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REVIEW

Tactile sensory processing deficits in genetic mouse models of autism spectrum disorder

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Abstract

Altered sensory processing is a common feature in autism spectrum disorder (ASD), as recognized in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). Although altered responses to tactile stimuli are observed in over 60% of individuals with ASD, the neurobiological basis of this phenomenon is poorly understood. ASD has a strong genetic component and genetic mouse models can provide valuable insights into the mechanisms underlying tactile abnormalities in ASD. This review critically addresses recent findings regarding tactile processing deficits found in mouse models of ASD, with a focus on behavioral, anatomical, and functional alterations. Particular attention was given to cellular and circuit-level functional alterations, both in the peripheral and central nervous systems, with the objective of highlighting possible convergence mechanisms across models. By elucidating the impact of mutations in ASD candidate genes on somatosensory circuits and correlating them with behavioral phenotypes, this review significantly advances our understanding of tactile deficits in ASD. Such insights not only broaden our comprehension but also pave the way for future therapeutic interventions.

KEYWORDS
autism spectrum disorder (ASD), mouse models, sensory processing, somatosensory cortex, tactile sensitivity

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AP, action potential; AS, Angelman syndrome; ASD, autism spectrum disorder; BK_{Ca}, calcium-activated potassium channels; CALB2, calbindin 2; CASPR2, contactin-associated protein-like 2; CaV2.2, voltage-gated calcium channel 2.2; CNS, central nervous system; *CNTNAP2*, contactin associated protein 2 gene; CNV, copy number variation; DCML, dorsal column-medial lemniscus; DCN, dorsal column nuclei; DRG, dorsal root ganglion; DSM, Diagnostic and Statistical Manual of Mental Disorders; E/I, excitation/inhibition; EEG, electroencephalography; *EN2*, homeobox protein engrailed-2 gene; *FMR1*, Fragile X messenger ribonucleoprotein 1 gene; fMRI, functional magnetic resonance imaging; FMRP, Fragile X mental retardation protein; FOXP, forkhead box P; *FOXP1*, forkhead box P1 gene; GABA, gamma-aminobutyric acid; $GABA_AR$, gamma-aminobutyric acid type A receptors; *GABRB3*, GABAA receptor subunit β3 gene; GAD1, glutamate decarboxylase 1; HCN, hyperpolarization-activated cyclic nucleotide-gated channels; Kv2.1/3.1, voltage-dependent potassium channel 2.1 and 3.1; KO, knockout; L2/3, cortical layers 2 and 3; L4, cortical layer 4; L5, cortical layer 5; LTMR, low-threshold mechanoreceptor; *MECP2*, X-linked methyl-CpG-binding protein 2 gene; MEG, magnetoencephalography; MGE, medial ganglion eminence; NKCC1, sodium, potassium, chloride co-transporter; Nkx2.1, NK2 homeobox 1; NMDA, N-methyl-D-aspartate receptor; NPY, neuropeptide Y; OIS, optical imaging of intrinsic signals; P, postnatal day; PAK, serine/threonine-protein kinase; PNS, peripheral nervous system; PPI, pre-pulse inhibition test; PSD, postsynaptic density; PV, parvalbumin; RP, receptor potential; RTT, Rett syndrome; S1, primary somatosensory cortex; S1HL, primary somatosensory cortex of the hind limb; S1HP, primary somatosensory cortex of the hind paw; S2, secondary somatosensory cortex; SC, spinal cord; *SHANK2*, SH3 and multiple ankyrin repeat domains 2 gene; *SHANK3*, SH3 and multiple ankyrin repeat domains 3 gene; SNAP, somatosensory nose-poke adapted paradigm; SSC, somatosensory cortex; SST, somatostatin; *SYNGAP1*, synaptic Ras GTPase activating protein 1 gene; tNORT, textured novel object recognition test; *UBE3A*, ubiquitin-protein ligase E3A; V1, primary visual cortex; VGLUT1/2, vesicular glutamate transporter 1 and 2; VPM, ventral posteromedial thalamic nucleus; WN, whisker nuisance test; wS1, whisker primary somatosensory cortex; WT, wild type.

This article is part of the special issue "Autism Spectrum Disorder".

1 | INTRODUCTION

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by alterations in social interaction, repetitive behaviors and interests, that include atypical sensory responses (American Psychiatric Association, 2013). ASD is typically diagnosed within the first 3 years of life, with symptoms persisting into adulthood and exhibiting varying degrees of severity across individuals along a continuum (American Psychiatric Association, 2013). The core behavioral features of ASD can co-occur with other symptoms such as emotional deficits, anxiety and depression, signs of aggression, intellectual disability, speech and language delay, motor dysfunction, hyperactivity, epilepsy, sleep disturbances, metabolic disorders, and gastrointestinal problems (Balasco et al., 2020; Lord et al., 2018; Reis & Monteiro, 2024; Takumi et al., 2020). Atypical sensory responses are often observed in ASD, with approximately 90% of those afflicted showing altered responses to visual, auditory, olfactory, gustatory, or tactile stimuli (Balasco et al., 2020). Because sensory impairments are observed very early in ASD, they anticipate (and, perhaps, underlie) social deficits (Baranek et al., 2013). In fact, a correlation has been observed between the severity of sensory disruptions and behavioral phenotypes in individuals with ASD (Thye et al., 2018). In multiple species, touch is closely linked to the development of communication and social behaviors (Hertenstein et al., 2007) and is essential for the neurodevelopment of neocortical areas where sensory stimuli are represented, such as the somatosensory cortex (Carozza & Leong, 2021). Therefore, altered tactile processing takes special significance in ASD, potentially impacting human bonding and environment exploration and causing social withdrawal.

Altered responses to tactile stimuli are observed in 60% of ASD patients displaying sensory abnormalities (Tomchek & Dunn, 2007). Different studies involving self- and parent questionnaires and interviews, as well as direct observation of behavior, have identified altered behavioral responses to tactile stimuli in the form of lower or increased detection thresholds, avoidance/defensive behaviors, lack of habituation to repetitive stimuli, as well as abnormal tactile-seeking behavior (Espenhahn et al., 2023; Foss-Feig et al., 2012; McKernan et al., 2020; Puts et al., 2014; Rogers et al., 2003; Tomchek & Dunn, 2007). Psychophysics studies with both children and adults diagnosed with ASD also reported altered behavioral responses to electrical, piezo-electrical, and vibro-tactile stimulation applied to body regions such as the fingers, palm, or forearm (Cascio et al., 2008; Failla et al., 2017; Sapey-Triomphe et al., 2019). A few studies have also found altered functional responses of the somatosensory system in response to tactile stimulation in ASD patients using electroencephalography (EEG; Espenhahn et al., 2021), magnetoencephalography (MEG; Khan et al., 2015), and functional magnetic resonance imaging (fMRI; Kaiser et al., 2016). However, the neurophysiological correlates of these alterations remain poorly understood.

One approach to studying the neurobiology of ASD and unraveling its functional impact on brain circuits is to conduct investigations on animal models. Despite its complex etiology, and potential multifactorial origin, ASD has a strong genetic component with 20–30% of the cases being associated with de novo mutations in more than 1000 genes (Constantino et al., 2010; Le Couteur et al., 1995; Sandin et al., 2014; Volfovsky, 2024). Furthermore, there is a significantly higher concordance rate in monozygotic twins when compared with dizygotic twins (Sandin et al., 2014), and ASD prevalence tends to cluster in family trees (Lord et al., 2018). Of note, monogenic mutations in particular genes are highly penetrant and account for at least 5% of ASD cases (Yoo, 2015). They are typically associated with other congenital conditions such as Angelman, Fragile-X, Rett, and Phelan-McDermid Syndromes, where ASD features co-occur with other symptoms (Lord et al., 2018). Rodents carrying specific mutations in ASD candidate genes, such as *Shank3*, *Fmr1*, and *Mecp2*, can play a critical role in the investigation of tactile sensory alterations in ASD. These animal models display several ASD-like behaviors, such as increased anxiety, abnormal social behavior, deficits in learning and memory (Gemelli et al., 2006; Peça et al., 2011; Saré et al., 2019), as well as altered sensory responses at functional and behavioral levels (Chen et al., 2020; He et al., 2017; Orefice et al., 2016; Zhang et al., 2014). Tactile deficits, however, have received far less attention in these models compared to impairments in other sensory modalities, such as hearing. Here, we review recent studies focusing on behavioral, histological, and functional correlates of tactile sensory deficits in genetic mouse models of ASD.

2 | PROCESSING OF TACTILE STIMULI BY THE SOMATOSENSORY SYSTEM

The somatosensory system is characterized by three fundamental primary functions: proprioception (sense of oneself), interoception (visceral sensation), and exteroception (sense of interaction with the outside world; Mundy et al., 2010). The transduction of touch by the sensory afferents enervating the skin is the core function of the exteroceptive branch in humans. As a result, the somatosensory system includes a variety of modalities, pathways, and receptors to translate a wide and dynamic range of tactile inputs that enable object recognition, texture discrimination, sensorimotor feedback, and social exchange (Abraira & Ginty, 2013). Stimulus detection on glabrous skin occurs via specialized mechanosensory cells, called low-threshold mechanoreceptors (LTMR), that respond to low-force indentation of the skin. These mechanosensory neurons arising from the dorsal root ganglion (DRG) have end organ structures in the skin called auxiliary cells (Meissner and Pacinian corpuscles, Merkel cells, or Ruffini endings), which vary in size, shape, morphology, and location in the skin and are fundamental for translating different properties of tactile inputs such as force, frequency, direction, texture, and localization (Fleming & Luo, 2013; Nakatani et al., 2015; Roudaut et al., 2012). Different LTMRs also directly innervate hair follicles and are responsible for transducing tactile inputs mediated by hairy skin (Roudaut et al., 2012). The main role of mechanosensory neurons is to transduce mechanical stimuli into electrophysiological potentials

and conduct them to the central nervous system (CNS). Receptor potentials (RPs) are locally generated at the skin in LMTRs in response to mechanical stimulation in a graded fashion, that is, proportionally to stimulus intensity (Handler & Ginty, 2021; Maksimovic et al., 2014). When these reach threshold, action potentials (AP) are generated and conducted to the CNS by numerous nerve fibers called afferent fibers. Each sub-type of LTMRs has fibers with different biophysical properties, including distinct conduction velocities, that contribute to multidimensional encoding and transmission of tactile information (Handler & Ginty, 2021). The two main ascending afferent pathways for tactile stimuli in the somatosensory system include the dorsal column-medial lemniscus (DCML) pathway, for signals coming from the upper and lower body or the posterior third of the head; and the trigeminal nerve pathway, for signals coming from the face (Kandel et al., 2013; Purves et al., 2004). Figure 1 depicts the ascending somatosensory pathways from the skin to the brain in humans.

In the DCML pathway, tactile sensory information signaling starts when an RP is generated in the skin and reaches the AP threshold. The AP then travels along the LTMR cell (or first-order neuron or primary somatosensory neuron) axon until it reaches the spinal cords' (SC) dorsal horn. From the dorsal horn the pathway continues according to receptor type and body location in the dorsal column nuclei (DCN) up to the brainstem (first synapse), projecting ipsilaterally to the medial lemniscus. From the medial lemniscus, this neuron travels to the ventral posterior nucleus in the thalamus, where it joins with the trigeminal system (second synapse). Finally, the third-order neuron projects to cortical regions of the brain, more specifically, to layers 4 and 5 (L4/5) of the somatosensory cortex (SSC) (R. Barker et al., 2012; Chauhan et al., 2021). Here, the electrical signal is scrutinized and processed in the primary (S1) and secondary (S2) somatosensory cortices. In humans, S1 is located in the postcentral gyrus and is divided into four different regions: Brodmann's area 1, 2, 3a, and 3b, each with their own body map (Brodmann & Garey, 2006; Delhaye et al., 2018; Purves et al., 2004). Figure 2a shows the organization of human S1. S2 is located in the superior bank of the sylvian fissure and the posterior parietal cortex (Schluppeck & Francis, 2015).

Human somatosensory pathways are well preserved in rodents, including mice (O'Connor et al., 2021; Robertson & Baron-Cohen, 2017). However, besides having glabrous and hairy skin mechanoreceptors as described above, rodents also display specialized guard hairs, called whisker or vibrissa, located in the snout (Ebara et al., 2002). These whiskers can move back and forth (a movement called whisking) at variable frequencies to scan the environment, providing both spatial and textural information (Adibi, 2019; Berg & Kleinfeld, 2003). As such, they are critical for rodent's tactile exploration of the environment, together with their paws. All whiskers are innervated by trigeminal ganglion neurons that terminate with end organs that are also found in hairy skin, such as Merkel cells, lanceolate endings, and free nerve endings (Bosman et al., 2011). Neurons from each whisker follicle ascend through the trigeminal pathway in somatotopically organized discrete clusters called "barrelettes" in the brainstem nuclei, "barreloids" in the thalamus, and "barrels" in the S1, forming the whisker S1 (wS1) (or vibrissa S1, vS1, or barrel cortex) (Adibi, 2019; Petersen, 2019; Woolsey & Van der Loos, 1970). The wS1 is a somatotopic map in which each whisker on the snout is individually represented in the SSC by each barrel, allowing precise segregated processing of tactile inputs encoded by each whisker (Adibi, 2019). Although wS1 is a specialized and highly organized region of rodents' SSC, additional somatotopic representation of other body parts, such as the hindlimbs and forelimbs or the jaw, can be observed in their S1 (Díaz-Parra et al., 2017; Franklin & George, 2007; Sarko et al., 2011). Figure 2b shows the organization of the rodent's S1.

3 | TACTILE SENSORY PROCESSING DEFICITS IN GENETIC MOUSE MODELS OF ASD

Considering that the neural mechanisms underlying sensory processing are well conserved between humans and rodents (O'Connor et al., 2021; Robertson & Baron-Cohen, 2017), genetic mouse models of ASD are of great importance for the investigation of tactile sensory deficits in ASD, with the advantage of having a controlled genetic background. Studying tactile deficits in mice can, however, be a hard task as altered tactile responses are difficult to measure at the behavioral level. To reach this goal, researchers have to use tactile-guided learning paradigms or even adapt some classic rodent behavioral tests, such as the novel object recognition (Ennaceur & Delacour, 1988) and the pre-pulse inhibition (Ioannidou et al., 2018) tests to rely on tactile cues (Orefice et al., 2016, 2019). To study the underlying physiological alterations of the somatosensory cortex in mouse models of ASD, studies have also been employing electrophysiology (Zhang et al., 2014), two-photon imaging (He et al., 2017; Michaelson et al., 2018), and optical imaging of intrinsic signals (OIS) (Arnett et al., 2014) approaches to unveil circuit and cell-specific activity alterations. The genetic mouse models of ASD used so far to study altered tactile sensitivity are described below and summarized in Table 1.

3.1 | X-linked methyl-CpG-binding protein 2 (*Mecp2*)

X-linked methyl-CpG-binding protein 2 (*MECP2*) gene codes for a protein that binds to methylated DNA, thus having an important role in gene expression through chromatin architectural regulation (Lewis et al., 1992; Ragione et al., 2016; Zachariah & Rastegar, 2012). Mutations in this gene are the primary cause of Rett Syndrome (RTT), a neurological disorder commonly co-occurring with ASD (Rasalam et al., 2005). *Mecp2* loss of function mutations can cause increased anxiety, abnormal social behavior, and deficits in learning and memory in mice (Gemelli et al., 2006; Na et al., 2013).

Mecp2 KO mice, as well as mice with a *Mecp2* missense mutation commonly observed in Rett patients ($Mecp2^{R306C}$) (Lyst et al., 2013),

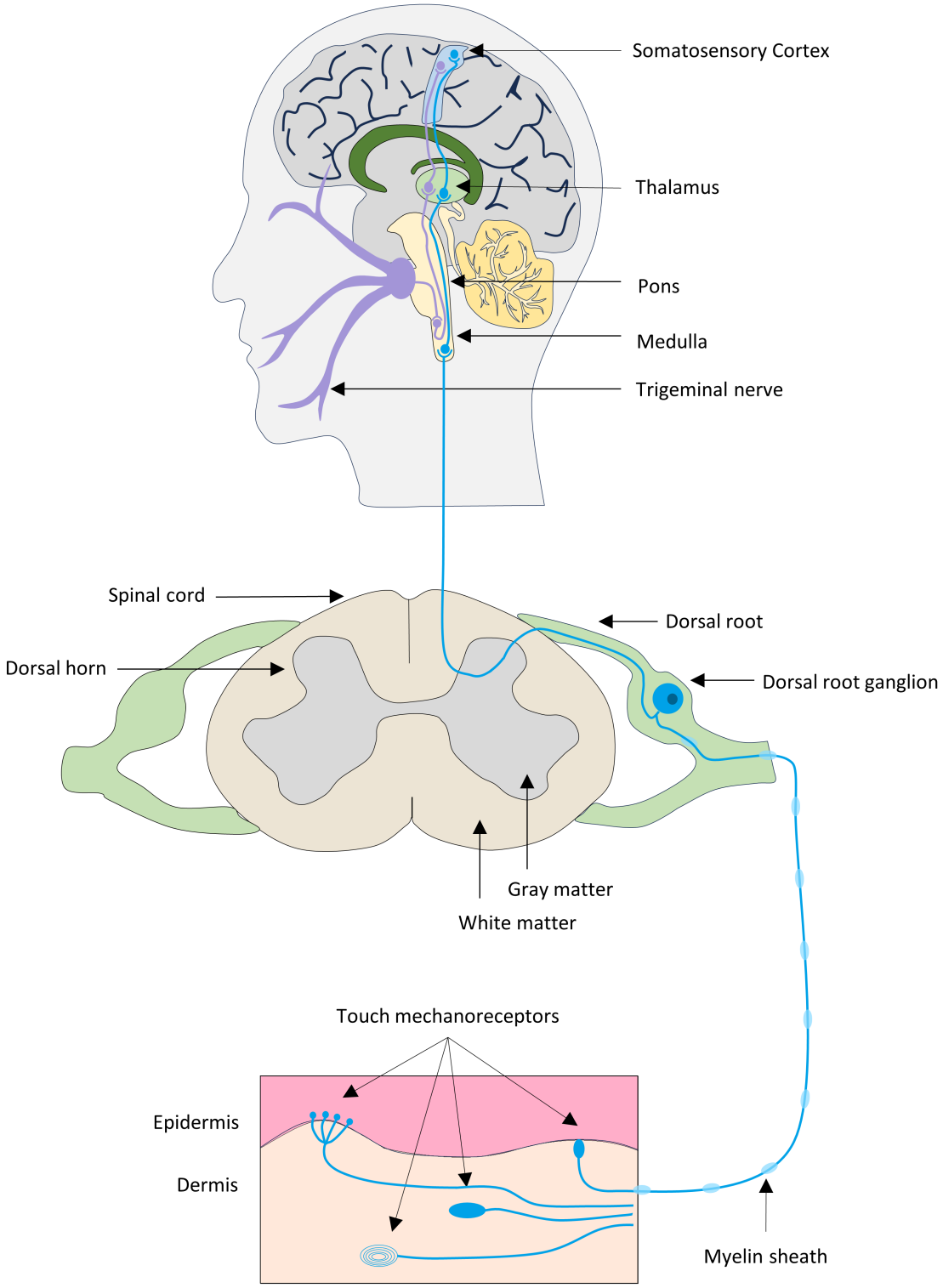

FIGURE 1 The human somatosensory system for transmitting and processing tactile stimuli. Tactile sensory stimuli coming from the periphery are sent to the brain through somatosensory neurons. Tactile stimuli transduced in the skin ascend through the dorsal column-medial lemniscus pathway (blue), if they originate in the upper and lower body, and the posterior third of the head or through the trigeminal nerve pathway (lilac), if they originate in the face. Tactile stimuli from the skin are transduced by mechanoreceptors and travel through the afferent first-order neuron axon that innervates auxiliary cells or hair follicles until they reach the dorsal horn in the spinal cord, through the dorsal root. From the dorsal horn, the pathway continues to the dorsal column tract at the back of the spinal cord according to receptor type and body location. The pathway continues in the dorsal column nuclei (DCN) until it reaches the medulla, where neurons synapse, stepping up to the second-order neuron. This neuron travels to the ventral posterior nucleus in the thalamus, where it joins with the trigeminal system, with incoming signals from the face, and the second synapse occurs. The third-order neuron then projects from the thalamus to the primary somatosensory cortex (S1).

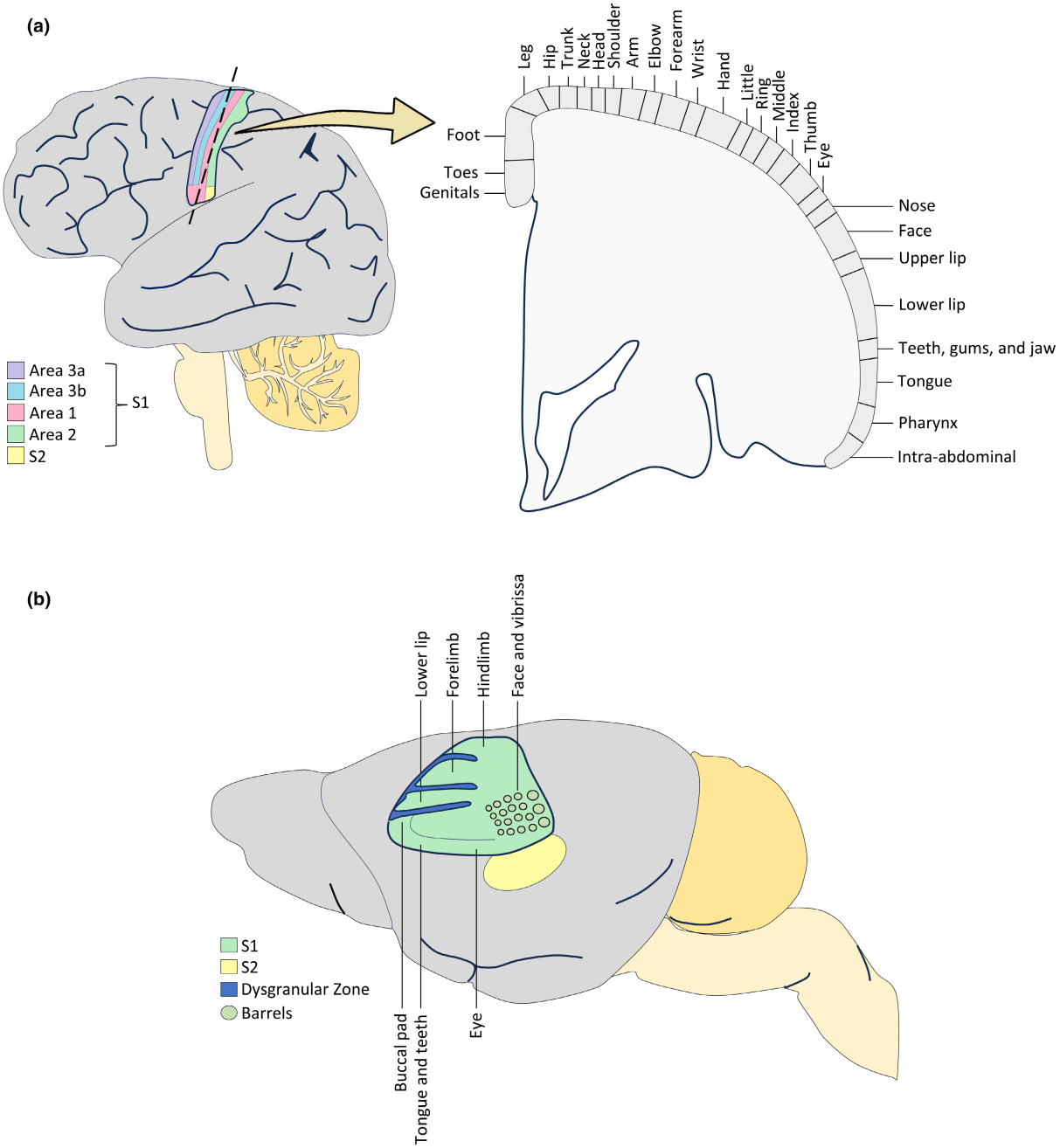

FIGURE 2 Human (a) and mice (b) somatosensory cortex functional organization. (a) Brodman areas 1, 2, 3a, and 3b (pink, green, lilac, and blue, respectively) of the primary somatosensory cortex (S1), and the secondary somatosensory cortex (S2; yellow) of the human brain. Each Brodman area of the S1 has its own homunculus. (b) Spatial location of the S1 (green) lower lip, forelimb (S1FL), hindlimb (S1HL), face and whisker, buccal pad, tongue, teeth, and eye cortical area, as well as the S2 (yellow), in the mouse brain.

show discrimination deficits in a textured version of the novel object recognition test (tNORT) without reduction of novelty-seeking behavior. Furthermore, increased responses have been reported in a tactile version of the pre-pulse inhibition test (tactile PPI), where an air puff tactile stimulus precedes the auditory stimulus (Orefice et al., 2016, 2019), suggesting hairy skin hypersensitivity. Notably, these hypersensitivity phenotypes may be rescued by region-specific deletion of *Mecp2* in the nervous system. Conditional *Mecp2* deletion in forebrain excitatory neurons does not seem to impact tNORT and tactile PPI behavioral outcomes, while conditional *Mecp2* deletion in the SC and primary somatosensory neurons leads to deficits in texture discrimination and hairy skin hypersensitivity in both behavioral tests (Orefice et al., 2016, 2019). Interestingly, selective expression of *Mecp2* in primary somatosensory neurons can rescue glabrous and hairy skin sensory deficits in *Mecp2* KO mice (Orefice et al., 2016).

At the molecular level, *Mepc2* KO mice exhibit a >80% decrease in $GABA_A$ receptor subunit β3 (GABRB3) in LTMR terminals located in the dorsal horn, suggesting that tactile hypersensitivity in this model may also arise because of insufficient inhibition of

TABLE 1 Principal findings of tactile sensory processing deficits in mouse models of ASD.

Candidate gene	Technique	Phenotype	Age	Sex	References
Mecp2	tNORT	Glabrous skin texture discrimination deficits	6 weeks	Male	(Orefice et al., 2016, 2019)
	Tactile PPI	Hairy skin hypersensitivity			
Gabrb3	Von Frey	↓ glabrous skin detection thresholds	10–36 weeks	Male	(DeLorey et al., 2011)
		↓ glabrous skin detection thresholds	17–21 weeks	N/A	(Ugarte et al., 1999)
Ube3a	Texture Discrimination Assay	Novel tactile environment aversion	13–17 weeks	Male/Female	(McCoy et al., 2017)
Syngap1	Go/No-Go task	Whisker hyposensitivity	11–13 weeks	Male	(Michaelson et al., 2018)
	Ca2+ imaging	↓ wS1 L2/3 excitatory and inhibitory evoked activity		Male/Female	
	IOS and Patch Clamp	↓ wS1 L2/3 evoked activity	9 weeks		
	Go/No-Go task	Whisker-dependent task learning deficits	8–15 weeks	Male/Female	(Zhao & Kwon, 2023)
	Ca2+ imaging	↓ wS1 L2/3 evoked activity			
Fmr1	Von Frey	↓ glabrous skin detection thresholds	6–12 weeks	Male	(Martin et al., 2022)
	tNORT	Glabrous skin texture discrimination deficits	6 weeks	Male	(Orefice et al., 2016, 2019)
		Whisker texture discrimination deficits	3–4 weeks	Male	(Pyronneau et al., 2017)
	Gap-Cross Assay	Deficits in tactile learning	12–14 weeks	Male	(Arnett et al., 2014)
	IOS	↑ wS1 evoked receptive field			
		↑ wS1 L2/3 evoked activity	P16, P17, P60	Male	(He et al., 2019)
	Gap-Cross Assay	Altered whisker-guided exploration	9–13 weeks	Male	(Juczewski et al., 2016)
	In vivo juxtacellular recordings	↑ wS1 L2/3 PC evoked receptive field and inter-stimulus activity			
		↓ wS1 L2/3 to L4 evoked response latency			
	Whisker stimulation	Tactile defensiveness	P15-20, P45-50	Male/Female	(Kourdougli et al., 2023)
	Ca2+ imaging	↓ PV+ wS1 spontaneous and evoked activity	2 weeks		
	Silicon Probes	↓ wS1 L2/3 INT spontaneous, PC/INT evoked activity	6–13 weeks	Male	(Antoine et al., 2019)
	VSD Imaging	↑ S1 spread of whisker evoked activity	10–16 weeks	Male	(Zhang et al., 2014)
	Patch Clamp	↑ L2/3 PC evoked activity	2 weeks		
	Whisker stimulation	Tactile defensiveness	P14-16, P35-41	Male/Female	(He et al., 2017)
	Patch Clamp	Thalamocortical → L4 wS1 connectivity deficits	P3-4 weeks	Male	(Harlow et al., 2010)
		↑ S1HP L2/3 PC excitability	3–6 weeks	Male	(Bhaskaran et al., 2023)
		↑ S1 spontaneous activity			
		Altered S1HP L2/3 PC evoked receptive field			

TABLE 1 (Continued)

Candidate gene	Technique	Phenotype	Age	Sex	References
Shank3	Von Frey	↓ glabrous skin detection thresholds	N/A	Male/Female	(Deemyad et al., 2021)
	Touch Escape Assay	Hairy skin evoked tactile defensiveness	N/A	N/A	(Drapeau et al., 2018)
	tNORT	Glabrous skin texture discrimination deficits	6 weeks	Male	(Orefice et al., 2016)
	Tactile PPI	Hairy skin hypersensitivity			
	Tactile PPI	Hairy skin hypersensitivity	6–8 weeks	Male/Female	(Orefice et al., 2019)
	tNORT	Glabrous skin texture discrimination deficits			
		Whisker texture discrimination deficits	13–26 weeks	Male/Female	(Balasco et al., 2021)
	c-Fos	↓ S1 whisker evoked			
	Go/No-Go task	Whisker hypersensitivity	17–26 weeks	Male/Female	(Chen et al., 2020)
	Ca2+ Imaging	↑ excitatory and ↓ inhibitory wS1 L2/3 evoked and spontaneous activity			
Shank2	Von Frey	↑ glabrous skin detection thresholds	>8 weeks	Male	(Ko et al., 2016)
	Texture Discrimination Assay	↓ tactile sensitivity	N/A	Male	(Heuvel et al., 2023)
En2	Whisker stimulation	Whisker hypersensitivity	13–26 weeks	Male/Female	(Chelini et al., 2019)
	c-Fos	↓ S1 whisker evoked			
Cntnap2	Von Frey	↓ glabrous skin detection thresholds	8–16 weeks	Male/Female	(Dawes et al., 2018)
			N/A	Male/Female	(Deemyad et al., 2021)
	tNORT	Whisker texture discrimination deficits	13–26 weeks	Male/Female	(Balasco et al., 2022)
	Silicon Probes	↓ wS1 L2/3 INT evoked activity	6–13 weeks	Male	(Antoine et al., 2019)
16p11.2 del	Tactile PPI	Hairy skin hyposensitivity	6–8 weeks	Male/Female	(Orefice et al., 2019)
	Silicon Probes	↓ wS1 L2/3 INT evoked activity	6–13 weeks	Male	(Antoine et al., 2019)

Abbreviations: INT, interneuron; IOS, intrinsic optical signal; L2/3, cortical layer 2/3; L4, cortical layer 4; N/A, information not available; PC, principal cell; PPI, pre-pulse inhibition; PV, parvalbumin; S1, primary somatosensory cortex; S1HP, hind paw region of the primary somatosensory cortex; tNORT, textured novel object recognition test; VSD, voltage-sensitive dye; wS1, whisker primary somatosensory cortex (barrel cortex).

somatosensory neurons (Orefice et al., 2019; Samaco et al., 2005). Decreased GABRB3 expression has also been previously described in the brain of *Mecp2*$^{-/+}$ *and Mecp2*$^{-/y}$ mice (Samaco et al., 2005). Interestingly, selective restoration of *Gabrb3* expression in somatosensory neurons improves hairy skin hypersensitivity and texture discrimination deficits in *Mecp2* KO mice (Orefice et al., 2019).

3.2 | GABA$_A$ receptor subunit β3 (*Gabrb3*)

Neuronal inhibition in the central nervous system is predominantly mediated by gamma-aminobutyric acid (GABA; Castellano et al., 2021; Schmidt-Wilcke et al., 2018). GABA type A receptors (GABA$_A$R) are GABA-activated receptors composed of five subunits, one of which is the β3 subunit, encoded by the *GABRB3* gene (Lee & Maguire, 2014). Human mutations in this gene have been associated with ASD (Abrahams & Geschwind, 2008; Delahanty, 2011; Fatemi et al., 2009), and with tactile sensitivity in typically developing children (Tavassoli et al., 2012). In mice, *Gabrb3* mutations lead to ASD-like behaviors such as impaired social and exploratory behaviors (DeLorey et al., 2008; Samaco et al., 2005).

As for tactile deficits, decreased detection thresholds in response to hind paw tactile stimulation with Von Frey filaments were observed in male *Gabrb3*$^{+/-}$ mice, suggesting glabrous skin hypersensitivity (DeLorey et al., 2011). Female *Gabrb3*$^{+/-}$ mice also displayed a tendency for decreased thresholds in the same test.

Nevertheless, detection thresholds were lower when the missing *Gabrb3* allele was of paternal origin on both male and female mice. In an additional study also using hind paw tactile stimulation with Von Frey filaments, *Gabrb3* KO mice, but not *Gabrb3*$^{+/-}$, exhibited decreased detection thresholds (DeLorey et al., 2011). In developing (P7) mice, selective *Gabrb3* deletion in pyramidal neurons (*Emx1*.*Gabrb3* mice) led to an increase of wS1-responsive neurons following whisker tactile stimulation with air puffs (Babij et al., 2023). These results point to an overall hyperresponsive state of both glabrous skin and whiskers in *Gabrb3* deficient mice.

3.3 | Ubiquitin-protein ligase E3A (*Ube3a*)

Angelman syndrome (AS), another syndromic form of ASD (Hulbert & Jiang, 2016), is caused by loss-of-function mutations or deletions in the maternal allele of ubiquitin-protein ligase E3A (*UBE3A*) gene (Rougeulle et al., 1997). UBE3A enzyme targets intracellular proteins for degradation through ubiquitination, and interacts with several components of the proteasome, a protease complex that performs the hydrolysis of client proteins (Lopez et al., 2019; Tanaka, 2009). AS patients (including, but not exclusively with a *UBE3A* mutation) have been described to exhibit altered tactile sensitivity and altered tactile seeking behaviors (Heald et al., 2020; Walz & Baranek, 2006). *Ube3a* mutant mice show typical ASD phenotypes such as impaired social behavior and communication and increased repetitive behaviors (Vatsa & Jana, 2018).

Ube3a$^{m-/p+}$ mice showed aversion to novel tactile environments in a variation of the 2-chamber conditioned place preference test by choosing to spend significantly less time in a chamber with novel textures (water, gravel, stones, or sand; McCoy et al., 2017). Tactile environment aversion was not observed upon conditional deletion of the *Ube3a* maternal allele in the dorsal root ganglion (*Ube3a*$^{FLOX/p+}$), suggesting that the observed tactile deficits may be centrally mediated (McCoy et al., 2017). Of note, no alterations were observed in detection thresholds using the Von Frey test in this model (McCoy et al., 2017).

3.4 | Synaptic Ras GTPase activating protein 1 (*Syngap1*)

SYNGAP1 encodes a Ras GTPase activating protein that plays an important role in regulating not only synaptic plasticity but also neuronal homeostasis (Jeyabalan & Clement, 2016). Mutations in this gene have been associated with intellectual disability comorbid with ASD (Berryer et al., 2013). *Syngap1* haploinsufficiency (*Syngap1*$^{+/-}$), which can cause autistic traits in humans (O'Roak et al., 2014), as well as abnormal responses to tactile stimuli (Michaelson et al., 2018), leads to significant cognitive, emotional, and social deficits in mice (Berryer et al., 2013; Guo et al., 2009; Ozkan et al., 2014).

Syngap1$^{+/-}$ mice exhibit both whisker and glabrous skin sensory deficits. In the tNORT (called Novel Texture Discrimination task in this report), *Syngap1*$^{+/-}$ mice failed to distinguish novel objects based on their texture (Michaelson et al., 2018). *Syngap1* haploinsufficient mice have been shown to have normal object recognition memory (Muhia et al., 2010), re-enforcing that the observed discrimination deficits are likely tactile-mediated. Additionally, *Syngap1*$^{+/-}$ also failed to perform a Go/NoGo learning task based on whisker deflection perception (Michaelson et al., 2018). These behavioral alterations were paralleled by a reduction of neuronal activity in response to whisker piezo-electric stimulation, both in excitatory and inhibitory SSC neurons, particularly in L2/3. The same study also showed a reduction of excitatory synapses in upper-lamina SSC neurons and reduced dendritic lengths and densities in both L2/3 and L4 neurons of *Syngap1*$^{+/-}$. Another study using interneuron-specific *Syngap1* haploinsufficient mice showed normal neuronal responses in wS1 L2/3 with comparable magnitude and temporal dynamics to wild-type (WT) mice, but elevated responses to sensory stimuli that were irrelevant to a learning task (Zhao & Kwon, 2023). These results suggest that decreased SYNGAP1 expression in inhibitory interneurons disrupts sensory representations in S1.

3.5 | Fragile X messenger ribonucleoprotein 1 (*Fmr1*)

Fragile X syndrome occurs in individuals with a Fragile X messenger ribonucleoprotein 1 (*FMR1*) full mutation or other loss-of-function variant and has high comorbidity with ASD (Kaufmann et al., 2017). *FMR1* gene codes for the Fragile X mental retardation protein (FMRP), which binds to mRNA and regulates synaptic protein translation (Vithayathil et al., 2018). Importantly, *Fmr1* has been shown to control voltage-gated calcium channel 2.2 (CaV2.2) surface expression by targeting these channels for degradation (Ferron et al., 2014). Fragile X patients have been described to exhibit both hypo- and hypersensitivity to tactile stimuli (Heald et al., 2020). *Fmr1* KO mice display ASD-like behaviors, including impaired sociability (Saré et al., 2019), but no deficits in learning and memory (Fisch et al., 1999).

Decreased detection thresholds to glabrous skin tactile stimulation and texture discrimination deficits in the tNORT have been observed in *Fmr1* KO mice (Martin et al., 2022; Orefice et al., 2016), including at P20-30 (Pyronneau et al., 2017) (although one study found no differences between mechanical thresholds of adult *Fmr1* KO and control mice in the Von Frey test (Price et al., 2007)). Hairy skin hypersensitivity was also observed in these mice through enhanced tactile PPI responses (Orefice et al., 2016). In the gap crossing assay, a whisker-dependent exploration test (Voigts et al., 2015), *Fmr1* KO mice showed reduced whisker sampling periods, and an inability to improve performance with experience, while displaying normal exploratory behavior (Arnett et al., 2014; Juczewski et al., 2016). In accordance with previous reports describing hyperexcitability of cortical networks (Gonçalves et al., 2013) (possibly because of deficient feedback inhibition of excitatory neurons (Gibson et al., 2008)), *Fmr1* KO mice have been shown to exhibit elevated neuronal responses in L2/3 of the S1 to both whisker and glabrous

skin stimulation (Arnett et al., 2014; Bhaskaran et al., 2023; He et al., 2019; Juczewski et al., 2016; Zhang et al., 2014), increased trial-by-trial response variability (Bhaskaran et al., 2023), and increased inter-stimulus activity (Juczewski et al., 2016). Elevated spontaneous activity of S1 L2/3 pyramidal neurons and changes in S1 upstates, with consequences for sensory information processing, have also been described (Bhaskaran et al., 2023). In addition to globally elevated responses in S1, and a faster lateral spread of S1 excitation to adjacent cortical areas in response to whisker stimulation (Zhang et al., 2014), one of these studies also found increased neuronal excitability in S1 L5B neurons mediated hyperpolarization-activated cyclic nucleotide-gated (HCN) and calcium-activated potassium (BK_{Ca}) channels, which could be corrected by boosting BK_{Ca} with the highly selective BK_{Ca} agonist BMS-191011. Local application of BMS-191011 to the S1 also rescued responses to hind paw stimulation, and normalized spontaneous activity firing (Bhaskaran et al., 2023). Altered whisker stimulation frequency encoding by S1 neurons and a reduction in whisker selectivity index, suggestive of degraded somatotopic maps and abnormal receptive fields, were also observed in *Fmr1* KO mice (Juczewski et al., 2016). Others have also reported increases in barrel cortex tuning map sizes (Antoine et al., 2019; Arnett et al., 2014), as early as P16/17 (He et al., 2019), although the arealization of wS1 and size of individual barrel patch areas appear to be normal at P7 and P60 (Harlow et al., 2010). Reduction of neuronal tuning selectivity in this model also extends to paw tactile stimulation responses, with a higher proportion of S1-hind paw (S1HP) neurons responding to front paw stimulation in *Fmr1* KO compared to WT (Bhaskaran et al., 2023). Importantly, several alterations of thalamocortical projections to wS1 L4, as well as defective wS1 L2-L3 connectivity, during a developmental critical period (Bureau et al., 2008; Harlow et al., 2010) have been reported in *Fmr1* KO and may be contributing to these altered responses and somatotopic maps (Antoine et al., 2019; Arnett et al., 2014; He et al., 2019). Treatment with bumetanide, an inhibitor of the chloride co-transporter NKCC1, during the first two postnatal weeks, corrected the elevated responses and altered somatotopic maps in *Fmr1* KO, lasting into adulthood (He et al., 2019). Contrary to these observations, another report failed to observe elevated responses in L2/L3 of the wS1 in response to whisker stimulation, in both young and adult (P14-16 and P35-41, respectively) *Fmr1* KO mice (He et al., 2017). Nevertheless, the authors observed a 45% reduction in the number of tuned neurons to whisker stimulation and a pronounced deficit in neuronal adaptation to repetitive tactile stimuli in these mice (He et al., 2017). In another study, the same group showed that parvalbumin (PV), but not somatostatin (SST), interneurons in S1 L2/3 have reduced spontaneous activity and lower evoked responses to whisker stimulation in P15 *Fmr1* KO mice (Kourdougli et al., 2023). Concomitantly, these mice showed a drastic reduction in the density of PV-positive cells across all layers of the S1 at P10, but also at 9–10 months old. Reduction of both spontaneous and whisker-evoked firing rates of fast-spiking interneurons in L2/3 of the S1 was also observed in another study, with simultaneous reduction of whisker-evoked firing rate and firing synchrony of regular spiking neurons (Antoine et al., 2019). Alterations of S1 synchronous activity were also present in the early postnatal period, with *Fmr1* KO mice showing hypoactive medial ganglion eminence (MGE) immature precursor cells to PV and SST interneurons (Nkx2.1-positive) at P6, and a functional decoupling between putative future PV interneurons and pyramidal cells at P10 (Kourdougli et al., 2023). Interestingly, post-critical period (P15-P20), but not early neonatal, chemogenetic activation of PV interneurons caused a significant increase in the percentage of whisker-responsive pyramidal cells (but no changes in response adaptation to whisker stimulation). Administration of compound AG00563 (1-(4-methylbenzene-1-sulfonyl)-N-[(1,3-oxazol-2-yl)methyl]-1H-pyrrole-3-carboxamide), a modulator of the voltage-gated Kv3.1 channels expressed by PV interneurons, at any time after P15, also increased evoked responses to whisker stimulation, ameliorated the stimulus adaptation deficits, and robustly reduced tactile defensive behaviors (Kourdougli et al., 2023). Tactile discrimination deficits in this model have also been correlated with increased S1 Rac1-PAK1-cofilin signaling and actin polymerization, involved in spine morphogenesis and synaptic plasticity, during the critical period (Pyronneau et al., 2017). Injection of PAK inhibitor FRAX486 at P7 rescued altered glutamatergic signaling in S1, and its administration both during the critical period or after it rescued the tactile behavioral deficits (Pyronneau et al., 2017).

3.6 | SH3 and multiple ankyrin repeat domains 2 and 3 (*Shank2* and *Shank3*)

SHANK proteins make up a family of scaffold proteins, located in the postsynaptic density (PSD) of excitatory/glutamatergic synapses, that contain multiple sites for protein–protein interaction (Monteiro & Feng, 2017; Sala et al., 2015) connecting membrane receptors to the neuron cytoskeleton (Kim & Sheng, 2004; Phelan & McDermid, 2012). Phelan-McDermid syndrome is a neurodevelopmental disorder usually associated with ASD, with loss or disruption of chromosome region 22q13.3, in which the *SHANK3* gene is present (Phelan & McDermid, 2012). Phelan-McDermid syndrome patients have been reported to exhibit alterations in tactile sensitivity, and abnormal sensory-seeking behaviors (Serrada-Tejeda et al., 2022). *Shank* mutant mice show cardinal ASD features including deficits in social interaction, repetitive behaviors, and motor coordination deficits, among other impairments (Bozdagi et al., 2010; Mei et al., 2016; Peça et al., 2011; Wang et al., 2011).

Shank3B$^{+/-}$ and *Shank3B* KO, but not heterozygous *Shank3*$^{\Delta 4-9}$ mice, exhibited texture discrimination deficits by displaying no object preference in the tNORT (Balasco et al., 2021; Orefice et al., 2016, 2019). In addition, *Shank3B*$^{+/-}$ mice also exhibited hairy skin hypersensitivity through enhanced tactile PPI responses (Orefice et al., 2016, 2019). In the Von Frey test, *Shank3* KO mice displayed decreased detection thresholds to weak mechanical stimulation of the dominant paw (Deemyad et al., 2021). *Shank3*$^{\Delta 4-22}$ homozygous mice, which have constitutive disruption of all SHANK3 isoforms, showed increased defensive behavior to tactile stimuli through increased

escape responses to lighter mechanical strokes of hairy skin (Drapeau et al., 2018). Tactile-mediated behavioral deficits in *Shank3B*$^{+/-}$ have been correlated with a reduction of HCN1-containing punta in presynaptic terminals in the dorsal horn and loss of HCN1 expression in large, but not small, DRG cell bodies (Orefice et al., 2019). Additionally, cultured DRG somatosensory neurons from these animals also revealed altered excitability mediated by HCN (Orefice et al., 2019). In accordance with these alterations in the peripheral nervous system (PNS), selective *Shank3* peripheral restoration in somatosensory neurons rescued texture discrimination deficits and hairy skin hypersensitivity (Orefice et al., 2019). Lower detection thresholds in response to whisker stimulation, and in particular to weaker stimuli, have also been reported in *Shank3B* KO mice (Chen et al., 2020). This alteration was correlated with increased calcium activity of wS1 L2/3 excitatory neurons and decreased activity of inhibitory interneurons, in both spontaneous and whisker evoked paradigms (Chen et al., 2020). Conditional *Shank3* deletion in S1 interneurons recapitulated both the cellular and behavioral hyperexcitability/hypersensitivity phenotypes observed in KO animals, while conditional *Shank3* deletion in S1 excitatory neurons led to reduced spontaneous and evoked activity, and a tendency for increased detection thresholds (Chen et al., 2020). Contrary to these results, whisker hyposensitivity and reduced global S1 activation in response to repeated whisker stimulation in the whisker nuisance test (WN) have been observed through c-fos mRNA in situ hybridization in *Shank3B* KO mice (Balasco et al., 2021). Another study also reported a reduction in the number of PV-expressing cells in the S1 dominant hemisphere and a global decrease of PV levels in the S1 (Deemyad et al., 2021). This reduction was highly correlated with Von Frey scores of glabrous skin tactile hypersensitivity.

Shank2 KO mice have been reported to have reduced baseline sensitivity and increased glabrous skin detection thresholds in response to hind paw stimulation in the Von Frey test (Heuvel et al., 2023; Ko et al., 2016). One of these studies also found that *Shank2* KO mice displayed an increase in the latency to escape a chamber with a textured floor (gritty sandpaper), but no preference between chambers in a textured version of the two-chamber conditional place preference test (Heuvel et al., 2023).

3.7 | Homeobox protein engrailed-2 (*En2*)

Homeobox protein engrailed-2 (*EN2*) codes for the homeobox-containing transcription factor Engrailed-2. *EN2* is expressed throughout CNS development and is important in numerous cell biological processes, such as morphological organization and circuit connectivity, among others (Choi et al., 2011; Poudel et al., 2022). Genetic alterations in the *EN2* gene have been previously associated with ASD (Carratala-Marco et al., 2018). *En2 KO* mice display impairments in social behaviors, but not in social communication, and cognitive deficits in fear memory, novel object recognition, spatial learning, and motor coordination (Brielmaier et al., 2012).

Following repeated whisker stimulation in the WN test, *En2 KO* mice displayed elevated fear behavior and reduced *c-Fos* expression in S1 L4 cells (Chelini et al., 2019). Although whisker-guided exploratory behavior was comparable to WT, *En2 KO* mice presented reduced basal connectivity between sensory areas, and between the SSC and the thalamus (Chelini et al., 2019).

3.8 | Contactin-associated protein 2 (*Cntnap2*)

Contactin-associated protein 2 (*CNTNAP2*) gene codes for the contactin-associated protein-like 2 (CASPR2) (George-Hyslop et al., 2022), a transmembrane protein that plays a role in cell–cell adhesion, extracellular matrix interactions (Rodenas-Cuadrado et al., 2014), and synapse formation and functioning (George-Hyslop et al., 2022). Mutations in this gene have been linked to human ASD (Chen et al., 2015; O'Roak et al., 2011). *Cntnap2* KO mice exhibit ASD traits such as social behavior deficits (Jang et al., 2023), learning impairments, hyperreactivity to thermal stimuli, and increased locomotion (Peñagarikano et al., 2011; Thomas et al., 2017).

In the tNORT, *Cntnap2* KO mice showed abnormal texture discrimination (while displaying normal exploratory behavior) (Balasco et al., 2022), as well as tactile hypersensitivity and lower detection thresholds in the Von Frey test (Dawes et al., 2018; Deemyad et al., 2021). Contrarily to WT, these mice also showed a preference towards rough textures in the Somatosensory Nose-Poke Adapted Paradigm (SNAP), a whisker-guided texture-preference test (Binder & Bordey, 2023). Whisker stimulation in anesthetized *Cntnap2* KO mice led to increased *c-fos* mRNA expression in S1 but not in the ventral posteromedial thalamic nucleus (VPM), when compared with control animals (Balasco et al., 2022). The same study also reported resting state functional hyperconnectivity in *Cntnap2* KO mice's SSC, but not between the SSC and the thalamus, as well as increased cortical VGLUT1 and 2 expression, suggestive of altered excitation/inhibition (E/I) ratio. The latter is also supported by another study reporting a reduced number of GABAergic (GAD1^{+}) neurons and of PV, Calbindin 2 (CALB2), and Neuropeptide Y (NPY) expressing interneurons in the SSC of P14 *Cntnap2* KO mice (Peñagarikano et al., 2011). An asymmetric reduction of the number of PV cells and PV expression in the S1 of *Cntnap2* KO mice was also correlated with glabrous skin tactile hypersensitivity in the Von Frey test (Deemyad et al., 2021). Confirming the hypothesis of reduced inhibition in *Cntnap2* KO mice's S1, another study showed a significant reduction of fast-spiking interneurons' firing rate in L2/3 in response to whisker stimulation, while displaying normal evoked firing rate and sensory tuning in regular-spiking neurons (Antoine et al., 2019). However, L4 regular spiking units showed abnormally low firing rates in response to whisker stimulation, suggestive of L4-L2/3 network excitability disruption. Increased calcium activity in response to hind paw tactile stimulation was also observed in DRG neurons, and correlated with loss of Kv1.2 potassium channels in these cells (Dawes et al., 2018). *Cntnap2* KO mice have also been shown to have abnormal activity in the cerebellar Crus I/II region, which is involved in the integration of sensory inputs from the whiskers (Fernández et al., 2021). This was observed for both spontaneous activity and evoked responses following whisker electrical stimulation.

3.9 | 16p11.2 deletion syndrome (*16p11.2*$^{del/+}$)

Deletions, duplications, and copy number variations (CNVs) of the human chromosomal region 16p11.2 are linked to multiple neurodevelopmental and neuropsychiatric disorders, including ASD (Hippolyte et al., 2016). Patients with either 16p11.2 deletion or duplication with a co-occurring diagnosis of ASD show greater levels of sensory behaviors in the Sensory Behavior Questionnaire (Smith et al., 2022). *16p11.2* deletion mutant mice show reduced body weight, deficits in novel object memory, and social approach (Lynch et al., 2020).

Regarding tactile deficits, *16p11.2* deletion mutant mice (*16p11.2*$^{del/+}$) exhibited hairy skin hyposensitivity, observed in the tactile PPI, yet performed comparably to WT in the tNORT (Orefice et al., 2019). Fast spiking interneurons in S1 L2/3 of *16p11.2*$^{del/+}$ mice showed significant decreases in firing rate in response to whisker stimulation when compared to WT controls (Antoine et al., 2019). Despite this reduced inhibition, the spontaneous and evoked firing rates of regular spiking neurons in L2/3 were not affected. Unlike other models, neuronal tuning to whisker stimulation was normal.

3.10 | Forkhead box P1 (Foxp1)

The Forkhead box P1 (*FOXP1*) gene codes for a transcription factor of the forkhead box P (FOXP), a subfamily of FOX transcription factors (Trelles et al., 2021). Mutations in this gene are associated with neurodevelopmental syndromes, including ASD (Trelles et al., 2021). In mice, *Foxp1* haploinsufficiency leads to decreased body weight and altered feeding behavior (Fröhlich et al., 2019), and brain-specific deletion leads to impaired short-term memory, impaired social behavior, and increased repetitive behaviors (Bacon et al., 2015).

Mice with cortex-specific deletion of *Foxp1* displayed increased tactile defensiveness (in the form of guarding and evasion behaviors) in response to repeated whisker stimulation but without an increase of *c-fos* activity in L4 of the S1 which was observed in the WTs (Li et al., 2023). The same study also described that cortical deletion of *Foxp1* led to abnormal barrel formation in the wS1, with an almost complete absence of barrel structures. Additionally, these animals also showed altered distribution of neurons in the L4 of the S1, as well as reduced dendritic arbors and reduced number of spines, suggestive of thalamocortical connectivity alterations.

4 | DISCUSSION

The studies here reviewed confirm that several genetic mouse models of ASD display atypical tactile responses as well as sensory tactile processing deficits that recapitulate those observed in ASD patients. Although the reviewed ASD models represent a highly heterogeneous genomic landscape in terms of specific mutations and genes, altered tactile sensitivity appears to be a shared phenotype. At the behavioral level, the most common findings include lower detection thresholds and defensive behaviors in response to tactile stimulation of both the paws and the whiskers (Juczewski et al., 2016; Kourdougli et al., 2023; Peça et al., 2011; Pyronneau et al., 2017; Rougeulle et al., 1997; Selby et al., 2007), texture discrimination deficits (Balasco et al., 2021, 2022; Michaelson et al., 2018; Orefice et al., 2016, 2019; Pyronneau et al., 2017), altered adaptation to repetitive tactile stimulus (He et al., 2017), avoidance of novel textures (McCoy et al., 2017), and impairments in tactile-based learning tasks (Arnett et al., 2014). This heterogeneous, but consistent, constellation of responses is also observed in children and adults diagnosed with ASD (Heald et al., 2020; Michaelson et al., 2018; Serrada-Tejeda et al., 2022; Smith et al., 2022; Tavassoli et al., 2012; Walz & Baranek, 2006). The functional neurobiological alterations underlying these behaviors are less understood, but one advantage of using mouse models to study tactile sensory deficits in ASD is that they allow the use of more advanced techniques to probe the synaptic and circuit-level alterations, such as electrophysiology and calcium imaging, and permit cell−/circuit-specific manipulations. The studies reviewed here have consistently found that the S1 region is a site of tactile processing deficits across models, but the specific impact is heterogeneous and may be dependent on the affected gene. Nevertheless, both increased (Arnett et al., 2014; Chen et al., 2020; He et al., 2019; Juczewski et al., 2016; Zhang et al., 2014) and decreased (Antoine et al., 2019; Balasco et al., 2021; Chelini et al., 2019; Chen et al., 2020; Michaelson et al., 2018) global evoked activities in the S1 have been reported in response to tactile stimulation, as well as alterations in intrinsic neuronal excitability (Bhaskaran et al., 2023), synchrony (Antoine et al., 2019; Peñagarikano et al., 2011), tuning selectivity (Bhaskaran et al., 2023), and connectivity (Balasco et al., 2022; Bureau et al., 2008) of S1 neuronal cells.

An often proposed hypothesis to explain heightened sensory responses in ASD at the cellular level is an imbalance in the excitation-inhibition (E/I) ratio (Lee et al., 2017), which can potentially drive excessive spiking and responses in S1. This could be because of increased excitation or reduced inhibition, or a combination of both, into cortical pyramidal cells. *Shank3B* KO mice, for example, show increased spontaneous and whisker-evoked activity of L2/3 pyramidal neurons, while simultaneously having reduced activity of PV interneurons (Chen et al., 2020). Imbalanced local circuit synaptic E/I ratio in S1 has also been shown for *Fmr1* KO, *Cntnap2* KO, *16p11.2*$^{del/+}$ (Antoine et al., 2019), and *Mecp2*$^{-/y}$ (Dani et al., 2005) models. Reduced inhibitory signaling can lead to E/I imbalance, and alterations of GABAergic markers have been described in several postmortem analysis studies of brains from ASD patients (Fatemi et al., 2009; Oblak et al., 2011), including in S1 (Puts et al., 2017). There is also broad evidence for reduced number/density of inhibitory PV interneurons in the S1 of *Fmr1* KO (Kourdougli et al., 2023; Selby et al., 2007), *Shank3* KO (Deemyad et al., 2021), *Cntnap2* KO (Peñagarikano et al., 2011), *Mecp2* KO (Morello et al., 2018), *En2* KO (Sgadò et al., 2013), and *Syngap1*$^{+/-}$ (Berryer et al., 2016) mice, although reduced cell counts may be because of loss of PV expression and not necessarily cell number reduction (Filice et al., 2016). A reduced number of GABAergic (GAD1^{+}) cells, as well as CALB2

and NPY-interneurons, was also described for *Cntnap2* KO mice (Peñagarikano et al., 2011). Regardless of changes in densities of inhibitory cells, *Fmr1* KO, *16p11.2*$^{del/+}$, *Cntnap2* KO (Antoine et al., 2019), *Shank3B* KO (Chen et al., 2020), and *Syngap1*$^{+/-}$ (Michaelson et al., 2018) mice showed reduction of S1 inhibitory interneurons firing rates or calcium activity. On the other hand, abnormal glutamatergic signaling can also contribute to E/I imbalance and increased cortical spiking through excessive excitation, but there is less evidence for specific glutamatergic alterations in the S1 of ASD mouse models. Although increased cortical expression of VGLUT1 and 2 has been shown for *Cntnap2* KO mice (Balasco et al., 2022), several other studies in the mouse models reviewed here have shown glutamatergic dysfunction in other brain areas involved in sensory processing and sensorimotor integration such as the thalamus, striatum, and cerebellum (Montanari et al., 2022). In *Syngap1*$^{+/-}$ mice, changes in the ratio of AMPA/NMDA receptors in thalamocortical neurons conveying tactile information were also shown to interfere with synaptic maturation correlated with reduced S1 responses to tactile stimulation (Clement et al., 2013; Michaelson et al., 2018).

Although increased synaptic E/I ratio and reduced inhibitory activity have been described across different models, it is important to note that it may not necessarily lead to excessive spiking/hyperactivity in cortical networks. For example, *Cntnap2* KO and *16p11.2*$^{del/+}$ mice showed reduction of fast-spiking interneurons' firing rate in the L2/3 of the S1 in response to whisker stimulation, while displaying normal spontaneous and evoked activity in regular-spiking neurons (Antoine et al., 2019). *Fmr1* KO and *Syngap1*$^{+/-}$ mice, on the other hand, showed reduced whisker-evoked S1 activity despite reduced inhibitory activity (Antoine et al., 2019; Michaelson et al., 2018); although multiple studies describe increased global responses in S1 of *Fmr1* KO (Arnett et al., 2014; He et al., 2019; Juczewski et al., 2016; Zhang et al., 2014). A plausible explanation may be related to the differential expression and importance of certain genes for interneuron function, such as *Shank3*, whose loss of function may weaken inhibition beyond possible correction by compensatory mechanisms (Monday et al., 2023). Indeed, strong chemogenetic inhibition of PV-interneurons in the wS1 of WT mice can lead to tactile hyperreactivity and altered detection thresholds, similar to what is observed in *Shank3B* KO mice (Chen et al., 2020).

Tactile processing deficits are not only reflected in E/I imbalance and changes in cortical spiking rates. Degraded coding of tactile stimuli in the somatosensory cortex, which can manifest as blurred or expanded somatotopic maps, altered neuronal tuning, and variable or noisy responses, is also a common feature across different ASD mouse models, even when E/I balance or tactile-evoked somatosensory activity is apparently normal. These alterations can interfere with stimulus detection and discrimination and impair performance in tactile-guided learning tasks, the latter having been shown for *Fmr1* KO and *Syngap1*$^{+/-}$ mice (Arnett et al., 2014; Michaelson et al., 2018; Orefice et al., 2016; Zhao & Kwon, 2023). Degraded S1 somatotopic maps and altered neuronal tuning to tactile stimulus have been consistently reported in the *Fmr1* KO model (He et al., 2019; Juczewski et al., 2016), although it is not evident if they have been explicitly tested in other models. For example, although altered S1 somatotopic maps have not been reported for *Ube3a* KO and *Shank3*$^{+/-}$ mice, they show broader and narrower tuning than WTs, respectively, in visual cortex (V1) neurons (Ortiz-Cruz et al., 2022; Wallace et al., 2017). Abnormal anatomical development of somatosensory pathways in the forebrain can contribute to altered somatotopic maps, and reduced cyto-architectonic segregation of S1 L4 barrels has been found in *Syngap1*$^{+/-}$ mice (Barnett et al., 2006), indicating that *Syngap1* is necessary for boundary formation between S1 barrels (in fact, in mice lacking SYNGAP, S1 L4 cells do not aggregate to form barrels (Barnett et al., 2006)). However, *Fmr1* KO mice showed normal barrel cortex development and arealization in the early postnatal period and adulthood (Harlow et al., 2010), which suggests that circuit level alterations can also be driving degraded maps in some ASD mouse models. Changes in cortical feedforward or lateral connectivity can contribute to the blurring of sensory tuning and expanded cortical maps, as well as local circuit E/I imbalance. *Cntnap2* KO and *Syngap1*$^{+/-}$ mice show altered S1 L4-L2/3 gain (Antoine et al., 2019; Michaelson et al., 2018), and *Fmr1* KO mice display faster lateral spreading of responses to tactile stimulation in L2/3 (Zhang et al., 2014). Because the thalamus is a hub for ascending sensory information in the brain where ascending tactile inputs converge before traveling in topographically defined fashion to the S1, functional connectivity alterations between the thalamus and S1 may also be a cause of abnormal map formation and tuning and altered S1 development and arealization (He et al., 2019; Juczewski et al., 2016; Zhang et al., 2014). Alterations in thalamocortical connectivity or in the intrinsic electric properties of thalamocortical neurons have been reported for the *Fmr1* KO (Harlow et al., 2010), *Shank3*$^{\Delta 13-16}$ (Zhu et al., 2018), and *Syngap1*$^{+/-}$ models (Clement et al., 2013), as well as in human ASD studies (Green et al., 2017). Other critical features for neuronal coding of tactile stimuli such as neuronal response variability or adaptation to repeated stimulation also appear to be altered in the *Shank3* (Balasco et al., 2021; Chen et al., 2020), and *Fmr1* models (He et al., 2017; Zhang et al., 2014). Increased spontaneous activity firing rates in S1 can also contribute to degraded tactile stimulus coding, as the stimulus-to-background activity ratio is reduced leading to altered stimulus thresholds and discrimination. Accordingly, *Shank3B* KO showed increased spontaneous firing rates in S1, parallel to altered stimulus detection thresholds and coding variability to whisker stimulation (Balasco et al., 2021; Chen et al., 2020). Alterations of spontaneous firing in other sensory brain areas, such as V1, have also been observed for *Shank3* KO mice, including when *Shank3* was deleted in PV interneurons only (Pagano et al., 2023), suggesting possible cortical-wide E/I dysfunction. On the other hand, S1 spontaneous firing rates have been reported to be normal for *Fmr1* KO, *Cntnap2* KO, and *16p11.2*$^{del/+}$ mice (Antoine et al., 2019; He et al., 2017).

Understanding the developmental timeline of tactile sensory deficits, and how critical periods of development may play a role in the establishment or compensation of these deficits, is fundamental to linking genetic mutations to circuit-level alterations as well

as defining when they could be corrected by therapeutic interventions. Abnormal alterations during early postnatal critical periods, where heightened plasticity to environmental sensory inputs shape the development and stabilization of cortical sensory circuits, can also contribute to many of the tactile processing deficits discussed here. Importantly, S1 critical period starts before those of other cortical sensory primary areas, potentially as early as P0, and has a longer duration, extending up to P20/P21 (Pedrosa et al., 2022), reinforcing the fundamental function of touch in development, social bonding, and environment exploration. However, although this has been investigated more closely in the *Fmr1* KO mouse model, whether many of the somatosensory deficits observed occur before, after, or during the S1 critical period is an open question for most of the other models. Nevertheless, the reduction of interneuron cell densities, and in particular of PV interneurons, appears to be consistently altered both in the early postnatal period and adulthood across most models (Berryer et al., 2016; Deemyad et al., 2021; Kourdougli et al., 2023; Montanari et al., 2022; Morello et al., 2018; Peñagarikano et al., 2011; Sgadò et al., 2013). Because PV cells are important regulators of neural circuit plasticity during critical periods, alterations to PV functioning during development may drive persistent functional alterations in S1 in many of the ASD mouse models reviewed here. For example, *Fmr1* KO mice show clear alterations of network connectivity between PV and pyramidal cells very early in development (Kourdougli et al., 2023), and alterations of inhibitory activity possibly driving altered E/I ratio, somatotopic maps, and neuronal tuning, persist into adulthood. The correct migration, organization, and connection of thalamocortical afferents to S1 is also dependent on the processing of sensory stimuli during the early postnatal period (Antón-Bolaños et al., 2018; Martini et al., 2021). Accordingly, many of the reported changes in somatotopic maps, observed as early as P16/17 in *Fmr1* KO, may be because of changes in these connections. Interestingly, modulation of the juvenile chloride co-transporter NKCC1 in *Fmr1* KO during the critical period, stabilizes thalamocortical synapses in S1 L4, leading to a remodeling of the proteome of the barrel cortex and correction of abnormal somatotopic maps.

Although most of the reviewed models show some form of altered central processing of tactile information in the S1, the somatosensory processing cascade is a gradual path running from the peripheral to the central nervous system, mediated by mechanoreceptors and somatosensory neurons. Therefore, abnormal development/functioning at any steps of the pathway may lead to abnormal sensory processing (Balasco et al., 2020; Mikkelsen et al., 2018). In accordance, selective deletion of *Mecp2*, *Gabrb3*, and *Shank3* at P5 and P28 in all peripheral somatosensory neurons led to hairy and glabrous skin hypersensitivity and texture discrimination deficits (Orefice et al., 2016, 2019). Loss of *Mecp2*, but not of *Ube3a* maternal allele, in the DRG only also led to tactile hypersensitivity (McCoy et al., 2017; Orefice et al., 2016). Although the locus of tactile deficits in ASD most likely does not lie exclusively in peripheral receptors and neurons, these can be targeted for improving altered behavioral responses. Promising studies have shown that peripheral restoration of *Mecp2* or *Gabrb3* in *Mecp2* KO, or *Shank3* in *Shank3* KO mice somatosensory neurons, rescued tactile discrimination deficits and hairy skin hypersensitivity (Orefice et al., 2016, 2019). Chronic treatment with isoguvacine, a peripherally restricted $GABA_A$ receptor agonist that acts directly on mechanosensory neurons, also reduced tactile overreactivity in *Mecp2* KO and *Shank3* KO models (Orefice et al., 2019). Importantly, even though the tactile deficits were present in *Mecp2* KO and *Shank3* KO mice during the early postnatal period, later restoration of these genes' expression in somatosensory neurons (at P28) was sufficient to rescue hairy skin hypersensitivity. Peripheral administration to the paw of a PAK inhibitor, modulating actin dynamics, during or after the critical period also rescued glabrous skin hypersensitivity in *Fmr1* KO mice (Pyronneau et al., 2017).

5 | CONCLUDING REMARKS

In this review, we highlighted tactile sensory deficits across different genetic mouse models of ASD. Given the heterogeneity of the phenotypes described, as well as the number of genes involved, it is unlikely that a single particular functional alteration or mechanism is behind the observed tactile deficits at the behavioral level. It is nevertheless clear that these mouse models show marked alterations in tactile information processing, from peripheral receptors up to the primary sensory cortex. Notwithstanding the fact that the behavioral and functional somatosensory deficits are present in both human patients and mouse models of ASD, studies where modifying attempts were performed to reverse these alterations are outnumbered, and a cautious approach in extrapolating findings from mouse models to humans must be considered. Thus, collaborative efforts between researchers and clinicians toward translating these findings into clinical studies could be groundbreaking. Understanding a possible common ground for all these deficits may ultimately pave the way for more effective treatments targeting the core symptoms of ASD.

AUTHOR CONTRIBUTIONS

Margarida Falcão: Conceptualization; writing – original draft. **Patricia Monteiro:** Conceptualization; funding acquisition; supervision; writing – review and editing. **Luis Jacinto:** Conceptualization; supervision; funding acquisition; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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