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Peripheral Somatosensory Neuron Dysfunction: Emerging Roles in Autism Spectrum Disorders

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Abstract

Alterations in somatosensory (touch and pain) behaviors are highly prevalent among people with autism spectrum disorders (ASDs). However, the neural mechanisms underlying abnormal touch and pain-related behaviors in ASDs and how altered somatosensory reactivity might contribute to ASD pathogenesis has not been well studied. Here, we provide a brief review of somatosensory alterations observed in people with ASDs and recent evidence from animal models that implicates peripheral neurons as a locus of dysfunction for somatosensory abnormalities in ASDs. Lastly, we describe current efforts to understand how altered peripheral sensory neuron dysfunction may impact brain development and complex behaviors in ASD models, and whether targeting peripheral somatosensory neurons to improve their function might also improve related ASD phenotypes.

I. Mammalian Somatosensory Circuits

The sense of touch allows us to navigate our physical world. It endows us with the remarkable ability to feel a soft breeze or a gentle embrace. The first step in tactile processing involves the activation of a diverse set of sensory neurons with highly specialized axonal endings innervating the skin surface. Two main types of sensory neurons transmit signals from mammalian skin and they generally respond to either innocuous, light touch information or painful, noxious stimuli. Painful signals are conveyed by a range of nociceptor neurons that preferentially respond to noxious mechanical, thermal and/or chemical stimuli. Noxious mechanical stimuli include sensations such as high pressure or stretching, and a thermal pain stimulus would be extreme heat or cold (Markus, 2006). High-threshold mechanoreceptor neurons (HTMRs) encode harmful mechanical stimuli, while low-threshold mechanoreceptor neurons (LTMRs) respond to innocuous mechanical stimuli. LTMRs are further classified based on functional properties, molecular expression profiles and their responsivity to specific types of light touch stimuli (Abraira and Ginty, 2013). For example, A β Field-LTMRs are strongly activated during skin stroking (Bai et al., 2015), while A δ -LTMRs preferentially respond to hair follicle deflection (Rutlin et al., 2014) and

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slowly conducting C-fiber LTMRs are proposed to convey information about social touch (Vrontou et al., 2013). This diverse set of LTMRs mediate perception of object shape, texture, skin stroking, skin indentation, hair movement, and vibration (Abraira and Ginty, 2013). Through this diverse group of highly specialized and complex peripheral somatosensory neuron subtypes, information about the physical world is conveyed to the central nervous system (CNS).

As with all mammalian somatosensory neurons, cutaneous LTMRs and nociceptors are pseudo-unipolar neurons with one peripheral axonal branch that innervates the skin and another branch that innervates the spinal cord dorsal horn (Zimmerman et al., 2014). Activation of sensory neuron endings in the periphery leads to signals propagated through their axons, up to their cell bodies, which are located in the dorsal root ganglia (DRG) or cranial sensory ganglia just outside the spinal cord (Jenkins and Lumpkin, 2017). Sensory neuron central projections terminate in a somatotopic manner within the spinal cord dorsal horn, forming synaptic contacts onto both postsynaptic dorsal column projection neurons and local interneurons (Koch et al., 2018). A large subset of myelinated LTMRs also send an axonal branch via the dorsal column that terminates in the dorsal column nuclei of the brainstem (Abraira and Ginty, 2013). Thus, the spinal cord dorsal horn and dorsal column nuclei are initial sites of integration and processing of somatosensory information that is then conveyed to thalamus, followed by the primary somatosensory cortex and additional brain regions. Furthermore, primary somatosensory cortex has strong efferent and afferent connectivity with many other brain regions, including prefrontal cortex, superior colliculus, striatum, other sensory cortices, and many other regions that are thought to be critical for a wide range of emotional and social behaviors (Aronoff et al., 2010; Bedwell et al., 2014; Zakiewicz et al., 2014).

II. Touch is Critical for Normal Development

Somatosensory perception is a critical component of early human development, with tactile sensory responses beginning in humans as early as 8 weeks *in utero* (Montagu, 1984). Indeed, touch is a primary mode of communication between young children and their caregivers, as infants use touch to relay emotions such as distress (Ferber et al., 2008). Abnormalities in tactile processing or tactile experiences are strongly associated with early life emotional and social distress (Mikkelsen et al., 2018). In both human and rodent studies, a lack of parental touch leads to impaired somatosensory development, increased stereotyped behaviors, as well as deficits in social behavior and cognitive abilities (Hertenstein et al., 2006; Main and Stadtman, 1981). Indeed, human, non-human primate, and rodent tactile deprivation studies showed that early life experiences and developmental tactile stimulation are essential for proper brain development, cognition and adult social behaviors. Tactile sensations in juveniles enable refinement of motor skills, visual coordination, and postural responses (Corbetta and Snapp-Childs, 2009), and early tactile experiences are also crucial for the acquisition of normal social behavior and communication skills (Hertenstein et al., 2006).

In line with this, children who experienced institutional rearing with low caregiver investment and physical handling exhibited deficits in cognitive function, delayed or

impaired language acquisition and social interactions, and an increased incidence of anxiety and psychiatric disorders (Frank et al., 1996; Sheridan et al., 2012). In addition, rodents reared in the absence of physical interactions with other rodents, including those that experienced maternal deprivation, exhibited alterations in neuroanatomical development, as evidenced by decreased dendritic arbor complexity and spine number in cortical areas as well as aberrant hypothalamic-pituitary-adrenal axis development and increased anxiety-like behaviors (Pascual and Zamora-Leon, 2007; Schmidt et al., 2002). Despite the profound implications of early tactile input for brain development and cognitive function, the mechanisms that govern somatosensory circuit development and function are not fully understood.

Together, these studies indicate that tactile experiences are necessary for normal brain and behavioral development in mammals and that altered somatosensory-related experiences during development can negatively impact brain function and social behaviors. Could somatosensory circuits be altered in individuals with ASD and lead to altered touch behaviors, which ultimately impacts behavior and brain function in ASD? Evidence for a causal role of altered touch circuitry in the genesis of some ASD-related phenotypes in mice is discussed below.

III. Sensory Impairments are a Hallmark of ASD

ASDs are a highly prevalent class of neurodevelopmental disorders, characterized by impairments in social interaction, verbal and non-verbal communication deficits, as well as restrictive, repetitive behaviors (DSM-V, 2013). While ASDs are heterogeneous in etiology and severity, the vast majority of individuals with ASD also exhibit a complicated array of co-morbid symptoms, including aberrant reactivity to sensory stimuli (Rogers and Ozonoff, 2005; Tomchek and Dunn, 2007) which dramatically affects the quality of life for both ASD patients and their caregivers. Sensory processing abnormalities are among the most common behavioral concerns for parents of children with ASD, with an estimated 95% of parents indicating that their child experiences at least some differences in sensory processing (Rogers and Ozonoff, 2005). Aberrant sensory processing is increasingly recognized as a critical component of ASD, and altered sensory reactivity is now a criterion for ASD diagnosis (DSM-V, 2013). While the focus of this review is on alterations in somatosensory circuits and related behaviors, it is important to note that sensory abnormalities may also impact visual, auditory, olfactory and gustatory processes in ASD (Rogers et al., 2003; Rogers and Ozonoff, 2005; Tomchek and Dunn, 2007).

Strikingly, a majority of individuals with ASD have altered tactile reactivity in both glabrous (smooth) and hairy skin, and these symptoms are present in both children and adults with ASD (Cascio et al., 2016b; Foss-Feig et al., 2012; Tavassoli et al., 2014). An earlier study reported that 60.9% of patients with ASD exhibit tactile sensitivity abnormalities (Tomchek and Dunn, 2007). Adults with ASD have been shown to exhibit lower thresholds for the tactile perception of vibro-tactile stimuli, suggesting a specific hypersensitivity in A β -rapidly adapting II (RAII) LTMRs/Pacinian corpuscle pathways (Blakemore et al., 2006). In concordance with this finding, Cascio and colleagues found that adults with ASD display increased sensitivity to both vibration and thermal pain (Cascio et al., 2008). A second group

described a negative correlation between the presence of autistic traits in human subjects and neural responses to C-LTMR-targeted affective touch stimuli, indicating that people with greater numbers of autistic traits have impaired processing of affective touch (Voos et al., 2013). Because young children with ASD are often reported to be highly averse to specific types of light touch, caregivers may provide less nurturing touch and this lack of tactile input may have a profound impact on behavior and development (Cascio, 2010). Indeed, some evidence indicates that behavioral interventions such as additional tactile stimulation or massage may improve developmental outcomes including caregiver-child interactions, sensorimotor behaviors and verbal communication (Cascio, 2010; Casler, 1965; Underdown et al., 2006).

Several studies have indicated that there is a negative correlation between the presence of ASD traits in human subjects and their neural responses to affective touch (Scheele et al., 2014; Voos et al., 2013). Thus, individuals with ASD exhibiting the greatest expression of archetypal ASD traits have the highest degree of impairment in neural processing of affective touch (Voos et al., 2013). In line with this, regression analyses indicate that sensory over-reactivity predicts the presence of gastrointestinal symptoms, anxiety and the severity of ASD core symptoms in subjects with ASD (Mazurek et al., 2013). A recent study also identified significant correlations between tactile over-reactivity and social impairments in children with ASD, as well as an inverse relationship between pleasantness ratings to touch stimuli and impaired communication (Cascio et al., 2016a).

In addition to altered light touch sensitivity, altered responsivity to pain has also been observed in ASD subjects. While testing methodologies and patient/caregiver reports vary across studies, a number of studies identified that people with ASD exhibit under-reactivity to painful stimuli including hypo-responsivity to mechanical pain as well as hot and cold temperatures (Klintwall et al., 2011; Militeri et al., 2000). Yet, there are still a number of other studies that suggest hyper-responsivity to painful stimuli or no significant changes in people with ASD compared to control subjects (Moore, 2015), highlighting a need to better understand the heterogeneity of sensory symptoms among subjects with ASD and potential differences in sensitivity across tactile modalities.

Recent work on ASD has focused on identifying the origins and development of ASD, in which the heritability of ASD was estimated to be approximately 80% (Bai et al., 2019). Genetic influences on ASD are highly complex, which include single gene, copy number variations (including both deletions and duplications) and single nucleotide variations that are each identified as significant factors in ASD etiology (Rylaarsdam and Guemez-Gamboa, 2019). Previous studies have been successful in identifying genes, such as *Mecp2*, *Gabrb3*, *Fmr1* and *Shank3*, which are implicated in both syndromic and non-syndromic forms of ASD (Silverman et al., 2010). As with idiopathic or non-syndromic ASD, pervasive developmental disorders that cause syndromic forms of ASD are also associated with altered somatosensation (Tomchek and Dunn, 2007). For example, abnormal somatosensory responses for both light touch and painful stimuli are common among patients with Rett syndrome, which is caused by mutations in the X-linked methyl-CpG-binding protein 2 (*Mecp2*) gene (Amir et al., 1999). Rett syndrome is characterized by reduced lifespan, intellectual disabilities, motor impairments, seizures, breathing abnormalities, and

stereotyped behaviors, as well as communication and social interaction deficits (Mount et al., 2003; Wulffaert et al., 2009). Indeed, ‘giant’ amplitude somatosensory evoked potentials and altered spinothalamic connectivity are observed across multiple studies of females with Rett syndrome (Guerrini et al., 1998; Yoshikawa et al., 1991).

Similarly, abnormalities in tactile perception are typically observed in patients with fragile X syndrome and Tuberous sclerosis, disorders that are highly associated with ASD and caused by mutations in *Fmr1* and *Tsc1* or *Tsc2*, respectively (Battaglia, 2011; Braat and Kooy, 2015; Miller et al., 1999). In a study investigating sensory abnormalities in children with ASD and fragile X syndrome, investigators found that children with fragile X syndrome or ASDs exhibited higher tactile sensitivity compared to typically developing children. Furthermore, while no association was identified between abnormal sensory reactivity and developmental level or IQ, abnormal touch reactivity correlated significantly with the presence of adaptive behaviors and social impairments (Rogers et al., 2003).

Taken together, these studies indicate that individuals with ASD display abnormalities in tactile modalities and that these impairments correlate with deficits in social behavior and additional ASD-related phenotypes. Although tactile impairments are commonly reported in ASD, the neural mechanisms underlying somatosensory processing deficits in ASD remain poorly understood. A major goal of ASD research is to understand how these co-morbid ASD symptoms including altered sensory reactivity arise and whether they are causally linked to the core features by which ASD is traditionally diagnosed (social impairments and restricted, repetitive behaviors). While it is feasible that these numerous and seemingly disparate symptoms associated with ASD arise independently of each other, it may perhaps be more likely that the defining ASD features and co-morbid symptoms share a mechanistic link.

IV. Somatosensory Dysfunction: A Translatable Symptom to Study in Mice

Given the genetic contributions to ASD, there is a tremendous need to investigate the role of known ASD gene mutations in sensory circuit development and behavioral outcomes. A major area of emphasis has been on generating mouse genetic models that recapitulate core ASD phenotypes, such as anxiety-like behaviors and social interaction deficits (Silverman et al., 2010). These models with known ASD monogenic mutations are useful for understanding the pathophysiological basis of ASD. Recent findings suggest that both tactile reactivity abnormalities and social behavior deficits are present in mouse models of both syndromic and non-syndromic forms of ASD, highlighting the value of these mouse models for investigation of the etiological basis of ASD traits (Crawley, 2012).

While these genetic models provide valuable tools to study the underlying biology of ASD, it is unknown where in the nervous system their functions are disrupted. Therefore, a key question in ASD research is identifying a neural locus of dysfunction with regards to specific ASD phenotypes, in order to enable the development of effective treatments. When considering somatosensory alterations and tactile dysfunction, it is critical to consider that somatosensory processing begins with a stimulus impinging on the skin and activation of peripheral somatosensory neurons that transmit these signals from the skin to the CNS. As

discussed above, somatosensory information is processed, transformed and propagated through a diverse group of spinal cord interneurons and projection neurons, and this information is further conveyed to the brainstem, thalamus and onward to primary somatosensory cortex. Therefore, abnormal development or dysfunction along any of these steps of the somatosensory circuitry could result in abnormal sensory processing and altered tactile behaviors.

The great majority of ASD research has focused on brain-specific mechanisms and circuits, with less attention to the contributions of the peripheral nervous system and spinal cord to ASD phenotypes. In the following portion of this review, we will describe recent studies that implicate peripheral somatosensory neurons as a major locus of dysfunction that cause abnormal somatosensory reactivity across a range of mouse models for ASD. We will review recent evidence that links peripheral somatosensory neuron dysfunction to aberrant brain development and the genesis of related ASD behaviors including anxiety-like behaviors and social impairments. Lastly, the possibility of targeting peripheral somatosensory neurons to improve select ASD features will be explored.

V. Mouse Models for ASD: Evidence for Peripheral Somatosensory Neuron Dysfunction

V.1: *Gabrb3*

Human mutations in the GABA_A receptor subunit $\beta 3$ (*Gabrb3*) gene are a known cause of ASD, and individuals with these mutations display hypersensitivities to tactile stimuli (Tavassoli et al., 2012). Male mice that are heterozygous for *Gabrb3* exhibit phenotypes relevant to ASD, including hypersensitivity to both thermal and mechanical stimuli, sensorimotor impairments and social behavior deficits (DeLorey et al., 2011). In line with this, selective loss of *Gabrb3* in nociceptive neurons causes hypersensitivity to both mechanical and thermal pain but no apparent alterations in cold pain sensitivity (Chen et al., 2014). Furthermore, deletion of *Gabrb3* in all peripheral somatosensory neurons also causes abnormalities in light touch sensitivity, including hairy skin over-reactivity, mechanical hypersensitivity in hind paw glabrous skin and texture discrimination deficits (Orefice et al., 2016; Zimmerman et al., 2019). Electrophysiological experiments determined that loss of *Gabrb3* in peripheral sensory neurons leads to a significant reduction in GABA_A receptor-mediated presynaptic inhibition of peripheral sensory neuron inputs to the spinal cord (Orefice et al., 2016). This deficit in presynaptic inhibition led to increased flow of sensory information to the CNS and ultimately somatosensory over-reactivity (Orefice et al., 2016).

V.2: *Mecp2*

In addition, mice lacking one copy of *Mecp2* also exhibit phenotypes relevant to ASDs and Rett syndrome, including impaired social behaviors, abnormal ultrasonic vocalizations, stereotyped behaviors and sensory integration deficits (Gogolla et al., 2014; Silverman et al., 2010). Recent studies have also demonstrated that *Mecp2* mutant mice and rats exhibit somatosensory alterations consistent with patient observations, including mechanical/light touch hypersensitivity in both glabrous and hairy skin, as well as increased responsivity to noxious cold stimuli but decreased thermal sensitivity (Bhattacharjee et al., 2017; Orefice et

al., 2016). In both mice and rats, loss of *Mecp2* specifically in DRG neurons leads to mechanical hypersensitivity (Bhattacharjee et al., 2017; Orefice et al., 2016). Using conditional mouse genetics, selective deletion of *Mecp2* in all peripheral sensory neurons led to mechanosensory neuron dysfunction through loss of GABA_A receptor-mediated presynaptic inhibition of inputs to the CNS (Orefice et al., 2016). Additional pathophysiological mechanisms of dysfunction leading to somatosensory alterations were observed in rat models of Rett syndrome: lentiviral knockdown of *Mecp2* in foot-pad innervating DRG neurons led to a hyperinnervation of the cutaneous nerves to the skin and a concomitant increase in mechanical sensitivity measured by Von Frey fibers (Bhattacharjee et al., 2017). In line with these rodent studies, a recent paper investigated potential abnormalities in peripheral somatosensory neuron innervation of the skin in patients with Rett syndrome. Skin biopsies from subjects with Rett syndrome exhibited an increased number of total epidermal sensory neuron fiber density as well as increased density of peptidergic, calcitonin gene-related peptide-positive fibers (Symons et al., 2019). Lastly, hyperexcitability of trigeminal neurons that innervate the jaw and facial muscles has also been observed in *Mecp2* knockout mice, which was linked to alterations in sodium and potassium channel function (Oginsky et al., 2017). Together, these studies indicate there are a range of potential pathophysiological mechanisms of peripheral somatosensory neuron dysfunction that may contribute to altered somatosensory behaviors in mouse models for, and potentially patients with, Rett syndrome.

V.3: Shank3

SHANK3 is a synaptic scaffolding protein located at excitatory glutamatergic synapses (Sheng and Kim, 2000). *Shank3* is commonly implicated in ASDs, with *Shank3* mutations identified in ~2% of ASD cases (Moessner et al., 2007). Genetic deletion of the *Shank3* gene is also observed in patients with 22q13 deletion syndrome, also known as Phelan-McDermid syndrome. Patients with Phelan-McDermid syndrome often exhibit enhanced sensitivity to light touch stimuli and tactile defensiveness and, paradoxically, reduced responsivity to certain painful stimuli (Phelan and McDermid, 2012; Philippe et al., 2008; Sarasua et al., 2014). While studies of *Shank3* function have primarily focused on its expression at postsynaptic densities of excitatory glutamatergic synapses in the brain, *Shank3* is also expressed in the presynaptic terminals of peripheral somatosensory neurons including nociceptor neurons and LTMRs in the spinal cord dorsal horn (Han et al., 2016; Orefice et al., 2019). *Shank3* function is necessary in peripheral somatosensory neurons for normal light touch and thermal pain-related behaviors. Sensory neuron-specific loss of *Shank3* leads to deficits in thermal heat sensitivity, inflammation-induced heat hyperalgesia, as well as capsaicin-evoked pain responses in the hind paw of mice (Han et al., 2016). Furthermore, loss of *Shank3* in peripheral somatosensory neurons also leads to over-reactivity to light touch stimuli in hairy skin, as well as deficits in texture discrimination via glabrous skin on the paws of mice (Orefice et al., 2019). Interestingly, the physiological deficits underlying impaired heat transmission and light touch over-reactivity are distinct: loss of *Shank3* in nociceptive neurons leads to a reduction in TRPV1 expression which impairs pain signaling, while *Shank3* mutations in LTMRs causes deficits in HCN channel function and ultimately increased excitability of this neuronal population (Han et al., 2016; Orefice et al., 2019).

V.4: *Fmr1*

Fmr1 mutant mice exhibit many fragile X syndrome and ASD-related phenotypes including decreased thermal pain sensitivity and self-injurious behaviors, but also increased light touch sensitivity (Orefice et al., 2016; Price et al., 2007; Spencer et al., 2011; Symons et al., 2003). *Fmr1* mRNA is expressed in all peripheral somatosensory neurons (Zheng et al., 2019). The protein product produced by the *Fmr1* gene, fragile x mental retardation protein (FMRP), has been found to localize to the axons of nociceptor neurons as well as neurons within the spinal cord dorsal horn (Price et al., 2006). Evidence for peripheral somatosensory neuron dysfunction comes from pharmacological studies in which intraplantar injection of a peripherally-restricted mGluR1/5 agonist (RS)-3,5-dihydroxyphenylglycine (DHPG) produces thermal hyperalgesia in wildtype mice through sensitization of TRPV1 on peripheral terminals of DRG neurons (Kim et al., 2009; Price et al., 2007). However, administration of DHPG in *Fmr1* knockout mice failed to produce a thermal hyperalgesia phenotype (Price et al., 2007). In line with this, spared nerve injury causes neuropathic allodynia (painful response to a stimulus that does not normally cause pain) in wildtype mice, within five days of the surgery. However, *Fmr1* knockout mice did not exhibit mechanical allodynia behaviors until three weeks after the spared nerve injury surgery (Price et al., 2007). These findings indicate there is a lack of peripheral neuron sensitization in response to mGluR1/5 stimulation in the periphery of *Fmr1* knockout mice, which may contribute to altered pain sensitivity and possibly self-injurious behaviors in these animals.

V.5: *Cntnap2*

Humans with homozygous, loss-of-function mutations in the *Cntnap2* gene, which encodes for contactin-associated protein-like 2 (CASPR2), exhibit developmental delays and a number of core ASD features in addition to somatosensory abnormalities, pain hypersensitivity and peripheral neuron hyperexcitability (Masood and Sitamagari, 2019; Strauss et al., 2006). Mice with mutations in *Cntnap2* demonstrate ASD-like behaviors including abnormal social interactions, reduced vocal communication as well as restrictive, repetitive behaviors (Penagarikano et al., 2011). Importantly, *Cntnap2* knockout mice exhibit over-reactivity to both mechanical Von Frey fiber stimulation to the hind paw, as well as increased sensitivity to painful pin-prick stimuli and enhanced nocifensive responses to intraplantar injections of either capsaicin or formalin (Dawes et al., 2018). In line with this, DRG neurons from *Cntnap2* knockout mice are hyper-responsive to both mechanical and chemical stimuli, due to a loss of potassium channel Kv1.2 membrane expression and increased excitability (Dawes et al., 2018). Finally, injection of patient-derived, peripherally-restricted CASPR2 autoantibodies into wildtype mice lead to decreased CASPR2 and Kv1 channel expression on DRG neurons but not inflammation or DRG nerve damage (Dawes et al., 2018). Mice treated with peripherally-restricted CASPR2 autoantibodies exhibited mechanical hypersensitivity compared to mice injected with IgG-treated control mice (Dawes et al., 2018). Taken together, these experiments indicate that immune or genetic disruption of CASPR2 causes DRG neuron hyperexcitability and alterations in somatosensory behaviors.

V.6: Non-genetic models for ASD

In addition to a wide range of genetic models used to study ASD, environmental models have also been developed and are useful for understanding the complex etiologies for ASD. For example, studies over the past four decades have indicated that maternal use of valproic acid (VPA) during pregnancy is associated with significantly increased risk of ASD in offspring (Christensen et al., 2013; Roullet et al., 2013). Animals exposed to VPA in utero have been successful in recapitulating many anatomical, functional and behavioral alterations observed in ASD, including altered cortical circuit properties, social impairments and restricted, repetitive behaviors (Mabunga et al., 2015). In line with this, rats exposed to VPA on embryonic day 12.5 exhibit hypersensitivity to light touch stimuli but decreased sensitivity to painful stimuli when assessed for behavioral alterations in adolescence and adulthood (Schneider and Przewlocki, 2005). *In vitro* application of VPA to DRG neurons inhibited the collapse of sensory neuron growth cones, increased growth cone area and increased total neurite outgrowth (Shaltiel et al., 2007; Williams et al., 2002). Furthermore, embryonic treatment with VPA leads to alterations in DRG neuron anatomy, including abnormal branching patterns *in vivo* (Bold et al., 2018). While additional experiments are needed to ascertain whether VPA-induced changes in DRG neurons cause somatosensory alterations in mammals, these studies indicate that non-genetic models for ASD also exhibit abnormalities in somatosensory behaviors and alterations in DRG neuron properties.

Similarly, recent studies have suggested that viral infection during pregnancy correlates with increased risk of ASD in the offspring (Atladdottir et al., 2010; Lee et al., 2015). A rodent model of maternal immune activation (MIA) has been developed, in which pregnant mice are injected intraperitoneally with synthetic double-stranded RNA [polyinosinic-polycytidylic acid, 'poly(I:C)'] that mimics viral infection (Shi et al., 2003; Smith et al., 2007). Pregnant mothers injected with poly(I:C) on embryonic day 12.5 leads to elevated IL-17Ra mRNA expression and abnormal neural circuit development in the offspring (Choi et al., 2016). The offspring also exhibit ASD-related behavioral symptoms including social impairments and repetitive behaviors (Malkova et al., 2012; Shi et al., 2003). Furthermore, MIA-affected offspring exhibit anatomical and functional abnormalities in the dysgranular zone of the primary somatosensory cortex (Shin Yim et al., 2017), as well as tactile over-reactivity (Orefice et al., 2019). Future studies are necessary to determine whether peripheral somatosensory neuron dysfunction contributes to these phenotypes observed in MIA-affected offspring.

V.7: Animal Models for ASD, Conclusions

Somatosensory alterations in ASD models can therefore arise from a range of distinct cellautonomous, pathophysiological mechanisms that affect peripheral somatosensory neuron function. Tactile over-reactivity may result from loss of GABA_A receptor signaling and presynaptic inhibition of somatosensory neuron inputs to the spinal cord, as is the case for *Mecp2* and *Gabrb3* mutants (Chen et al., 2014; Orefice et al., 2019; Orefice et al., 2016; Zimmerman et al., 2019). Conversely, loss of K channel function may lead to somatosensory neuron hyper-excitability, as seen in *Shank3* and *Cntnap2* mutants (Dawes et al., 2018; Han et al., 2016; Orefice et al., 2019). Furthermore, alterations in activity-dependent protein translation and downstream signaling cascades observed in *Fmr1* knockout mice (Price et

al., 2007) may also contribute to abnormalities in somatosensory behaviors. The observation of HCN channel dysfunction in peripheral somatosensory neurons is consistent with prior work indicating that alterations in HCN channel function lead to hippocampal neuron hyperexcitability (Crozier et al., 2007; Watanabe et al., 2000; Yi et al., 2016; Zheng et al., 2013). Whether loss of ASD-related genes in peripheral sensory neurons also affects other ion channels, receptors and regulators of excitability is not known and would be interesting to evaluate in future studies. It is noteworthy that mutations in ASD-associated genes may differentially affect sensitivity of LTMRs and small diameter nociceptive neurons (Han et al., 2016; Orefice et al., 2016). For example, reduced sensitivity to painful thermal and chemical stimuli is observed in mice with conditional deletion of *Shank3* in nociceptive neurons and this nociceptive dysfunction is due to alterations in TRPV1 expression (Han et al., 2016; Orefice et al., 2016). Mutations in *Shank3* also contribute to reduced excitability of small-diameter nociceptive neurons, but increased excitability of LTMRs (Orefice et al., 2019). These studies may help to explain the seemingly paradoxical findings that many subjects with ASD can exhibit both hypersensitivity and aversion to light touch but also decreased responsiveness to noxious stimuli (Downs et al., 2010; Tomchek and Dunn, 2007).

VI. Peripheral Sensory Neuron Dysfunction Contributes to the Genesis of Some Other ASD Phenotypes in Mice

Could altered somatosensation contribute to social impairments and anxiety observed in patients with ASDs? The parallel anxiety-like behavior and social interaction deficits in ASD models and in animals reared in the absence of normal developmental tactile experiences led us to speculate the existence of a common mechanistic link between these two conditions. Consistent with this idea, young children with ASD are typically averse to tactile stimuli and an aversion to nurturing touch has been suggested to impact their development and behavior (Cascio, 2010). On the other hand, environmental enrichment such as increased maternal licking and grooming in mice during early postnatal periods can improve behavioral outcomes in ASD models (Lonetti et al., 2010). Increased tactile stimulation of young rodent pups, prior to weaning, also leads to greater dendritic complexity and spine density in cortical areas, as well as enhanced performance on cognitive/memory tests and reduced anxiety-like behaviors in adulthood (Richards et al., 2012).

Recent studies found that developmental loss of either *Mecp2*, *Gabrb3* or *Shank3* only in peripheral somatosensory neurons that causes tactile over-reactivity, is sufficient to cause increased anxiety-like behaviors and social impairments in adult mice (Orefice et al., 2019; Orefice et al., 2016). Ablation of each of these ASD-associated genes in peripheral somatosensory neurons at four weeks of age also leads to tactile over-reactivity, but anxiety-like behaviors are not observed in adult mice and social impairments are milder than with embryonic deletions (Orefice et al., 2016; Orefice et al., 2019; Zimmerman et al., 2019). These studies suggest that there is a developmental requirement for normal touch reactivity for the acquisition of normal brain development as well as cognitive and social behaviors. In line with this, several studies have shown that proper sensory input is critical for the development of the brain (Lacoste et al., 2014), and the absence of normal sensory inputs in

children negatively affects brain development and results in cognitive and social deficits in adulthood (Casanova et al., 2002; Frank et al., 1996; Gogolla et al., 2009; Just et al., 2007; Markram and Markram, 2010; Sheridan et al., 2012; Yizhar et al., 2011).

Indeed, development loss of either *Shank3* or *Mecp2* only in peripheral somatosensory neurons, led to anatomical and functional changes in primary somatosensory cortex of adult mice. Mice with conditional deletion of either *Mecp2* or *Shank3* in peripheral somatosensory neurons exhibited alterations in parvalbumin-positive inhibitory interneuron density in primary somatosensory cortex in adulthood, compared to control littermates (Orefice et al., 2019). The investigators also used whole-cell patch clamp electrophysiology to assess the function of cortical microcircuits in these conditional mutant mice compared to control littermates. Loss of either *Mecp2* or *Shank3* in peripheral somatosensory neurons led to a shift in the excitation/inhibition balance towards increased inhibition of layer 2/3 pyramidal neurons in trunk primary somatosensory cortex, but not primary visual cortex, from transverse brain slices taken from 8 to 10-week-old conditional mutant mice (Orefice et al., 2019). These results are consistent with a recent study (Antoine et al., 2019), which suggested that changes in sensory cortex excitation/inhibition balance observed in ASD models may reflect adaptations to altered sensory input from the periphery. It is therefore possible that alterations in cortical inhibitory neuron density or cortical microcircuit function reflect homeostatic mechanisms for increasing inhibitory neuron response rates under conditions of enhanced sensory drive to the cortex. Together, these findings indicate that developmental loss of ASD-associated genes in peripheral mechanosensory neurons leads to region-specific brain abnormalities, revealing links between developmental somatosensory over-reactivity and the genesis of aberrant behaviors.

While peripheral somatosensory neuron dysfunction may contribute to several ASD-related phenotypes, there are many other key loci of dysfunction including critical brain regions, that are significantly implicated in ASD etiology. For example, loss of *Mecp2* or *Shank3* in peripheral sensory neurons does not recapitulate all ASD behavioral phenotypes observed in the germline mutation models, including memory impairments and overgrooming behaviors observed in *Shank3* mutants. In addition, *Mecp2* mutant mice exhibit motor deficits, early lethality, memory impairments and respiratory dysfunction that is unrelated to somatosensory circuit dysfunction (Orefice et al., 2019; Orefice et al., 2016). These studies indicate that these ASD-associated genes also function in additional cell types and neural circuits to cause other ASD-related phenotypes. In summary, peripheral sensory neuron dysfunction may contribute to a subset of ASD-related phenotypes in mice, including somatosensory behavior disruptions, altered brain development, social impairments and anxiety-like behaviors. Future studies are needed to understand the mechanisms through which peripheral sensory neuron dysfunction leads to changes in brain development and complex behaviors.

VII. Peripheral Sensory Neurons: A Potential Therapeutic Target for ASDs?

Tactile hypersensitivity is commonly reported by patients with ASD, and the degree of somatosensory impairments strongly correlates with increased anxiety behaviors as well as impairments in social behaviors (Voos et al., 2013). Suppressing tactile hypersensitivity is therefore a large unmet need for patients with ASD. As predicted by recent rodent studies (Orefice et al., 2019; Orefice et al., 2016; Zimmerman et al., 2019), this strategy may also improve core ASD phenotypes such as social impairments. In line with this hypothesis, acute treatment with a peripherally restricted GABA_A receptor agonist, isoguvacine, acts directly on mechanosensory neurons to reduce their excitability, and isoguvacine treatment attenuates tactile over-reactivity that is observed in six distinct ASD mouse models (Orefice et al., 2019). Furthermore, chronic treatment of *Mecp2* and *Shank3* mutant mice beginning neonatally improves body condition, cortical abnormalities, anxiety-like behaviors, and some social impairments (Orefice et al., 2019). Thus, a peripherally restricted pharmacological approach to suppress tactile over-reactivity during early postnatal development has the potential to improve some behavioral abnormalities associated with ASD.

Other new treatment strategies that show promise for ASD may also work, at least in part, through affecting peripheral nerve function. A recent study reported that intraperitoneal administration of bumetanide from P0-P10 significantly improves functional abnormalities in the somatosensory cortex of *Fmr1* knockout mice (He et al., 2018). However, systemic administration of bumetanide leads to extremely low brain concentrations (Romermann et al., 2017), likely below those needed to inhibit the bumetanide target NKCC1. It is possible that bumetanide, akin to isoguvacine, exerts some of its effects outside of the brain. Perhaps bumetanide acts directly on peripheral somatosensory neurons, which express high levels of NKCC1 into adulthood, to affect tactile sensitivity during development. These studies also suggest that a significant benefit of peripheral restriction of drug action may be that it enables effective peripheral target engagement and optimal dosing, without the complications of brain actions and adverse effects on brain development.

VIII. Summary

Abnormal sensory reactivity is now regarded as a diagnostic feature of ASDs. The present review describes a growing body of work demonstrating that peripheral somatosensory neurons are dysfunctional and contribute to behavioral phenotypes in a wide range of genetic models for ASD, including *Mecp2*, *Gabrb3*, *Shank3*, *Cntnap2*, and *Fmr1* mutant mice as well as environmental models for ASD. These findings, together with evidence of impaired peripheral sensory neuron function in humans with both syndromic and non-syndromic forms of ASD (Bader et al., 1989; Boyle and Kaufmann, 2010; Brandt and Rosen, 1998; Haas and Love, 1988; Hagerman et al., 2007; Jellinger et al., 1988; Khalifa et al., 2001; Torres et al., 2013) suggest that targeting peripheral sensory neurons may provide an opportunity for therapeutic intervention. Future studies are necessary to understand the mechanisms through which altered peripheral sensory neuron function ultimately impacts

brain function and the development of complex behaviors. Furthermore, determining whether peripheral sensory neuron dysfunction contributes to alterations in other sensory circuits such as vision or audition will be of great interest. Together, these findings support a neuro-constructivist model, in which genetic and/or environmental perturbations that alter peripheral sensory neuron functions impact brain development and contribute to altered behaviors associated with ASD.

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Highlights

- Somatosensory alterations are highly prevalent among people with ASD.
- The mechanisms underlying abnormal somatosensation in ASD are not fully understood.
- Peripheral sensory neuron dysfunction causes altered somatosensation in ASD models.
- Peripheral somatosensory neuron dysfunction affects brain development and behavior.
- Therapies that target peripheral sensory neurons may improve some features of ASD.