involving distinct functional roles for its two primary

routes. The ascending pathway, carrying signals toward the brain, is primarily responsible for sensory perception. In contrast, the descending pathway, which transmits signals away from the brain, modulates the body's responses to these stimuli. Tactile information transmitted via the ascending pathway involves a three-step relay system, ultimately reaching the primary somatosensory cortex for processing. The reception and transmission of sensory information at each stage are as follows:

Primary sensory neurons extend to peripheral sensory organs, including the skin, muscles, and visceral tissues, initially collecting sensory information and transmitting it through the dorsal root ganglia (DRG) to the spinal cord within the CNS. For example, primary sensory neurons in the skin capture stimuli through specialized receptors distributed across various layers of the skin. During this process, mechanical energy from external stimuli is converted into receptor potentials, a form of membrane potential that encodes the sensory information for further transmission [36, 37]. Receptors expressed on primary sensory neurons are classified into low-threshold mechanosensitive receptors (LTMRs) and high-threshold mechanosensitive receptors (HTMRs) based on mechanical sensitivity thresholds. LTMRs, with relatively low thresholds, allow the detection of fine tactile stimuli such as stretch, vibration, and light brushing. In contrast, HTMRs, which have higher thresholds, primarily mediate the perception of nociceptive signals [38]. Information detected by LTMRs and HTMRs is transmitted through nerve fibers classified into Aβ, Aδ, and C fibers, depending on their axonal diameter and the presence of myelination. For tactile stimuli detected by LTMRs, signals are conveyed through either myelinated Aβ fibers (axon diameters: 6-12 μm) or unmyelinated C-fiber LTMRs (axon diameters: 0.2-1.5 μm). In contrast, nociceptive stimuli detected by HTMRs are transmitted via myelinated Aδ fibers (axon diameters: 1-5 μm) or unmyelinated C-fiber HTMRs [38].

Tactile stimuli applied to the skin are received by various mechanoreceptors distributed across the epidermis and dermis, including Merkel cells, Meissner corpuscles, Pacinian corpuscles, and Ruffini endings [36]. Signals from these mechanoreceptors are then transmitted primarily via Aβ fibers or through free-nerve endings that utilize C-fiber LTMRs. Mechanoreceptors exhibit differential response patterns to stimuli. For instance, Meissner and Pacinian corpuscles rapidly adapt receptors that respond quickly to stimuli but cease to respond if the stimulus persists. In contrast, Merkel cells and Ruffini endings have slowly adapting receptors that react more gradually and continue responding to sustained stimuli. Free-nerve endings exclusively receive nociceptive signals transmitted via Aδ fibers and C-fiber HTMRs. This intricate organization enables the perception of a wide range of tactile stimuli [36].

Primary sensory neurons connect to the DRG and extend into the spinal cord, forming synapses with secondary sensory neurons that relay signals to the thalamus. During this process, tactile and nociceptive information ascend to the thalamus via different routes within the spinal cord [39, 40]. Tactile information is conveyed via the dorsal column-medial lemniscal (DCML) pathway. Primary sensory neurons carrying tactile signals enter the spinal cord through the dorsal column, a white matter tract, and project to the dorsal column nuclei in the medulla, where they synapse with secondary neurons. These secondary neurons then decussate at the medial lemniscus and ascend to the ventral posterolateral (VPL) nucleus of the thalamus. In contrast, nociceptive information is conveyed via the spinothalamic pathway. Primary sensory neurons transmitting nociceptive signals enter the dorsal horn, a region of gray matter in the spinal cord, and form synapses with secondary neurons. These secondary neurons decussate within the spinal cord as they traverse the ventral horn, eventually ascending to the VPL nucleus of the thalamus [39, 40].

In the thalamus, secondary sensory neurons synapse with tertiary neurons, which relay signals to the primary somatosensory cortex (S1). S1, located in the postcentral gyrus of the parietal lobe, is subdivided into Brodmann's Areas 1, 2, 3a, and 3b. Area 1 and 3b primarily process cutaneous stimuli, Area 3a processes proprioceptive inputs, and Area 2 integrates both tactile and proprioceptive information [41]. While S1 serves as the primary region for sensory information processing and responding to the PNS, it also interacts extensively with the secondary somatosensory cortex (S2) for integration, sensory memory formation, and interpretation. S2 also connects to limbic structures, such as the hippocampus and amygdala, which play key roles in memory and emotional responses. These interconnections underscore the role of the somatosensory system in higher-order cognitive functions and social behaviors beyond simple sensory perception [42].

In addition to the three-step transmission system of sensory information from the PNS to the CNS, inhibitory interneurons also play a crucial role as regulators in sensory signal transmission. These interneurons are distributed throughout the sensory system, including the spinal cord, thalamus, and cortex. They enhance contrast for more explicit stimulus discrimination and maintain neural balance by regulating the intensity and scope of stimuli [43, 44]. Through this modulation, information on sensory signals can be transformed at each synapse along the pathway. Thereby, these synaptic points may represent potential sites of sensory processing abnormalities observed in individuals with ASD. Notably, many studies have reported an imbalance in excitatory and inhibitory neuronal activity (E/I imbalance) in ASD, which may underlie sensory reception or processing deficits [45, 46]. This imbalance and its impact on somatosensory processing will be discussed in detail later.

The intricate pathway of the somatosensory system, from peripheral receptors to cortical areas and their regulation by the balance of excitatory and inhibitory neurons, highlights how this balance plays a critical role in essential sensory functions and complex behaviors. Understanding these mechanisms will offer insights into the pathogenesis of ASD, where sensory processing abnormalities contribute to the clinical manifestations of the disease (Fig. 1).

DEVELOPMENT OF THE SOMATOSENSORY SYSTEM

The developmental process of the somatosensory system is highly intricate. Although many aspects remain poorly understood, research has shown that the formation and specification of neurons within the somatosensory system, spanning from the peripheral to the CNS, are tightly regulated by specific transcription factors.

Studies on embryonic development have shown that multipotent neural crest progenitors originating from the dorsal neural tube migrate to form the DRG [47]. These progenitors subsequently differentiate into sensory neuron precursors. Initially present as unspecialized sensory neurons, they later undergo subtype specification through the regulated expression of transcription factors, as revealed by single-cell transcriptomic analyses in mouse models [47]. Furthermore, interactions with cells in the PNS have been shown to facilitate synaptic terminal formation in primary sensory neurons [48]. For instance, in mice, the activation of BDNF signaling by Merkel cells in the skin is critical for the maturation of slowly adapting type I (SA1) afferent neurons [49]. Similarly, in *C. elegans*, the interaction between chemotaxin-2 in muscle cells and L1CAM in the skin is essential for the specialization of sensory neurons [50].

Primary sensory neurons connected to the PNS must extend their axons through the DRG toward the brain. Although the precise mechanisms governing this process remain only partially understood, several studies have highlighted the critical role of specific proteins in directing proper axonal pathfinding. For

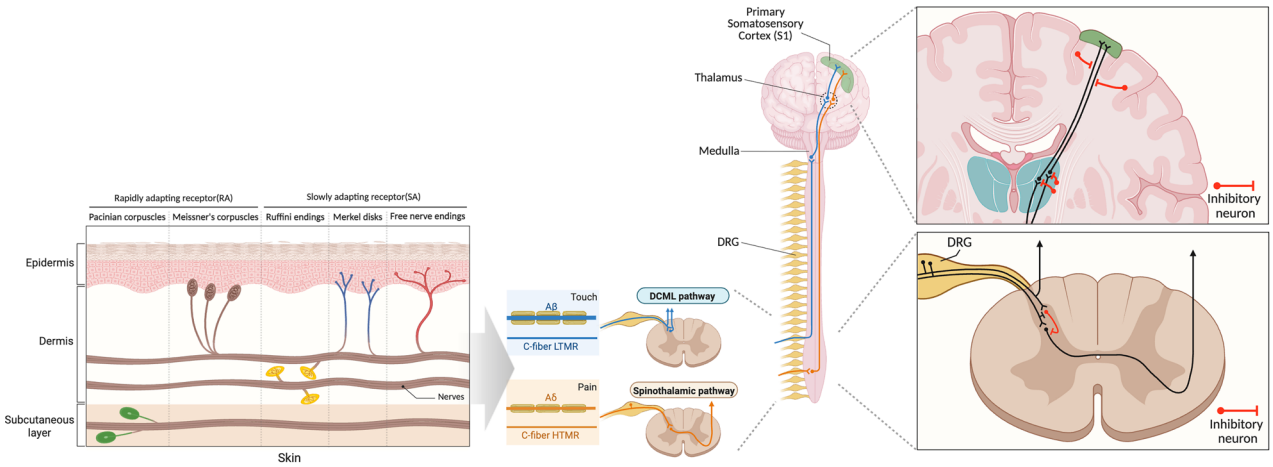

Fig. 1 Structure of the ascending pathway and E/I networks in the somatosensory system. Schematic representation of the ascending pathway transmitting touch or pain information from peripheral mechanoreceptors to the primary somatosensory cortex (S1). The regions where the E/I balance is established are highlighted (black: excitatory, red: inhibitory) [68–70, 108, 114, 129–132]. Created with BioRender.com.

instance, studies on chick spinal cords have demonstrated that axons of sensory neurons rely on the secreted protein Semaphorin for accurate projection within the spinal cord. Semaphorin functions as a short-range inhibitory cue, modulating axonal guidance by differentially regulating the projection of nerve growth factor-dependent axons and neurotrophin 3-dependent axons, thereby determining distinct projection patterns [51, 52]. Similarly, several transcription factors are also known to be essential for establishing neuronal connectivity from the spinal cord to the brain. Frizzled-3, a critical polarity protein involved in axon development, plays a pivotal role in establishing proper neuronal connectivity. Studies on mouse embryos have revealed that the absence of Frizzled-3 results in a substantial reduction in ascending axons targeting the brainstem, with a complete absence of axonal projection in the midbrain or thalamus [53, 54]. In a mouse model where Phox2a, a transcription factor transiently expressed in spinal neurons during embryonic stages, was knocked out, defects in axonal migration and formation of the anterolateral system and subsequent impaired nociception were observed [48, 55]. Since the temporal and spatial expression patterns of Phox2a in mice and humans are similar, it is likely that its role is conserved across species.

In the CNS, during early developmental stages, the brain prepares to receive and process sensory stimuli, even before actual signals are transmitted from the PNS. Notably, spontaneous neural signaling exchanges between the thalamus and cortex are observed before the sensory inputs arrive from the PNS. The circuit transmitting signals from the thalamus to the cortex is referred to as the thalamocortical neuronal circuit (TC). During development, TC activity plays a crucial role in the spatial organization of sensory areas within the cortex [56]. The formation of the TC circuit is known to be influenced by the transcription factor Btbd3, which regulates the directionality of dendrite growth. In neurons of the mouse somatosensory cortex, neuronal activation triggers Btbd3 to translocate to the nucleus, where it modulates dendritic morphology via transcriptional regulation [57]. Specifically, Btbd3 prunes dendrites that extend in directions not aligned with the active signal source, thereby orienting dendritic growth toward the activated neurons. For the TC circuit to form and cortical arealization during brain development, input signals from the thalamus are essential. Before receiving sensory stimuli from the PNS, the TC exhibits unstable and sporadic bursts of activity. As inhibitory circuits mature, this activity becomes finely tuned, enabling the cortex to precisely differentiate and process sensory inputs [58]. The formation of cortical areas is also influenced by calcium waves originating in the thalamic nuclei. Changes in the pattern of thalamic waves were shown to result in corresponding changes in cortical arealization [59]. Overall, this "pre-sensory period," during which thalamocortical axonal connections are established, is considered crucial for preparing the brain to process future sensory stimuli (Fig. 2).

In summary, the development of the somatosensory system is shaped by both intrinsic factors, such as transcription factor regulation, and external experiences. These mechanisms underscore the dynamic interplay between genetic programming and sensory experience in establishing a functional sensory system. Nowakowski and colleagues proposed the "proto-regions" hypothesis, which suggests that during early development, molecular differences drive arealization, and subsequent activity-dependent changes finely tune the functions of each region [60]. This perspective highlights that while neuronal fate in the mammalian brain is predetermined early on, it remains amenable to modification through plasticity. This viewpoint also underscores the importance of further investigating how genetic factors interact with external sensory inputs to shape the development of the somatosensory system, a critical area of study for advancing ASD research.

ASD-ASSOCIATED GENETIC FACTORS AND SENSORY ABNORMALITIES

According to the National Institute of Mental Health, ASD is classified as a neurodevelopmental disorder because its symptoms are typically observable within the first two years of life, and abnormal brain growth patterns can be detected as early as six months of age [61–63]. Diagnostic tools such as facial expression response analysis and electroencephalography (EEG) have been reported to help identify ASD symptoms [5, 6]. This suggests that intrinsic factors may play a fundamental role in the onset of ASD, rather than the classical view that its symptoms are primarily a consequence of deficits in social activity. In fact, studies involving monozygotic twins have shown that the manifestation of ASD symptoms is influenced by genetic factors, with heritability estimates ranging from 40 to 90% [64]. Beyond twin studies, recent findings from Genome-Wide Association Studies (GWAS) have identified genetic factors associated with ASD development [65]. In addition to genetic contributions, environmental factors such as parental age, maternal health during pregnancy, and perinatal conditions are also known to increase the risk of ASD [64]. As a result, understanding the interaction between genetic and environmental factors, and the mechanisms underlying their interplay, has become a critical area of ASD research.

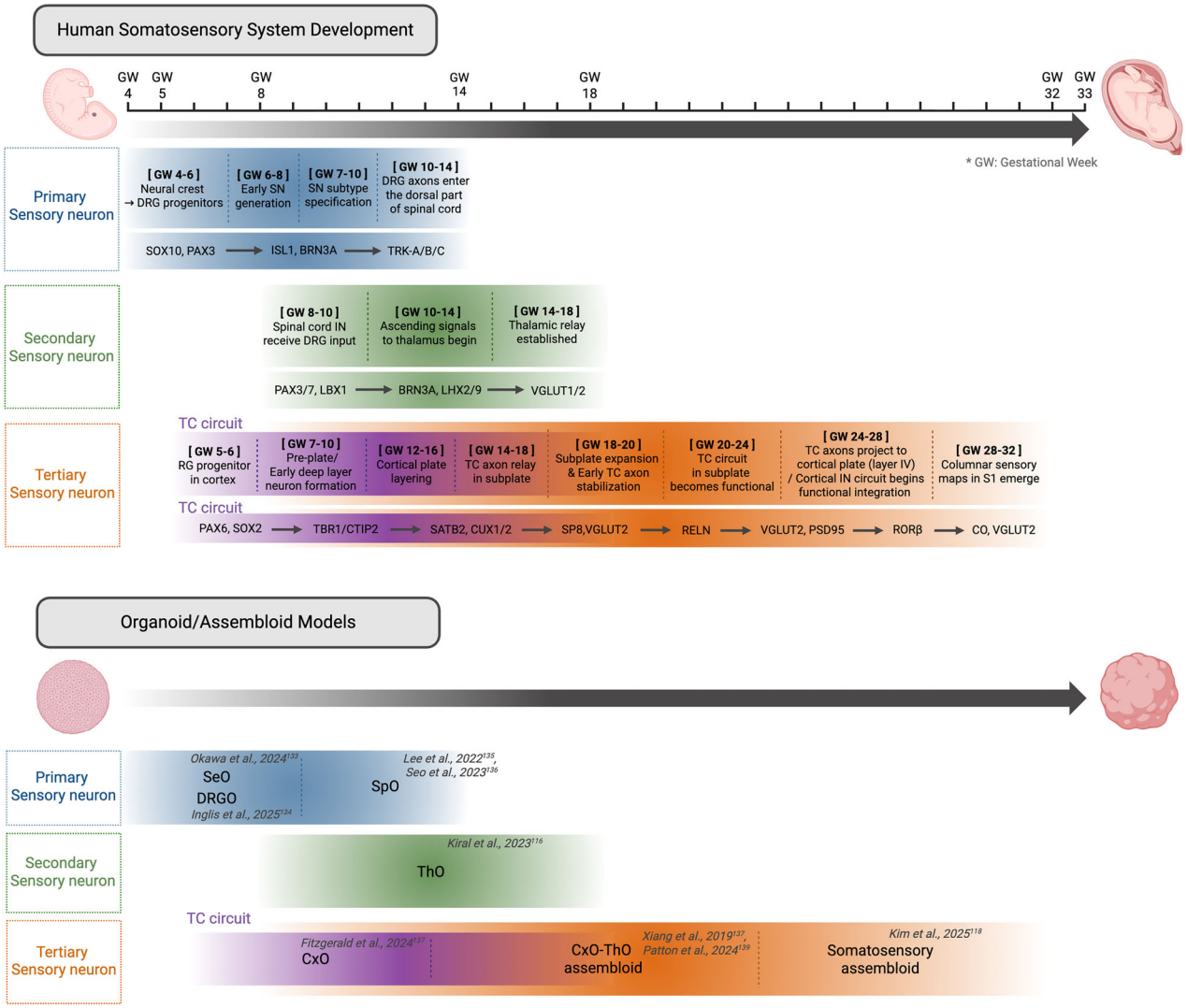

Fig. 2 A timeline of human somatosensory development and corresponding organoid models. The upper timeline indicates major developmental milestones of the human somatosensory system. The proteins listed at the bottom of each stage are characteristically expressed during that specific period. The lower section highlights region-specific organoid models that recapitulate the developmental stages of the human somatosensory system [85, 87, 133–146]. Created with BioRender.com.

Many of the diverse ASD-associated genetic factors identified through GWAS are not absolute causes of the disorder on their own. However, by analyzing the convergence of the cellular mechanisms influenced by these genetic variants, it is possible to uncover the core pathogenic processes underlying ASD. Such analyses reveal that the majority of ASD-related genetic variants are associated with synaptic structure and function (e.g., *SHANK2, SHANK3, CNTNAP2, FMRP, SYNGAP1, KATNAL2, ANK2, NRXN1*) or chromatin/transcriptional regulation (e.g., *CHD8, ARID1B, POGZ, TBR1, FOXP1, MECP2*) [64]. These findings suggest that abnormalities in neural network structure/function, together with dysregulation of gene expression required for neural information processing and storage, are key contributors to ASD pathology. A recent study employing brain organoids with ASD-associated genetic mutations such as SUV420H1, ARID1B, and CHD8 deficiency provides strong support for this hypothesis [66]. The study found that while each model had distinct gene expression patterns, they shared common cellular and functional abnormalities, including impairments in inhibitory neuronal differentiation and function, as well as in the differentiation and activity of deep-layer projection neurons. Further evidence comes from animal studies. Selimbeyoglu et al. investigated social deficits in *Cntnap2*-deficient mice by utilizing optogenetics to manipulate the balance between excitatory and inhibitory neurons in the prefrontal cortex [67]. Enhancing Parvalbumin (PV) neuron activity while simultaneously reducing the excitability of pyramidal neurons led to increased interaction times with littermates and greater social exploration behaviors, even in CNTNAP2-knockout mice. This study demonstrated that the E/I balance is crucial for proper social interactions. Another study explored sensory abnormalities in the SHANK3B-knockout mouse, a model of ASD-related sensory processing deficits [68]. This research demonstrated that mice with SHANK3B deficiency exhibited heightened sensitivity to fine vibrational stimuli compared to wild-type mice. Calcium imaging revealed increased responsiveness of pyramidal neurons in layers II/III of the somatosensory cortex, accompanied by reduced inhibitory neuron activity. The E/I imbalance is further proposed to be a key driver of ASD pathophysiology by many studies from mouse models for ASD: In NLGN3 R451C knock-in mice, increased GABAergic signaling was observed in the sensory cortex, and mice with MECP2 deletion in inhibitory neurons exhibited reduced GABA synthesis and release, along with sensory integration deficits. Likewise, CNTNAP2-deficient models displayed a reduction in inhibitory neuron populations, and in BTBR mouse models,

a decrease in inhibitory postsynaptic current (IPSC) frequency in the hippocampus was associated with impaired social behavior, which could be rescued by treatment with the GABA A receptor agonist clonazepam [45, 46].

Furthermore, the concept of E/I imbalance as a core mechanism extends beyond the cortical circuits in the brain. A compelling body of evidence suggests that disruptions across the entire somatosensory pathway, including the PNS, are critical contributors to ASD pathophysiology. For example, the role of MECP2 along different segments of the somatosensory pathway has been extensively explored using mouse models where the gene was selectively deleted in specific regions, including the spinal cord, DRG, and forebrain [69, 70]. Mice with MECP2 deletion in the spinal cord and DRG exhibited heightened sensitivity in the Air Puff Response test and showed significantly reduced preference for novel textures in the Textured Novel Object Recognition Test (NORT). In contrast, deletion of MECP2 specifically in the excitatory neurons of the forebrain did not lead to notable behavioral changes [69]. These findings suggest that the pathological role of ASD-associated genetic mutations may not be confined to the brain but could also involve disruptions in the reception and transmission of sensory stimuli at earlier stages of the somatosensory pathway, contributing to a broader excitatory and inhibitory imbalance across the entire somatosensory system. Mechanistic investigations revealed that MECP2 deletion caused reduced expression of GABRB3, a subunit of the GABA A receptor expressed from the dorsal horn of the spinal cord to the nerve terminals of LTMRs. As GABA A receptor-mediated inhibitory signaling is crucial for regulating sensory input, its downregulation likely contributes to impaired sensory modulation, leading to excessive sensory perception. This dysregulation correlates with anxiety-like behaviors and social deficits observed in the MECP2-deficient mouse models [69]. Further reinforcing the significance of peripheral contributions, subsequent research demonstrated that restoring GABRB3 expression in peripheral sensory neurons of MECP2-deleted mice ameliorated their heightened Air Puff Response and social deficits, although impairments in memory and motor function persisted [70].

Taken together, these findings underscore the importance of understanding how ASD-associated genetic factors influence not only brain regions that process sensory information but also the entire somatosensory pathway. They emphasize the need for further research into the mechanisms by which these genetic factors affect sensory input reception, transmission, and integration in ASD.

ADVANTAGES AND LIMITATIONS OF NON-HUMAN ANIMAL MODELS FOR ASD RESEARCH

Investigating the neurological mechanisms underlying ASD is challenging due to technical and ethical limitations associated with studying developmental stages of human brains, especially in infants aged 1-2 years, a critical period when ASD pathology typically emerges through genetic or prenatal environmental factors. It is nearly impossible to manipulate or control ASD-related genetic or environmental factors. Furthermore, recruiting a sufficiently large cohort for meaningful analysis poses significant difficulties. Although GWAS have identified numerous genetic factors associated with ASD, critical questions remain unanswered, such as whether these factors are necessary or sufficient for disease onset, the mechanisms through which they exert their effects, and how they interact with environmental factors to increase the risk of ASD. Addressing these questions is crucial for advancing current research.

One of the most significant advantages of non-human animal (hereafter referred to as 'animal') models in ASD research is their utility in behavioral experiments. Many representative symptoms of ASD, such as anxiety, deficits in social interactions, and altered responsiveness to auditory or tactile stimuli, can be quantitatively analyzed in animal models [45]. Moreover, these models allow researchers to observe behavioral changes caused by ASD-related genetic factors identified by GWAS [69] (Table 1). However, there are inherent limitations due to the biological differences between animal models and humans, making it challenging to generalize findings. For instance, early childhood is a period of rapid brain development in humans, particularly involving the formation of distinct cortical structures, including the ventricular zone (VZ), inner subventricular zone (iSVZ), outer subventricular zone (oSVZ), intermediate zone (IZ), subplate (SP), cortical plate (CP), and marginal zone (MZ). In mice, which are widely used in ASD research, the iSVZ and oSVZ are significantly underdeveloped compared to humans, and brain development occurs over a much shorter time frame (within just a few days) [66, 71]. Notably, the oSVZ is a characteristic structure of primates, known to contain neural progenitor cells and differentiating cells that contribute to the size and complexity of the primate brain. This distinction is particularly relevant when studying ASD, as abnormalities in cortical development are one of the key features of the disorder [72]. These differences can complicate the analysis of developmental processes and pathological mechanisms. In the context of somatosensory system research, comparative studies between human and mouse DRG using single-cell transcriptome analyses have revealed differences in the expression patterns of receptors and ion channels involved in somatosensory processing between the two species [73]. This underscores the importance of validating molecular findings from animal models in human systems, as discrepancies may impact the translational relevance of the results.

Overall, while animal models provide valuable insights, particularly in behavioral and genetic studies, their biological and developmental differences highlight the necessity of complementing animal research with human-based studies to achieve a comprehensive understanding of ASD mechanisms (Table 1).

HUMAN INDUCED PLURIPOTENT STEM CELLS FOR ASD RESEARCH

As human models, brain cells differentiated from human induced pluripotent stem cells (hiPSCs) are actively utilized in ASD research. A primary advantage of this model is its ability to use cells derived directly from individuals with ASD or related neurodevelopmental disorders, thereby capturing the patient's unique genetic characteristics [74–78]. By obtaining cells from ASD patients and comparing them with cells from non-ASD family members, such as parents or siblings, researchers can minimize variables such as genetic diversity and environmental differences. This enables researchers to investigate how disease-specific genetic mutations influence cellular development and physiological functions. For instance, comparisons between cells from ASD patients and their relatives provide valuable insights into genotype-phenotype relationships in ASD pathogenesis [79].

A particularly promising approach in this field is the utilization of brain organoid models, where cells self-organize into three-dimensional structures that mimic the developing human brain. Crucially, these organoids recapitulate the species-specific aspects of human brain development, such as the formation of an outer subventricular zone (oSVZ), which is underdeveloped in rodent models. This allows for a more accurate investigation of early neurodevelopmental processes that are difficult to model in non-human animals. These models are increasingly employed because they can replicate the complex architecture of the human brain and model the abnormalities associated with ASD-linked genetic factors. For example, brain organoids harboring CNTNAP2 mutations demonstrated abnormalities in embryonic cortical development. Specifically, these organoids exhibited an increased number of neural progenitor cells, leading to larger organoid sizes.

Table 1. Mouse models of ASD-associated genetic mutations and their phenotypes.

Gene	Models	Features	Sensory-related phenotypes	Reference
Synapse formation and function-related genes				
Shank1	Knockout mice	Loss of *Shank1* in parvalbumin(PV)-positive interneurons disrupted E/I balance, reducing both excitatory inputs and inhibitory outputs to pyramidal neurons in the hippocampus.	Not tested	Mao et al., (2015) [91]
	Knock-in mice (p.R882H)	In *SHANK1*(R882H) knock-in mice, reduced mGluR1-IP3R1 calcium signaling was observed, which corresponded with the manifestation of social deficits and repetitive behaviors.	Not tested	Qin et al., (2022) [92]
Shank2	Knockout mice	*Shank2* deficiency led to impaired NMDA receptor function, which may contribute to ASD-like behaviors. Restoring NMDAR function alleviated social impairments. Indirectly enhancing NMDAR activity through mGluR5 modulation presents a promising therapeutic approach.	Not tested	Won et al., (2012) [93]
	Knockout mice	In female *Shank2* knockout mice, deficits in signaling were observed within social attachment circuits, including the medial preoptic area, which resulted in reduced maternal bonding with their pups.	Not tested	Grabrucker et al., (2021) [94]
Shank3	Knockout mice	In *Shank3B* knockout mice, excitatory pyramidal neurons in the somatosensory cortex exhibited enhanced activity, whereas inhibitory interneurons showed diminished responsiveness.	Hypersensitivity to mild tactile stimuli	Chen et al., (2020) [68]
	Knock-in mice (e21-InsG)	*SHANK3*(e21-InsG) knock-in mice displayed ASD-like behaviors and impairments in hippocampal excitatory transmission, marked by altered NMDA receptor responses. These changes suggest that an imbalance between excitatory and inhibitory signaling underlies the observed phenotype.	Not tested	Speed et al., (2015) [95]
	Heterozygous knockout mice	*Shank3* haploinsufficiency caused aberrant actin cytoskeleton regulation and impaired NMDA receptor trafficking in excitatory neurons of the prefrontal cortex, contributing to an imbalance between excitatory and inhibitory signaling.	Not tested	Duffney et al., (2015) [96]
	Knockout mice	*Shank3*$^{\Delta e4\text{-}9}$ in mice induced neuronal hyperactivity by altering dendritic spine morphology and disrupting the excitatory/inhibitory balance within the PFC–BLA circuit, ultimately leading to impaired social behavior.	Not tested	Kim et al., (2022) [97]
Nlgn1	Knockout mice	In *Nlgn1* knockout mice, impaired spatial memory and increased repetitive grooming behavior were observed. These phenotypes was linked to a reduced NMDA/AMPA ratio and deficits in hippocampal long-term potentiation, which contribute to an excitatory/inhibitory imbalance relevant to ASD.	Not tested	Blundell et al., (2010) [98]
	Knockout mice	*Nlgn1* deficiency in the striatum resulted in hyperactivity of dopamine receptor D2-expressing medium spiny neurons, which was correlated with excessive restricted and repetitive behaviors.	Not tested	Lv et al., (2025) [99]
Nlgn3	Knockout mice	*Nlgn3* knockout mice exhibited disrupted synaptic plasticity and heterosynaptic competition defects reminiscent of those seen in Fragile X syndrome, suggesting a shared synaptic pathophysiology.	Not tested	Baudouin et al., (2012) [100]
	Knock-in mice (p.R451C)	In *NLGN3*(R451C) knock-in mice, an increased inhibition-to-excitation ratio onto Purkinje cells and reduced climbing fiber activity were observed. These findings indicate that NLGN3 plays a critical role in cerebellar development and may contribute to ASD-like behaviors.	Not tested	Lai et al., (2021) [101]

Table 1. continued

Gene	Models	Features	Sensory-related phenotypes	Reference
Syngap1	Heterozygous knockout mice	*Syngap1* haploinsufficiency selectively affected excitatory neurons in the forebrain, resulting in increased excitatory synaptic activity and cognitive deficits. This disruption caused a secondary imbalance between excitatory and inhibitory signaling, leading to persistent brain dysfunction into adulthood.	Not tested	Ozkan et al., (2014) [102]
	Heterozygous knockout mice	Haploinsufficiency of *Syngap1* in mice led to alterations in spine size and synaptic strength of indirect pathway striatal projection neurons, along with increased excitatory synaptic activity. Consistently, behavioral assessments revealed impaired rotarod motor performance and deficits in goal-directed behavior.	Not tested	Haetzel et al., (2024) [103]
Scn1a	Heterozygous knockout mice	*Scn1a* haploinsufficiency impaired GABAergic neurotransmission by reducing the excitability of forebrain interneurons, which led to an imbalance between inhibitory and excitatory signaling. This disruption contributed to ASD-like behaviors in mice, including deficits in social interactions, increased stereotyped behaviors, and impaired spatial memory.	Aversion to novel food odors / social odors	Han et al., (2012) [104]
	Heterozygous knockout mice	In *Scn1a* haploinsufficient mice, a delay in the GABA switch was observed, which has been identified as a cause of cognitive and social alterations resembling ASD-like features.	Not tested	Pizzamiglio et al., (2025) [105]
Neuronal development-related genes				
Cntnap2	Knockout mice	Real-time modulation of the excitatory/inhibitory balance in the prefrontal cortex of this mouse model rescued ASD-associated social deficits and hyperactivity, underscoring the critical role of E/I imbalance in ASD-like phenotypes.	Not tested	Selimbeyoglu et al., (2017) [67]
	Knockout mice	In *Cntnap2* knockout mice, selective impairment of inhibitory synaptic transmission onto hippocampal CA1 pyramidal neurons resulted in an excitatory/inhibitory imbalance.	Not tested	Jurgensen et al., (2015) [106]
	Knockout mice	Ectopic neuronal connectivity of perineuronal nets and PV-positive interneurons was formed across various sensory cortical regions and developmental stages in this mouse model, which may contribute to E/I balance disruptions associated with ASD.	Aberrant corticothalamic connectivity in primary sensory cortices	Gandhi et al., (2023) [107]
	Knockout mice	In the *Cntnap2* mouse model of autism, hyperexcitability within the reticular thalamic nucleus was identified, potentially disrupting thalamocortical inhibitory control and thereby contributing to ASD-associated behavioral phenotypes.	Not tested	Jang et al., (2025) [108]
Cntnap4	Knockout mice	*Cntnap4* knockout mice exhibited reduced inhibitory output from GABAergic basket cells and enhanced dopamine release in the nucleus accumbens. They also displayed abnormal sensory-motor gating and excessive grooming behaviors.	Auditory hypersensitivity	Karayannis et al., (2014) [109]
	Knockout mice	In male *Cntnap4* knockout mice, GABAergic transmission and receptor expression in the basolateral amygdala were reduced, accompanied by a decrease in gut Lactobacillus abundance.	Not tested	Zhang et al., (2022) [110]
Tbr1	Heterozygous knockout mice	*Tbr1* haploinsufficient mice displayed ASD-like social behavior and impaired amygdala axonal projection, linked to E/I imbalance, fewer c-fos-positive neurons and lack of Grin2b induction.	Not tested	Huang et al., (2014) [111]
	Heterozygous knockout mice	In *Tbr1* haploinsufficient mice, basolateral amygdala neurons exhibited aberrant axonal projections and mistargeting. These mice also displayed disrupted default-mode-network connectivity and reduced social interaction, hallmarks of ASD-like phenotypes, which were alleviated by deep-brain stimulation of the basolateral amygdala.	Not tested	Hsu et al., (2024) [112]

Table 1. continued

Gene	Models	Features	Sensory-related phenotypes	Reference
Foxp1	Conditional knockout mice	Brain-specific *Foxp1* deletion in mice disrupted striatal development and produces subtle hippocampal alterations including abnormal neuronal morphology and an E/I imbalance in the CA1 region.	Not tested	Bacon et al. (2015) [113]
	Conditional knockout mice	Cortex-specific *Foxp1* deletion disrupted barrel formation in the primary somatosensory cortex, impaired growth of layer IV neurons, and led to abnormal thalamocortical synapse formation. Mutant mice consequently showed delayed tactile responses and heightened sensitivity to tactile stimuli.	Barrel formation defects, abnormal tactile response	Li et al., (2023) [114]
Gene expression or Protein synthesis-related genes				
Eif4ebp2	Knockout mice	Deletion of *Eif4ebp2* enhanced translation of neuroligin, postsynaptic proteins implicated in ASD, and elevated the excitatory-to-inhibitory synaptic input ratio in mice, thereby eliciting ASD-like behaviors.	Barrel formation defects, abnormal tactile response	Gkogkas et al., (2013) [115]
	Conditional knockout mice	In mice with cerebellar *Eif4ebp2* deficiency, Purkinje cells were reduced in number and fired action potentials with greater regularity. While these animals showed impairments in spatial memory and motor learning, they did not exhibit ASD-like behaviors.	Net tested	Hooshmandi et al., (2021) [116]
Mecp2	Conditional knockout mice	In *Mecp2* knockout mice, tactile-sensory processing abnormalities were linked to reduced GABA A receptor expression, resulting in deficient presynaptic inhibition at low-threshold mechanoreceptor terminals.	Tactile hypersensitivity, tactile avoidance	Orefice et al., (2016) [69]
	Transgenic duplicated mice	In *MECP2*-duplication mice, layer II/III neurons in the primary visual cortex displayed unusually high trial-to-trial reliability of visually evoked responses, coupled with reduced response amplitudes and dampened intrinsic activity fluctuations.	Abnormalities in visual processing	Ash et al., (2022) [117]
Fmr1, Tsc2	*Fmr1* hemizygote, *Tsc2* heterozygote knockout mice	In both the tuberous sclerosis complex (TSC) and fragile X syndrome (FXS) mouse models, excessive protein synthesis triggered by mTOR hyperactivation in TSC or loss of FMRP in FXS disrupted the E/I balance, resulting in synaptic dysfunction and behavioral impairments.	Not tested	Auerbach et al., (2011) [118]
	Fmr1 hemizygote, *Tsc2* heterozygote knockout mice	In both mouse models, sensory deprivation disrupted PV homeostatic plasticity in the primary somatosensory cortex. Moreover, the expected increase in PV-neuron excitability following sensory enrichment was absent in heterozygous *Tsc2* mice, indicating a breakdown in the bidirectional homeostatic regulation of PV circuits.	Not tested	Monday et al., (2025) [119]
Pten	Conditional knockout mice	Loss of *Pten* in interneurons depleted somatostatin (SST)-positive interneurons, raising the PV/SST ratio, driving ectopic PV-cell projections into cortical layer I, and altering inhibition onto glutamatergic neurons. This E/I imbalance led to social deficits and abnormal EEG power.	Not tested	Vogt et al., (2015) [120]
	Conditional knockout mice	Selective *Pten* deletion in PV- and SST-expressing interneurons elicited ASD-like phenotypes in mice, including social deficits, impaired motor coordination and learning, and heightened repetitive behaviors.	Not tested	Shin et al., (2021) [121]

This finding mirrors the brain enlargement observed in clinical patients carrying CNTNAP2 mutations [80]. However, a significant limitation of current in vitro models is that iPSC-derived cells, organoids, and assembloids largely reflect fetal developmental stages and often fail to recapitulate the mature physiological characteristics observed in postnatal tissues. Therefore, developing advanced protocols to promote further maturation and model postnatal developmental trajectories is a critical next step for the field.

Currently, the majority of ASD studies using hiPSC-derived organoid models primarily focus on cerebral organoids that simulate cortical development and functions [66, 81, 82]. Although the cortex is crucial for processing and storing sensory information, a cortex-centric view overlooks the essential earlier stages of the somatosensory system, including sensory neurons, DRG, and the thalamus, which receive and relay incoming signals. Consequently, this narrow perspective inevitably leads to an incomplete and potentially misleading picture of the pathophysiology underlying sensory dysfunction in ASD. From this perspective, to overcome the limitations of single-region models, researchers have begun developing assembloids. This innovative approach involves integrating multiple, distinct region-specific organoids to recapitulate the complex neural circuits implicated in ASD. As previously mentioned, the imbalance between excitatory and inhibitory neuronal activity is proposed to be a major driver of ASD pathophysiology. In this regard, traditional cerebral organoid models primarily generating excitatory neurons have limitations in modeling E/I networks. However, recent advancements have enabled the development of ganglionic eminence organoids, where inhibitory neurons are generated and migrate to cortical areas [83, 84]. These organoids can now be fused with cerebral organoids to create cortical-ganglionic assembloids, allowing for the construction of functional E/I networks. Additionally, methods for producing thalamic organoids, specifically those mimicking the ventral posterior lateral thalamic nuclei capable of generating inhibitory neurons in the thalamic reticular nucleus, have further expanded the scope of these models [85]. By integrating these techniques, researchers can now create brain organoids that recapitulate balanced E/I networks, providing a robust platform for testing the E/I imbalance hypothesis in ASD. Recent organoid studies have revealed how ASD-associated genetic variants can disrupt the development, maturation, and reciprocal regulation of excitatory and inhibitory neurons, potentially leading to aberrations in the E/I balance of the somatosensory system. Building on this, the developing assembloid models will allow us to directly test whether E/I imbalances are induced at the network level using electrophysiological recordings and calcium/voltage imaging. This will provide an avenue to investigate underlying mechanisms and explore potential rescue strategies. Ultimately, knowledge gained from these in vitro systems can be translated to in vivo animal models to verify whether correcting these circuit-level dysfunctions can ameliorate abnormal social behaviors.

An advanced assembloid model was recently developed to integrate multiple brain regions. For example, cortical spheroids, spinal spheroids, and skeletal muscle spheroids were generated independently from hiPSCs and then physically connected to form a motor system assembloid [86]. Similarly, sensory system assembloids were created by connecting sensory neurons, the spinal cord, thalamus, and cortex [87]. The functional integrity of these assembloid models was validated through calcium imaging and electrophysiological analyses, demonstrating descending pathways from the CNS to the PNS in the motor system assembloid model and ascending pathways from the sensory system to the CNS in the sensory system assembloid.

While multi-regional assembloids offer exciting new avenues for ASD research, significant challenges concerning their reproducibility and reliability must be addressed. A primary concern is the considerable variability in model properties. As demonstrated by Lancaster and colleagues, organoids intended to model the same brain region can exhibit different cellular compositions and developmental stages depending on the differentiation protocol used [88]. Furthermore, significant variations can arise from the specific iPSC line employed, and even between different batches of the same line. Consequently, there is a critical need to standardize protocols to generate organoids with compositions that more faithfully recapitulate their in vivo counterparts. Efforts must also focus on minimizing process-induced variability and developing robust metrics for quality control to validate the maturity and composition of each organoid and assembloid prior to functional analysis. A further limitation lies in how these assembloids model neural connectivity. Current methods typically rely on fusing organoids via direct physical contact. This approach, however, does not fully replicate the in vivo environment, where distinct brain regions are connected by long-range axonal projections. Recent research has demonstrated that connecting two cerebral organoids via a bundle of reciprocally extended axons, rather than through direct contact, promotes the development of more mature neural networks. Furthermore, during their trajectory, these developing axons are influenced by a complex milieu of various neuronal and non-neuronal cells, which are absent in current assembloid models. Although this simplified system allows for the direct assessment of how the constructed circuit contributes to the acquisition and processing of sensory information, its physiological relevance remains a key question. Therefore, findings from assembloid models must be critically validated against data from more complex systems, such as in vivo non-human models or clinical data analyses.

Beyond these structural challenges, a major functional limitation is that assembloids cannot receive direct sensory inputs, making it difficult to model the experience-dependent plasticity central to sensory development. To circumvent this, researchers are exploring methods to mimic sensory signaling, such as using optogenetics to activate specific neural populations with light or applying chemical agonists to stimulate sensory pathways. However, a significant hurdle remains in designing these artificial stimuli with physiologically relevant resolution, duration, and intensity. It is also essential to validate whether these inputs can genuinely induce long-term, plasticity-like changes in the network. This challenge is amplified when considering that ASD often involves deficits in sensory discrimination, not just detection. As current assembloid systems lack the resolution to model these nuanced perceptual deficits, future work should move beyond assessing the propagation of single inputs to investigate how these models integrate and discriminate between multiple sensory signals. The aforementioned techniques, such as patterned optogenetic or chemical stimulation, provide a promising avenue to begin exploring these more sophisticated network functions, bridging the gap to real-world sensory impairments in ASD (Table 2).

CONCLUSIONS

Further advancements are necessary to accurately mimic and validate E/I networks at every stage of the somatosensory system. As discussed, future research will greatly benefit from integrating assembloid models with the aforementioned advanced techniques, such as optogenetics and calcium/voltage imaging, to systematically explore the effects of E/I imbalance on network function. Beyond these in vitro analyses, a critical next step is to bridge the gap to in vivo validation. Further advancements are necessary to accurately mimic and validate E/I networks at every stage of the somatosensory system. As discussed, future research will greatly benefit from integrating assembloid models with the aforementioned advanced techniques, such as optogenetics and calcium/voltage imaging, to systematically explore the effects of E/I imbalance on network function. Beyond these in vitro analyses,

Table 2. A summary of hiPSC-derived brain organoid and assembloid models in research for ASD or related disorders.

Models	hiPSC source	Genes	Features	Reference
Forebrain organoid	Patient-derived	Idiopathic ASD	This study compared DEGs between boys with ASD and their unaffected fathers using forebrain organoids. It identified an imbalance in excitatory cortical neuron subtypes and differential expression of transcription factors during early neurogenesis. Notably, organoids derived from macrocephalic ASD patients showed an excess of excitatory cortical neurons, whereas those from normocephalic ASD patients exhibited a reduction.	Jourdon et al., (2023) [79]
Forebrain organoid	Patient-derived	*CNTNAP2* (c.3709DelG)	Forebrain organoids derived from iPSCs of patients carrying the homozygous c.3709DelG mutation in *CNTNAP2* exhibited abnormalities in embryonic cortical development, characterized by increased neural progenitor cell proliferation and enlarged organoid size.	Jong et al., (2021) [80]
Telencephalic organoids	Patient-derived	*FOXG1*	iPSCs derived from ASD patients with macrocephaly and their unaffected family members were used to investigate neurodevelopmental process. The study demonstrated that FOXG1 overexpression resulted in excess of GABAergic inhibitory neurons, thereby disrupting the E/I balance.	Mariani et al., (2015) [122]
Telencephalic organoids	CRISPR-edited	*SHANK3*	Neurons in *SHANK3* haploinsufficient organoids exhibited impairments in intrinsic properties and excitatory synaptic function. In addition, dysregulated expression of multiple clustered protocadherins was observed.	Wang et al., (2022) [123]
Cerebral organoids	CRISPR-edited	*CHD8*	*CHD8* haploinsufficiency accelerated the production of inhibitory neurons while delaying excitatory neuron generation, thereby causing an imbalance in neuronal development. Additionally, it induced abnormal organoid overgrowth, a phenotype that mirrors the macrocephaly seen in ASD patients with CHD8 mutations.	Villa et al., (2022) [124]
Cerebral organoids	Patient-derived	*Idiopathic ASD*	Cerebral organoids derived from autistic infants with more severe social and cognitive impairments exhibited accelerated growth and larger size. Moreover, increased expression of the Ndel1 protein was associated with this organoid overgrowth phenotype.	Courchesne et al., (2024) [125]
Cortical Organoids and GABAergic-enriched organoids	Patient-derived	*TCF4*	The study explored how pathogenic variants in *TCF4* disrupt human neural development. These mutations reduced the proliferation of neural progenitor cells and impaired neuronal differentiation, leading to decreased neuronal activity. This abnormal developmental phenotype was shown to be linked to the downregulation of Wnt signaling pathways and decreased expression of SOX family genes.	Papes et al., (2022) [126]
Assembloid (hCO, hSO)	CRISPR-edited	*SMAD4, CSDE1, TERF2, LNPK*	A CRISPR/Cas9 pooled screen conducted in a human assembloid model identified 46 genes, including several linked to ASD, that directly disrupt interneuron development and migration.	Meng et al., (2023) [127]
Assembloid (hCO, hStrO, hMeO, hDiO)	CRISPR-edited	*ASH1L*	In a model employing brain loop circuits built from four region-specific organoids, neuronal hyperactivity was observed in every region except the human striatal organoids. This outcome suggests that ASD-associated genes may contribute to functional impairments at the circuit level.	Miura et al., (2024) [128]
Assembloid (hCS, hSpS, hSkM)	Healthy control	-	A 3D cortico-spinal-muscle assembloid that form functional, long-range motor circuits was generated. Functional connectivity was validated by cortical stimulation-induced muscle contraction. This system enables long-term in vitro modeling of human motor circuit development and disease.	Andersen et al., (2025) [86]
Assembloid (hCO, hDiO, hdSpO, hSeO)	CRISPR-edited	*SCN9A*	A four-part human assembloid was developed to model the ascending sensory pathway, demonstrating functional connectivity from sensory neurons to the cortex and synchronized network activity. In addition, loss-of-function mutations in the *SCN9A* gene were used to demonstrate that impairment of the NaV1.7 sodium channel disrupts network synchrony, highlighting the capacity of thie model to capture complex interactions in human sensory circuits.	Kim et al., (2025) [87]

hCO human cortical organoids, *hSO* human subpallial organoids, *hStrO* human striatal organoids, *hMeO* human medial ganglionic eminence organoids), *hDiO* human diencephalic organoids, *hCS* cortical spheroids, *hSpS* spinal cord spheroids, *hSkM* skeletal muscle spheroids, *hdSpO* human dorsal spinal cord organoids, *hSeO* human sensory organoids

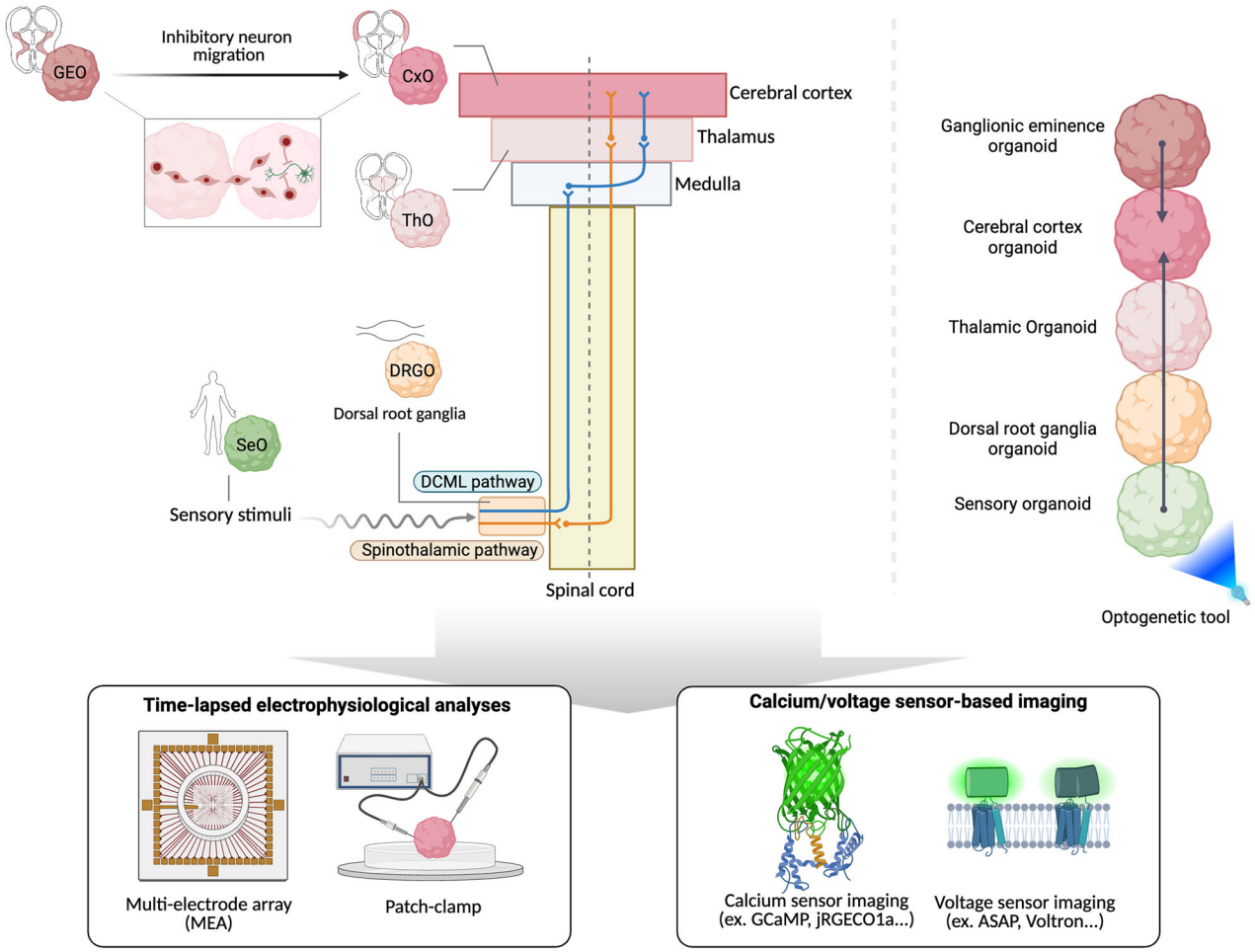

Fig. 3 Examples of somatosensory system organoid modeling and measurement techniques. Region-specific organoids, including sensory nerve, spinal cord, thalamus, ganglionic eminence and cortex, are fused to model the human somatosensory system. Neuronal activity and connectivity are assessed using multi-electrode array(MEA) recording and calcium or voltage imaging. human somatosensory system with distinct organoids. Created with BioRender.com.

a critical next step is to bridge the gap to in vivo validation. To this end, xenotransplantation approaches, where human brain organoids are implanted into the brains of animal models, are emerging as a powerful strategy [89, 90]. This method offers the unique advantage of allowing human-derived neural circuits to mature and be tested within a living network system. However, significant species-specific differences between the human implant and the host (e.g., a rodent) can prevent the circuits from becoming fully functional or may cause them to operate in an altered, constrained manner. Despite this, by applying these innovative methods in parallel, researchers aim to elucidate the causality between sensory integration deficits and ASD pathogenesis, deepen our understanding of the core pathological mechanisms, and ultimately pave the way for developing effective therapeutic interventions (Fig. 3).

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Taeyeon Kim, Juwon Lee, and Jinsoo Seo conceived the idea of this review. Taeyeon Kim, Juwon Lee, Jiye Lee, Hyeokjin Jo, and Jinsoo Seo wrote the manuscript. Yohan Oh and Yong Jun Kim provided scientific insights and reviewed the manuscript. Taeyeon Kim and Juwon Lee worked on the figures and tables.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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