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# Autism spectrum disorder in the scope of tactile processing

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ABSTRACT

Sensory processing abnormalities are among the most common behavioral phenotypes seen in autism spectrum disorder (ASD), typically characterized by either over- or under-responsiveness to stimulation. In this review, we focus on tactile processing dysfunction in ASD. We firstly review clinical studies wherein sensitivity to tactile stimuli has traditionally been assessed by self-, parent- and experimenter-reports. We also discuss recent investigations using psychophysical paradigms that gauge individual tactile thresholds. These more experimentally rigorous studies allow for more objective assessments of tactile abnormalities in ASD. However, little is understood about the neurobiological mechanisms underlying these abnormalities, or the link between tactile abnormalities and ASD symptoms. Neurobiological research that has been conducted has pointed toward dysfunction in the excitation/inhibition balance of the central nervous system of those with ASD. This review covers recent efforts that have investigated tactile dysfunction in ASD from clinical and behavioral perspectives, and some of the efforts to link these to neurobiology. On the whole, findings are inconsistent, which can be ascribed to the subjectivity of clinical assessments, the heterogeneity of ASD cohorts, and the diversity of tactile sensitivity measures. Future endeavors into understanding tactile processing differences in ASD will greatly benefit from controlled experiments driven by neurobiological hypotheses.



**Contents**

1. Introduction ..... 141
2. Clinical background ..... 141
   2.1. Clinical studies ..... 142
3. Psychophysics and sensitivity measures ..... 142
   3.1. Tactile detection threshold ..... 143
   3.2. Adaptation ..... 145
   3.3. Textures and proximal/distal stimulation ..... 145
4. Neuronal underpinnings ..... 146
   4.1. Imaging studies ..... 146
   4.2. Studies focusing on inhibition ..... 146
5. Discussion ..... 147
   5.1. Tactile abnormalities and social features in ASD ..... 147
   5.2. Limitations of the current field ..... 147
   5.3. Future directions ..... 148

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Funding sources ..... 148
References ..... 148

## 1. Introduction

Autism spectrum disorder (ASD) is defined by observed impairments in social and communicative interaction and excessive stereotyped patterns of behavior. Differences in the response to sensory stimulation (RSS) are described as phenotypically characteristic of ASD, and were reported in Kanner's original account of the disorder. Abnormalities in RSS are among the most common behavioral concerns of parents of children with ASD, with up to 95% of parents acknowledging some differences in sensory processing for their child (Rogers and Ozonoff, 2005). These sensory abnormalities are so prevalent that "hypo- or hyperreactivity to sensory input" was added to the diagnostic criteria of ASD in the DSM-5 (American Psychiatric Association, 2013). In the somatosensory domain, such abnormalities include hypersensitivity/over-responsiveness to textures (e.g., tags in shirts) and hypo-sensitivity/under-responsiveness to other sensations, particularly painful stimuli. Many parents report that their children with ASD have abnormal responses to being touched (e.g., being tickled) (Dunn, 2001; Kientz and Dunn, 1997).

Beyond the direct impacts of sensory processing abnormalities, it is possible that abnormal RSS removes the strong contribution of touch to the development of normal parental relationships in early life, and therefore exacerbates or contributes to the core social impairments of ASD. Dysfunction in tactile processing in particular has been closely linked to emotional and social distress early in life. These behaviors often impose limits on available family activities and environmental learning opportunities. Despite their prevalence and impact, the link between core features of ASD and abnormalities in tactile processing in ASD remains unclear. Furthermore, the underlying biological mechanisms are not well studied. Both the clinical and scientific literature on tactile dysfunction is variable and limited. There is also little consensus on the testing method most appropriate for assessing RSS and little specific empirical evidence for possible underlying mechanisms of tactile dysfunction.

In discussing dysfunction of the somatosensory system, it is important to consider that the sensory processing cascade involves a number of sequential steps, from conversion of mechanical information to electrical information in the skin, delivery of stimulus information to subcortical and cortical brain regions by ascending neuronal pathways, integration of information within the primary somatosensory cortex and higher-order somatosensory processing areas, to the conscious and subconscious selection of emotional and behavioral responses. Abnormal development at any one of these steps could result in abnormal sensory processing.

The majority of studies investigating tactile dysfunction have focused on parent- and teacher-reports, which, while informative, probe subjective assessments of both behavioral and emotional responses to touch and provide little information regarding the underlying and lower-order neurophysiology of tactile abnormalities in ASD. Recent work using psychophysics has reduced the degree of subjectivity, which helps to probe somatosensory processing more specifically. Finally, recent human and animal studies have suggested that excitation and inhibition imbalances, for instance in GABAergic processing, might contribute to sensory features of ASD. We will examine the clinical literature and methodology that has traditionally been employed. This is followed by a more detailed look into controlled scientific investigations of different aspects of tactile sensitivity in ASD in which the strengths of psychophysics have been exploited. Finally, the potential underlying neurophysiology of ASD, particularly within the primary somatosensory cortex where tactile information is initially processed, will be discussed as it pertains to tactile dysfunction.

## 2. Clinical background

Reviews of the clinical somatosensory literature in ASD (Baranek, 2002; Cascio, 2010; Rogers and Ozonoff, 2005) conclude that sensory impairments exist, that the degree and type of these impairments vary substantially, and that there are some weaknesses in previous studies with respect to small sample sizes and highly variable methodology. However, even with this substantial variability, sensory impairments in ASD do seem to differ significantly from those in other developmental disorders (Baranek, 2002; Wiggins et al., 2009). Several studies have described that the presence/absence, degree, and profile of sensory symptoms, as well as the behavioral response elicited, are heterogeneous in ASD (Baranek, 2002; Cascio, 2010; Rogers and Ozonoff, 2005), and constitute different metrics.

Typical dimensional metrics of sensory processing abnormalities are over-responsiveness, under-responsiveness, and failure to habituate to repetitive stimuli. Over-responsiveness (also called hyper-sensitivity) often refers to children being more "reactive" to sensory stimulation (Baranek et al., 1997, Cesaroni and Garber, 1991; Grandin, 1992), often with negative emotions or active avoidance of stimulation. However, these accounts show difficulties separating over-responsiveness from impaired habituation through self- or parent-report. Over-responsiveness of this kind may be fully explained by an impairment of adaptation to repetitive stimulation, rather than an increased response to a single instantaneous stimulus. Such a dysfunction of habituation to environmental stimuli can result in "inflexible behaviors" and abnormally focused attention (Baranek et al., 1997). It is, however, unclear whether this refers to hyper-excitability of the primary somatosensory cortex or to the expression of negative emotions to certain tactile stimuli. In contrast, under-responsiveness is characterized by reduced reactivity to sensory stimulation and is commonly associated with sensory seeking (Baranek et al., 1997).

Notably, both over- and under-responsiveness fall under the term tactile defensiveness (Baranek and Berkson, 1994; Royeen, 1984), and both characterize abnormal emotional responses to tactile stimulation (such as negative emotions towards a stimulus) or withdrawal from or avoidance of a situation. The link between over- and under-responsiveness remains unclear and it is possible that behavioral under-responsiveness results from cortical over-responsiveness as a mechanism for coping with excessive stimulation (Ben-Sasson et al., 2008; Rogers and Ozonoff, 2005). Thus, the terms over- and under-responsiveness, when applied at different stages of the somatosensory cascade, can even result in opposite descriptions of a single situation and may be biologically part of the same process. For instance, Plaisted et al. (1998) have suggested that the combination of local over-processing and global under-processing underlies both under- and over-responsiveness. They argue that autism is characterized by increased detection and discrimination in some cases (i.e., somatosensory hypersensitivity; see Bonnel et al., 2010; Bonnel et al., 2003) due to increased processing of stimulus details, but that global processing is impaired due to an inability to discern common stimulus features, leading to under-responsiveness in other cases. See also

the weak central coherence theory of autism (Booth et al., 2003; Frith, 1989; Happe, 1996).

In summary, there is substantial variability in the terminology used to describe sensory abnormalities in ASD, with possibly overlapping traits. It is possible that these stem from single mechanisms, with different emotional responses evoked under different stimulus conditions.

### 2.1. Clinical studies

Rogers et al. (2003) administered the Short Sensory Profile (SSP), a rating scale, to typically developing toddlers and to toddlers with ASD and fragile X syndrome. They found differences in tactile ratings and observed a correlation between abnormal sensitivity and adaptive behavior. In a similar study using the SSP with school-age children, negative correlations were found between tactile sensitivity and hyperactivity/attention in ASD, with the authors concluding that sensory difficulties in ASD could be a prominent driver of academic underachievement as a result of impact on attention (Ashburner et al., 2008).

Ben-Sasson et al. (2007) used a number of measures, including the Infant/Toddler Sensory Profile, Infant-Toddler Social and Emotional Assessment, Autism Diagnostic Interview-Revised, and Autism Diagnostic Observation Schedule-Generic, to examine the modulation of sensory behavior in toddlers with ASD and IQ-, age-matched controls. Toddlers with ASD were mostly characterized by under-responsiveness and stimulus-avoidance, with low frequency of sensation-seeking behaviors. These results suggest that stimulus-avoidance is not strongly linked to over-responsiveness as is often suggested (and more easily rationalized), and that under-responsiveness is not linked to more sensation-seeking. A more recent *meta*-analysis of 14 studies by Ben-Sasson et al. (2009) found that groups with ASD differed from typical groups, particularly in over-/under-responsiveness, but that the variability was mainly driven by age, symptom severity, and type of control group (e.g., age- or IQ-matched). Although correlations between different parent-reports were shown, there was no correlation between these reports and clinical observations.

In one of the first studies to move beyond pure questionnaire-based reporting, Foss-Feig et al. (2012) investigated under- and over-responsiveness and sensory-seeking in children with ASD by using observation of tactile activities in addition to parent-report. The data showed that under-responsiveness to touch correlated with stronger social and communicative impairments, and that active seeking of sensational experiences was correlated with social and non-verbal impairments and increased repetitive behaviors. Over-responsiveness, however, did not correlate with any core features of ASD. Active seeking (often associated with under-responsiveness) correlated with repetitive behavior, but repetitive behavior is often understood to be an inability to adapt, due to *over*-responsiveness. This once more exemplifies that under- and over-responsiveness are not likely to be separate symptoms. Recently, Cascio et al. (2016) investigated experimenter-reports of over-responsiveness, parent-reports of tactile symptoms and self-reports of pleasantness of textures in children with ASD. They showed that children with ASD had significantly greater over-responsiveness scores compared to controls. In addition, positive correlations between over-responsiveness and parent-reported tactile symptoms and between over-responsiveness and social impairments were observed. Pleasantness ratings were inversely related with impaired communication.

Crane et al. (2009) showed that abnormal sensory processing is also present in adults with ASD using the Adult/Adolescent Sensory Profile, although there is very high variability. More recently, Tavassoli et al. (2014) used the Sensory Processing Scale to demonstrate that adults with ASD showed greater over-responsiveness to sensory stimuli than controls. Over-responsiveness was also positively correlated with symptoms of autism. Finally, in a retrospective review of young children with ASD whose parent/caregiver completed the Sense and Self-Regulation Checklist (Silva and Schalock, 2012), Silva and Schalock (Silva and Schalock, 2013) found that for 129 children, parents reported signs of allodynia (painful response to touch) in 100% of the sample. This was confirmed by therapist-reports, in which allodynia was observed in 98% of 121 children. There was also a strong positive correlation between tactile abnormalities and severe global self-regulatory delay. This latter diagnostic represents significant inability to self-regulate in functions such as appetite, sleep, and attention, suggesting that abnormal responses to touch can have wide-ranging effects. Recently, we showed that parent-reported tactile sensory dysfunction and performance-based tactile sensitivity describe different behavioral phenomena, and that both are associated with attentional components (Wodka et al., 2016). We conclude that solely basing assessments of sensory abnormalities on parent-reports may omit inclusion of other contributing factors that may be assessed with performance-based studies.

In summary, and also as shown in Table 1, a number of studies have assessed tactile sensitivity in ASD using sensory profiles and parent-reports, and most have focused on tactile processing in children, but it appears abnormalities remain in adults with ASD. However, there is substantial inconsistency across studies with respect to patterns of response, correlations between measures, and, importantly, diagnostic terms. Especially with respect to over- and under-responsiveness, it is now thought that the underlying mechanisms are associated, possibly even stemming from a single deficit. Ultimately, sensory profiles and parent-reports are useful indicators of tactile dysfunction, but these measures do not always correlate with clinical observations nor do they provide useful indicators of cortical dysfunction.

## 3. Psychophysics and sensitivity measures

One historical difficulty in studying tactile processing in ASD has been that the main body of literature on tactile impairments in ASD are subjective or follows self-, parent- or experimenter-reports and profiles, leaving only the emotional and behavioral outputs of the sensory cascade probed. The result is that there is a blurring of higher-order cognitive dysfunction (e.g., impaired emotional processing and communication) with lower-order dysfunction of the somatosensory system. While there is substantial variability in the reported symptomatology of abnormal tactile processing in ASD, it does have a very strong prevalence within the ASD population, justifying more detailed assessment of its physiological basis. Using unbiased and objective methods of sensory processing, such as those used in psychophysical approaches, reduces the degree of subjectivity in findings. Although such measures still contain some degree of higher-order judgment, they more specifically probe somatosensory cortical processing.

The psychophysics of tactile detection and discrimination utilizes quantitative methods to study sensation and perception. Until recently, there was very limited application of these methods to examine tactile function in ASD. Applying psychophysical assessments might not only provide information regarding absolute sensitivity profiles, but may also provide more specific evidence for potential mechanisms underlying sensory impairments. Advantages of these tasks are that they reduce experimenter bias and allow for counterbalancing and proper threshold tracking (for a review, see Gescheider, 1997). One limitation of such techniques is that to capture threshold appropriately and objectively, often lengthy assessments are required. The following sections describe quantitative studies of different aspects of tactile sensitivity, focus-

**Table 1**
Summary of clinical studies investigating tactile processing abnormalities in ASD using self-/parent-/experimenter-reports of sensory and behavioral functioning.

| Study | Cohort | Sample size (ASD/TDC) | Sex (M:F) (ASD/TDC) | Age[a] (ASD/TDC) | Assessment(s) | Results (vs. TDC) |
|---|---|---|---|---|---|---|
| Rogers et al. (2003) | Toddlers | 26/24 | NA | 2.8/1.6 | SSP | ↑ tactile sensitivity scores |
| Ben-Sasson et al. (2007) | Toddlers | 100/199 | 76:24/148:51 | 2.3/1.9 | ITSP, ITSEA, ADI–R, ADOS–G | ↑ under-responsiveness; ↑ sensation avoidance; ↓ sensation seeking |
| Ashburner et al. (2008) | Children | 28/51 | 24:4/43:8 | 6–10[b] | SSP | Sig. diff. in SSP scores; neg. corrl. btw. tactile sensitivity and hyperactivity/inattention |
| Crane et al. (2009 | Adults | 18/18 | 10:8/10:8 | 41.8/39.5 | AASP | ↑ under-responsiveness; ↑ sensation avoidance; ↓ sensation seeking |
| Foss-Feig et al. (2012) | Children | 34/— | 29:5/— | 6.8/— | SP, SEQ, TDDT–R | Pos. corrl. btw. sensation seeking and social impairments; pos. corrl. btw. under-responsiveness and social impairments; no corrl. btw. over-responsiveness and core symptoms |
| Silva and Schalock (2012) | Children | 128/138 | 107:21/70:68 | 3.9/3.9 | SSC | ↑ tactile abnormality scores; pos. corrl. btw. tactile abnormalities and global self-regulatory delay; ↑ prevalence of allodynia |
| Tavassoli et al. (2014) | Adults | 221/181 | 106:115/52:129 | 38.7/37.1 | SPS | ↑ over-responsiveness; pos. corrl. btw. over-responsiveness and autistic traits |
| Cascio et al. (2016) | Children | 33/56 | NA | 8.2/6.7 | SEQ | ↑ over-responsiveness; pos. corrl. btw. over-responsiveness and tactile symptoms; pos. corrl. btw. over-responsiveness and social impairments |
| Wodka et al. (2016)[c] | Children | 57/— | 48:9/— | 10.6/— | SPM | No corrl. btw. parent-reports of tactile processing and psychophysical assessments; pos. corrl. btw. attention and tactile processing |

AASP, Adult/Adolescent Sensory Profile; ADI–R, Autism Diagnostic Interview–Revised; ADOS-G, Autism Diagnostic Observational Schedule–Generic; ASD, autism spectrum disorder; ITSEA, Infant–Toddler Social and Emotional Assessment; ITSP, Infant/Toddler Sensory Profile; NA, data not available; SEQ, Sensory Experiences Questionnaire; SP, Sensory Profile; SPM, Sensory Processing Measure; SPS, Sensory Processing Scale; SSC, Sense and Self-Regulation Checklist; SSP, Short Sensory Profile; TDC, typically developing controls; TDDT–R, Tactile Defensiveness and Discrimination Test–Revised.

[a] Mean chronological age in years.
[b] Age range of ASD and TDC groups.
[c] Used both performance-based and parent-report measures.

ing in particular on lower-level functions such as detection and discrimination (see Table 2). The different studies consider different cohorts. However, all studies included cohorts with ASD with at least normal-range IQs and either age- or developmentally matched typically developing controls.

### 3.1. Tactile detection threshold

Guclu et al. (2007) investigated, in six boys with ASD, whether they differed from six typically developing boys in their detection threshold for both flutter (40 Hz) and vibration (250 Hz), with and without forward-masking. In the forward-masking task, a 250-Hz vibration preceded the test stimulus to look at the effect of prior stimulation on detection threshold. No differences between the ASD group and the typically developing group were found in tactile detection thresholds, regardless of masking. Interestingly, the data presented in this study suggests a trend towards a lower effect of masking in the ASD group. The authors did show a correlation between tactile and emotional portions of the Touch Inventory for Elementary-School-Aged Children (Royeen and Fortune, 1990) and Sensory Profile (Dunn and Westman, 1997), suggesting that tactile perception is intact and that differences in under- and over-responsiveness might be due to emotional impairments instead.

Blakemore et al. (2006) investigated detection threshold for both flutter (30 Hz) and vibration (200 Hz) stimulation in adults with Asperger syndrome (AS) and found that adults with AS had significantly lower detection thresholds for the 200-Hz stimulus. No differences were found for flutter stimulation, although a trend was apparent. This suggests that adults with AS were less sensitive to flutter stimulation, hinting that over-responsiveness in AS is specific for vibration but not flutter. The authors also investigated the ability to perceive self- or experimenter-produced suprathreshold motion stimulation and found that while both groups perceived self-produced motion less intensely or less "tickly" than experimenter-induced motion, the adults with AS judged both situations as more intense and tickly than typical adults.

O'Riordan and Passetti (2006) used Von Frey hairs to determine contact detection threshold and found no differences between adults with ASD and controls, suggesting that detection threshold is intact in ASD. Cascio et al. (2008) investigated both contact detection threshold (also using Von Frey hairs) and sinusoidal detection threshold (for flutter; 33 Hz) on both the palm and the forearm in eight adults with ASD and eight typical controls. Contact detection threshold was significantly lower on the palm than on the forearm in both groups and no group difference was shown. However, not only was sinusoidal detection threshold found to be lower on the palm than on the forearm in both groups, detection thresh-

**Table 2**
Summary of psychophysical studies investigating tactile processing abnormalities in ASD.

| Study | Cohort | Sample size (ASD/TDC) | Sex (M:F) (ASD/TDC) | Age[a] (ASD/TDC) | Approach | Results (vs. TDC) |
|---|---|---|---|---|---|---|
| **Detection threshold** | | | | | | |
| Blakemore et al. (2006)[b] | Adults | 16/16 | 13:3/7:9 | 27.3/33.9 | Static detection threshold; supra-threshold sensitivity | ↓ detection thresholds (200 Hz only); ↑ ratings of ticklishness and intensity of tactile stimuli |
| O'Riordan and Passetti (2006) | Children | 13/13 | NA | 10.0/10.0 | Detection threshold: Von Frey hairs | No sig. diff. in detection thresholds |
| Guclu et al. (2007) | Children | 6/6 | 6:0/6:0 | 10.0/9.2 | Static detection threshold | No sig. diff. in detection thresholds (w/or w/o masking); no corrl. btw. sensory profiles and detection thresholds |
| Cascio et al. (2008) | Adults | 8/8 | 7:1/7:1 | 29.3/29.0 | Detection threshold: Von Frey hairs, sinusoidal vibrations | No sig. diff. in contact detection thresholds; ↓ vibrotactile detection thresholds (forearm only) |
| Puts et al. (2014) | Children | 32/67 | 27:5/54:13 | 10.7/10.1 | Static/dynamic detection threshold: vibrotactile battery | ↑ static detection thresholds; no sig. diff. in dynamic detection thresholds. Reduced feed-forward inhibition in ASD |
| Tavassoli et al. (2016) | Children | 21/21 | 17:4/9:12 | 9.8/10.3 | Static/dynamic detection threshold | No sig. diff. in static or dynamic detection thresholds; pos. corrl. btw. static detection thresholds and autistic traits |
| **Adaptation** | | | | | | |
| Tommerdahl et al. (2007) | Adults | 4/4 | 4:0/NA | 21–42/20–29[c] | Spatial localization | ↑ localization performance (short-duration adaption); ↓ localization performance (long-duration adaption) |
| Tannan et al. (2008) | Adults | 10/10 | 10:0/NA | 26.1/23.5 | Single-site adaptation | No sig. diff. in discrimination thresholds w/o adaptation; sig. reduced effect on discrimination thresholds w/adaptation |
| Tommerdahl et al. (2008) | Adults | 10/20 | 10:0/NA | 26.1/24.2 | Temporal order judgment | No effect on temporal order judgment w/carrier stimulus |
| Puts et al. (2014) | Children | 32/67 | 27:5/54:13 | 10.7/10.1 | Adaptation, temporal order judgment: vibrotactile battery | ↑ discrimination thresholds w/o adaptation; no sig diff. in discrimination thresholds w/adaptation; no sig. diff. in temporal order judgment w/or w/o carrier stimulus |
| **Textures, proximal/distal stimulation** | | | | | | |
| Kootz et al. (1981) | Children | 16/16 | 13:3/16:0 | 17.0/11.0 | Proximal/distal stimulation | ↑ reaction times for proximal (tactile)/distal (auditory/visual) stimuli |
| O'Riordan and Passetti (2006) | Children | 12/12 | NA | 8.6/8.6 | Roughness | No sig. diff. in sensitivity to textures |
| Cascio et al. (2008) | Adults | 8/8 | 7:1/7:1 | 29.3/29.0 | Pleasantness | No sig. diff. in hedonic ratings of textures |
| Cascio et al. (2012) | Adults | 14/16 | 13:1/16:0 | 26.4/31.6 | Roughness, pleasantness | No sig. diff. in roughness or hedonic ratings of textures |
| Haigh et al. (2016b) | Adults | 17/17 | 15:2/15:2 | 25.0/24.0 | Roughness | ↑ roughness ratings of textures |

NA, data not available.
[a] Mean chronological age in years.
[b] Recruited adults diagnosed with Asperger syndrome.
[c] Age range of ASD and TD groups.

olds on the forearm were lower in adults with ASD compared to controls. Cascio et al. (2008) also investigated the effect of a 15-s supra-threshold stimulus on detection threshold and found that while this stimulus increased detection threshold, this dampening effect was not significantly different between ASD and controls.

We recently introduced a tactile psychophysical battery (Puts et al., 2013) that consists of a variety of behavioral paradigms that aim to probe somatosensory function in children with neurodevelopmental disorders. Using this battery in cohorts of 32 children with ASD and 67 typically developing children (8–12 years old), we showed that children with ASD have higher sinusoidal static detection threshold (for flutter; 25 Hz) than age- and IQ-matched typically developing children, but that thresholds did not differ when the stimulus slowly increased from zero amplitude (dynamic threshold) (Puts et al., 2014). This means that while dynamically increasing threshold is higher than a static threshold in controls, this is not so in children with ASD, which may be evidence that the filtering of stimulus information via feed-forward inhibitory mechanisms is impaired in ASD (Zhang and Sun, 2011). These tactile findings have recently been reproduced by Tavassoli et al. (2016) in a similar cohort. They also showed that children with higher static sinusoidal detection thresholds showed more traits of ASD as mea-

sured with the Autism Spectrum Quotient, and that the effect of the dynamic stimulus was negatively correlated with the Autism Diagnostic Observation Schedule repetitive score, suggesting that children with lower inhibitory drive show more repetitive behaviors.

In summary, both O'Riordan and Passetti (2006) and Cascio et al. (2008) found that contact detection threshold was similar between individuals with ASD and controls, but the results for sinusoidal stimuli were not conclusive. Blakemore et al. (2006) showed both better vibration thresholds but marginally worse flutter thresholds in ASD. Worse flutter perception was also reported by Tavassoli et al. (2016) and Puts et al. (2014), which is suggestive of altered inhibition. Detection thresholds appear to correlate with Autism Spectrum Quotient scores and repetitive behaviors, showing some of the first evidence that tactile abnormalities are associated with core features of ASD (Tavassoli et al., 2016). However, in a small cohort, Cascio et al. (2008) showed better flutter detection in ASD (although on the palm). Vibrations and flutter stimuli are processed by different mechanoreceptors (Pacinian and RAI, respectively), which are dynamic in nature, but contact stimuli activate pressure receptors instead (Johansson et al., 1980). These studies suggest that while light touch processing remains intact in ASD, dynamic processing of vibrotactile stimuli might be altered in ASD. The differences and cross-modulation between vibration and flutter are unclear, indicating possible differences between RAI and Pacinian channels or in higher-order processing.

### 3.2. Adaptation

An interesting concept in vibrotactile processing is that of adaptation, the effect of repetitive stimulation on a subsequent stimulus (or discrimination of subsequent stimuli) (Kohn, 2007). Adaptation may be particularly relevant to ASD since difficulty adapting or habituating to sensory stimuli is commonly reported. The effect of adaptation is typically explained as inducing a "sharpening" or "increase of contrast" around the stimulus of interest by the tuning of the spatiotemporal patterns of neuronal activity (Kohn, 2007; Kohn and Whitsel, 2002). Several studies have shown that adaptation can facilitate (Goble and Hollins, 1993, 1994; Tannan et al., 2007, 2006; Tommerdahl et al., 2007) or worsen (Tannan et al., 2007) tactile discrimination in a healthy population.

Tannan et al. (2008) used a single-site adaptation task in adults with ASD and a group of controls. In the controls, amplitude discrimination threshold (for flutter) worsened significantly when an adapting stimulus preceded the standard stimulus, replicating the authors' previous results (Tannan et al., 2007). This is thought to occur because a single-site stimulus changes the relative gain of subsequent stimuli, reducing absolute intensity perception, hence making amplitude discrimination more difficult. Amplitude discrimination threshold without adaptation did not differ significantly between controls and adults with ASD, but the effect of adaptation was absent in adults with ASD, suggesting that cortical neurons do not adjust their response on the basis of repetitive sensory input in ASD. However, in our own study using larger cohorts (Puts et al., 2014), we showed that amplitude discrimination without adaptation is also worse in children with ASD, and that they also do not show an additional effect of adaptation, suggesting that both the connections necessary for accurate separation of signals in the amplitude discrimination task (thought to act on lateral inhibition) and the adjustment to repetitive stimulation are absent in children with ASD.

Tommerdahl et al. (2007) investigated the effect of a short or long adapting stimulus on spatial discrimination in four adults with ASD compared to four typical adult controls. In controls, a long adapting stimulus significantly improved spatial discrimination compared to the short adapting stimulus (as expected since an adapting stimulus is thought to increase contrast and better contrast would lead to increased spatial discrimination). While the adults with ASD outperformed the controls in the short stimulus condition, a long adapting stimulus did not significantly change the performance of adults with ASD, suggesting that an adapting stimulus has no effect on performance in ASD.

Finally, Tommerdahl et al. (2008) investigated whether the ability to determine the order of two subsequent stimuli on two fingers differs when there is a low-amplitude stimulus present throughout each trial. In 20 typical adults, this adapting pulse resulted in significantly poorer performance compared to a condition without the adapting stimulus, possibly because the adapting stimulus leads to synchronization between neuronal ensembles encoding the two digits, impairing separation of temporal encoding. Tommerdahl and colleagues also showed that the adapting stimulus did not alter performance in 10 adults with ASD, suggestive of local under-connectivity in ASD. However, in our study in children (Puts et al., 2014), we showed no difference in performance in typically developing children and children with ASD with or without the adapting stimulus.

Clinically, an inability to habituate to sensory information is common in ASD. Behaviorally, the ability to adjust to changes in sensory input by means of adaptation can be evaluated by testing the effect of repetitive and/or long-duration stimulation on tactile sensitivity. The majority of studies show that adaptation is impaired in ASD and that this may relate to altered neuronal, particularly inhibitory, functions. There do appear to be differences between children and adults with ASD, which could possibly be explained by alternate strategies that develop during the lifetime. However, none of these studies found associations between behavioral metrics of adaptation and clinical features of difficulty habituating, although they may not have tested for them. Moreover, clinical features of habituation are not well defined.

### 3.3. Textures and proximal/distal stimulation

While the studies described above focus on relatively low-level tactile function, a few other studies have investigated higher-level touch or haptic processing in a social, emotive, or communicative setting. As mentioned previously, Guclu et al. (2007) concluded that some tactile processing effects are due to impaired emotional processing. Haptic processing involves the processing of stimulus shape and form as well as textures. O'Riordan and Passetti (2006) investigated the ability of children around eight years of age with and without ASD to discriminate between the roughness of textures using different pieces of sandpaper and found no significant differences between cohorts.

Cascio et al. (2008) investigated how an emotional measure (the hedonic magnitude estimation) related to texture roughness and tactile force in adults with and without ASD. Although no group effect was seen, adults with ASD generally judged textures as more pleasant than controls. Cascio et al. (2012) investigated a similar task but combined it with functional magnetic resonance imaging (fMRI). They replicated the earlier behavioral finding (Cascio et al., 2008) that while adults with and without ASD did not differ in their mean ratings of roughness and pleasure, ratings were more extreme for adults with ASD, and that the ratings for neutral textures were more variable. fMRI results showed that adults with ASD showed less activation in the primary somatosensory cortex for neutral and pleasant stimuli but a larger response for unpleasant stimulation. The latter was found to be correlated with social impairments. Conversely, Haigh et al. (2016b) recently assessed roughness perception in adults with ASD and found that these participants were more overly responsive to roughness than controls. In addition, roughness ratings were more variable than for

typical adults. The authors concluded that this possibly reflects over-responsiveness of the somatosensory cortex.

The finding that adults with ASD are more sensitive to tactile stimulation on the forearm (as discussed in Cascio et al. 2008) might have a larger role in the context of social touch. Kootz et al. (1981) investigated distal versus proximal touch and argued that children with ASD prefer proximal stimulation (actively seeking sensory stimulation) to distal stimulation (hearing and vision). It was found that a subgroup of children with ASD had a slower reaction time for tactile processing, but the authors concluded that this may most likely reflect learning delays rather than differences in tactile sensitivity, and might be a continuation of immature behavior in a subgroup of ASD.

Ploog and Kim (2007) investigated over-selectivity to tactile stimulation in typically developing children and children with ASD. Over-selectivity refers to over-attention to certain stimuli while ignoring others. In this study, children were trained to be rewarded by certain tactile stimuli (e.g., a cloth moon) and not others. Children with ASD exhibited a much stronger preference, or selectivity, for certain objects over other "rewarded" objects, irrespective of mental age. The authors posit that this is due to decreased behavioral inhibition leading to over-selectivity to certain objects. This result may also relate to differences in attention in ASD.

In summary, psychophysical investigation of tactile processing in ASD has led to some interesting observations. While contact stimulation seems to be intact, there appear to be differences in sinusoidal stimulation in both the flutter and vibration ranges, although not consistently so. It is likely that non-significant results are due to small numbers of participants, as typical sample sizes for these behavioral tasks are around 10–12 participants per cohort, although our recent study used 32 and 67 children with and without ASD, respectively. Both adults and children with ASD appear not to exhibit adaptation, which is suggestive of altered inhibitory function. The absence of this low-level modulatory effect in particular is interesting both with respect to the inability to habituate and to the repetitive behaviors seen in ASD, although this relationship has not yet been investigated. A failure to habituate in ASD has been shown in the visual and auditory domains as well, perhaps suggesting that there are similar mechanisms within primary sensory processing (Barry and James, 1988; Blakemore et al., 2006). These relatively low-level studies may relate more to the specific somatosensory dysfunctions that exist in ASD. Nonetheless, only little is known about their associations with clinical features, although there does seem to be some evidence of a relationship (Tavassoli et al., 2016). Larger participant numbers will be needed to expand on this. Assessments of haptic processing, while more difficult to assess neurophysiologically, might reflect social aspects of tactile processing more directly by involving behavioral and emotive responses to touch. Translation between these assessments will be essential in understanding the link between neuronal function, perception, and behavioral and clinical features of ASD.

## 4. Neuronal underpinnings

Although attempts are being made to understand the mechanisms underlying impairments in tactile processing in ASD by linking behavioral tasks with known aspects of neuronal encoding of tactile information (Puts et al., 2014; Tannan et al., 2008; Tommerdahl et al., 2007; Tommerdahl et al., 2008 Tannan et al., 2008; Tommerdahl et al., 2007, 2008), our knowledge is still very limited. More recent studies have focused on the neural mechanisms underlying arousal, attention, and sensory integration, which involve the cerebellar, limbic and larger cortical systems (Marco et al., 2011). It appears that these observed sensory dysfunctions are not due to peripheral damage or abnormality, but arise from within the central nervous system. A number of studies have investigated the underlying cortical dynamics of tactile dysfunction in humans with ASD, with some investigating animal models.

### 4.1. Imaging studies

Several differences have been shown in the neuronal responses to tactile stimulation in adolescents with ASD, including differences in cortical map encoding (Coskun et al., 2009a) and decreased connectivity in finger regions of the somatosensory cortex (Coskun et al., 2013). Marco et al. (2012) showed with magnetoencephalography (MEG) that boys with ASD (7–11 years old) displayed lower amplitudes in contralateral S1 responses to tactile stimulation, which also correlated with behavioral responses, suggesting early cortical differences in tactile perception. Miyazaki et al. (2007) showed an earlier and increased peak in right somatosensory cortex to median nerve stimulation, suggesting stronger lateralization (also see Hashimoto et al., 1986).

The variability in neuronal responses appears increased in ASD. Dinstein et al. (2012) showed that while mean fMRI responses (percent change in BOLD signal) to somatosensory, visual, and auditory stimulation did not differ between adults with and without ASD, the trial-by-trial variability in the ASD group was significantly higher than in the control group, and was negatively correlated with symptom severity (also see Haigh et al., 2016a). These data suggest that the neuronal network of adults with ASD is noisier than in controls, possibly relating to imbalances in excitation and inhibition (Rubenstein and Merzenich, 2003). However, Coskun et al. (2009b) found that variability of the evoked potential (as measured with MEG) as a response to passive stimulation of the thumb and index finger did not differ between controls and adults with ASD. The discrepancy across studies may have to do with passive versus active stimulation in which a response is required.

Chang et al. (2014) used diffusion tensor imaging to compare structural connectivity in children with ASD and sensory processing disorder against controls. Using the Sensory Profile, the authors showed no relationship between parent-reported measures of tactile dysfunction and fractional anisotropy in any of 15 white matter tracts (after combining all groups). However, Pryweller et al. (2014) found that fractional anisotropy in the inferior longitudinal fasciculus was negatively correlated with tactile defensiveness scores in children with ASD, suggesting that structural connectivity between structures in the temporal and occipital lobes may be abnormal.

Although non-invasive neuroimaging methods are useful indicators of cortical function, they can only provide a macro-level perspective. In addition, most imaging studies thus far have involved a small number of participants, and it remains to be seen how findings in children compare with those in adolescents and adults, limiting the interpretability of findings. Moreover, many of these imaging studies did not control or test for other indicators, be it behavioral measures or sensitivity profiles of tactile sensitivity. As suggested by Marco et al., 2011, p. 49R, "because of the heterogeneity of ASD, the electrophysiology and functional imaging work in this domain should include behavioral measures so that within group differences do not obscure real between group differences. There is a tremendous need for further exploration in this domain as atypical tactile sensitivity appears with particularly high frequency in the autism population". In the future, it may be possible to predict tactile metrics (e.g., threshold or variability in responses) by studying brain function (e.g., brain chemistry, variability in cortical responses).

### 4.2. Studies focusing on inhibition

A number of studies have argued in favor of an excitation/inhibition imbalance in ASD (e.g., Rubenstein and Merzenich,

2003; Zhang and Sun, 2011). There is ample evidence that the main inhibitory neurotransmitter in the brain, γ-aminobutyric acid (GABA), plays important roles in shaping the neuronal response to tactile stimulation (Dykes et al., 1984; Juliano et al., 1989) and in brain development and cortical plasticity (Markram et al., 2004; McCormick, 1989). In a review, LeBlanc and Fagiolini (2011) describe the potential role of GABAergic processing in sensory problems in ASD, focusing on its potential role in early development and the so-called critical period.

In a recent human study, Tavassoli et al. (2012) investigated tactile detection threshold in typically developing children with three different expressions of the human GABRB3 gene, finding that detection threshold was associated with this gene and confirming findings from animal studies. Several studies have shown abnormal brain GABA levels in ASD as measured with edited magnetic resonance spectroscopy (for a methodological review, see Puts and Edden, 2012). For instance, Harada et al. (2011) showed reduced GABA/Glx (glutamate + glutamine + glutathione) in frontal regions of children with ASD and Rojas et al. (2014) showed reduced auditory GABA concentration in children with ASD. Gaetz et al. (2014) showed reduced auditory and motor, but not occipital, GABA levels in children with ASD. There was additionally trend-level associations between auditory GABA levels and language ability and Social Responsiveness Scale scores. Robertson et al. (2015) reported normal occipital GABA levels in adolescents and adults with ASD (including AS and pervasive developmental disorder), but showed an absence of a correlation between GABA and a measure of binocular rivalry, where an association existed in controls. In the tactile domains, our own work (Puts et al., 2016) shows reduced GABA levels in the sensorimotor but not occipital cortex. Moreover, we saw that lower GABA levels in children with ASD correlated with higher (worse) detection thresholds. Furthermore, GABA levels were not correlated with adaptation or frequency discrimination, while they were in control children. These results show that differences in brain chemistry may explain some of the behavioral features of tactile abnormalities in ASD.

Neuroanatomical differences in the GABAergic system have been seen in postmortem studies of brain tissue of individuals with ASD (Casanova et al., 2002, 2003). The GABRB3 gene encodes one subunit of GABA receptors on postsynaptic neurons, and is another gene that is thought to be associated with autism (Abrahams and Geschwind 2008; Delahanty et al., 2011; DeLorey 2005; Samaco et al., 2005). DeLorey et al. (2011) observed that mice that are heterozygous for the GABRB3 gene express reduced startle responses and that male heterozygous mice showed increased tactile sensitivity and reduced sensorimotor processing. Animals studies have also shown relationships between Fmr1 knockout mice (a mouse model for fragile X syndrome) and interneuron populations (Selby et al., 2007), as well as reduced synaptic inhibition and reduced cortical synchronization (Paluszkiewicz et al., 2011a,b). Other studies have shown associations between mouse models for the MECP2 gene (implicated in Rett syndrome) and the maturation of cortical thickness in the somatosensory cortex (Fukuda et al., 2005).

In summary, there are several lines of evidence suggesting that the GABA system is altered in ASD, and that this may relate to alterations in sensation and symptoms in both animal models and humans. Altered inhibition, or an imbalance of inhibition and excitation, can be, and has been, used to explain some of the tactile abnormalities seen in psychophysical and imaging studies. However, there is very little known about how symptoms in ASD relate to neurophysiological and neurochemical processing within the brain. While genetic markers have been linked to altered neuronal function and different patterns of connectivity (Belmonte et al., 2004; Casanova and Trippe, 2009; Casanova, 2006; Casanova et al., 2003, 2002), the specific nature of these abnormalities and how they differentially contribute to the array of developmental and behavioral features of ASD remains unclear. Given the diverse genetic origins of ASD represented in any human cohort and the heterogeneity of the resulting cortical dysfunction, it is perhaps unsurprising that studies of tactile abnormality are highly variable in their results and reproducibility. For instance, abnormal detection threshold would be expected from GABRB3 heterozygotes (DeLorey et al., 2011; Tavassoli et al., 2012) but perhaps not in other genetic subtypes linked to ASD. Indeed, we show that children in whom GABA is reduced display altered responses to detection threshold tasks, whereas those children with "normal" GABA levels show normal responses (Puts et al., 2016).

## 5. Discussion

### 5.1. Tactile abnormalities and social features in ASD

Given the importance of touch in early development, and the importance of touch in forming social and physical relationships, a link between tactile abnormalities and social features could be expected. However, findings are inconsistent. Some clinical studies suggest that under-responsiveness is associated with stronger social impairments, whereas over-responsiveness is linked to repetitive behaviors (Foss-Feig et al., 2012). Conversely, other studies show associations between over-responsiveness with social features in ASD (Cascio et al., 2016; Tavassoli et al., 2014). In the psychophysical literature, associations between controlled aspects of touch processing (detection, discrimination) and social impairments are less often reported. Altered detection threshold may contribute to the core features in ASD (Tavassoli et al., 2016), but with respect to amplitude and discrimination threshold, no studies have found links between psychophysical and clinical features. One possible reason for this dissociation is that basic features of touch processing contribute only marginally to the emotional and sensory symptoms captured by clinical assessments and may instead reflect differences in information processing more directly. Similarly, it may be that clinical reports of sensory dysfunction describe differences in broader behavioral regulation, as opposed to behavior associated specifically with sensory processing. In our recent study (Wodka et al., 2016), one of the first to combine parent-ratings with psychophysical assessments, we showed that tactile abnormalities in performance-based tasks correlate with attention but do not correlate with parent-reports (which did correlate with parent-reports of attention). These findings do not mean, however, that psychophysical differences do not contribute to a common core feature in ASD. Instead, it may be that tactile assessments that do find associations with social features probe aspects of touch that contain a higher-level social component., including pleasantness ratings (see Section 3.3), but the more complex the tactile assessment, the less clear the biological nature.

Although links between psychophysical and clinical assessments of tactile abnormalities would facilitate our understanding of these impairments in ASD, they instead are likely to measure complimentary, but not always directly related, aspects of tactile function in ASD, which ultimately may be more helpful in our understanding of differing aspects of tactile dysfunction in ASD. By teasing apart these relationships, intervention approaches could be adjusted to target the multifaceted nature of tactile dysfunction in ASD.

### 5.2. Limitations of the current field

While there is substantial evidence for tactile abnormalities in ASD, both from clinical experience and scientific literature, the findings from studies of tactile dysfunction are highly inconsistent and inconclusive. These inconsistencies reflect the heterogeneity

not only of cohorts with ASD, but also of methodologies and the descriptive language used. Many of the features presented in this review might be applicable to only certain subpopulations (i.e., high-functioning individuals), as little work has been done in children with ASD and intellectual disabilities. The underlying cortical dynamics are difficult to determine, particularly because ASD is such a heterogeneous disorder. It remains unclear what, if any, relationship there is between tactile under- and over-responsiveness in ASD. In addition, the clinical terminology itself remains vague. Even within the sensory domain, it is unclear what the relationship is between e.g. under- and over-responsiveness, sensory seeking, or avoidance. Many clinical diagnostics, although useful, are subjective and may not provide detailed information on the specific biological nature of tactile impairments. As can be seen in Table 1, studies investigating the clinical features use a range of assessments, cohort sizes, age ranges, as well as differing subpopulations on the spectrum. These differing aspects make comparisons across studies problematic, such that even within clinical assessments a clear picture of tactile abnormalities in ASD is absent.

The recent application of tactile psychophysics to study sensory dysfunction in ASD holds great promise as it allows for more precise quantification of specific tactile and somatosensory features, reducing the subjective element that hampers report-based metrics and the less modality-specific abnormalities of emotional responses. The downside of these biologically based studies is that they often have small numbers of participants (see Table 2), reducing statistical power and effect size. They also require a level of language and attention regulation to complete, limiting the range of individuals with ASD that could be reliably assessed. In addition, the methods focus on different aspects of tactile sensitivity (e.g., constant vs. sinusoidal stimulation), making comparisons between studies difficult. Due to these inconsistencies between studies, a big picture of somatosensory abnormalities is absent from the current literature. Controlling different aspects of such experiments (e.g., choice of stimulus or analysis) is incredibly important, and more care has to be taken in the future in order to come to an agreement and providing standardized batteries of testing different components is suggested.

### 5.3. Future directions

As mentioned in Marco et al. (2011), combining clinical diagnostics with psychophysical and neuroimaging data is becoming increasingly more important for understanding the link between brain function, perception, and clinical features. Rather than directly trying to link specific tactile features such as detection and discrimination to social features, a hierarchical approach might be more preferable to improve our understanding of tactile abnormalities in ASD and their contribution to other core symptoms. Differences in brain chemistry, structure, and function might give rise to altered stimulus processing of basic tactile information. Altered tactile information processing may lead to differences in clinical features, which in turn relate to core symptoms. A multimodal approach, by which these aspects are combined, allows for an investigation of these aspects within subpopulations of ASD. Biological data could contribute substantially to our understanding of the differences between studies described above; it is possible that the variability seen in the sensitivity of measures of brain activity, for instance, are related to symptom severity, and that different “clusters” of ASD can be pulled apart on the basis of genetic information, brain activity, or chemistry profiles. Only by combining clinical diagnostics with an understanding of cortical underpinnings (e.g., the genetics of neuronal dysfunction) will it be possible to get a better picture of how tactile abnormalities develop in ASD and how they contribute to core features across the spectrum, ultimately leading to therapies that can relieve sensory symptoms.

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## Conflict of interest

None.

## References

Abrahams, B.S., Geschwind, D.H., 2008. Advances in autism genetics: on the threshold of a new neurobiology. Nat. Rev. Genet. 9, 341–355.
Ashburner, J., Ziviani, J., Rodger, S., 2008. Sensory processing and classroom emotional behavioral, and educational outcomes in children with autism spectrum disorder. Am. J. Occup. Therapy 62, 564–573.
Baranek, G.T., Berkson, G., 1994. Tactile defensiveness in children with developmental disabilities: responsiveness and habituation. J. Autism Dev. Disord. 24, 457–471.
Baranek, G.T., Foster, L.G., Berkson, G., 1997. Tactile defensiveness and stereotyped behaviors. Am. J. Occup. Therapy 51, 91–95.
Baranek, G.T., 2002. Efficacy of sensory and motor interventions for children with autism. J. Autism Dev. Disord. 32, 397–422.
Barry, R.J., James, A.L., 1988. Coding of stimulus parameters in autistic retarded, and normal children: evidence for a two-factor theory of autism. Int. J. Psychophysiol. 6, 139–149.
Belmonte, M.K., Cook Jr., E.H., Anderson, G.M., Rubenstein, J.L., Greenough, W.T., et al., 2004. Autism as a disorder of neural information processing: directions for research and targets for therapy. Mol. Psychiatry 9, 646–663.
Ben-Sasson, A., Cermak, S.A., Orsmond, G.I., Tager-Flusberg, H., Carter, A.S., et al., 2007. Extreme sensory modulation behaviors in toddlers with autism spectrum disorders. Am. J. Occup. Therapy 61, 584–592.
Ben-Sasson, A., Cermak, S.A., Orsmond, G.I., Tager-Flusberg, H., Kadlec, M.B., Carter, A.S., 2008. Sensory clusters of toddlers with autism spectrum disorders: differences in affective symptoms. J. Child Psychol. Psychiatry Allied Discip. 49, 817–825.
Ben-Sasson, A., Hen, L., Fluss, R., Cermak, S.A., Engel-Yeger, B., Gal, E., 2009. A meta-analysis of sensory modulation symptoms in individuals with autism spectrum disorders. J. Autism Dev. Disord. 39, 1–11.
Blakemore, S.J., Tavassoli, T., Calo, S., Thomas, R.M., Catmur, C., et al., 2006. Tactile sensitivity in Asperger syndrome. Brain Cognit. 61, 5–13.
Bonnel, A., Mottron, L., Peretz, I., Trudel, M., Gallun, E., Bonnel, A.M., 2003. Enhanced pitch sensitivity in individuals with autism: a signal detection analysis. J. Cognit. Neurosci. 15, 226–235.
Bonnel, A., McAdams, S., Smith, B., Berthiaume, C., Bertone, A., et al., 2010. Enhanced pure-tone pitch discrimination among persons with autism but not Asperger syndrome. Neuropsychologia 48, 2465–2475.
Booth, R., Charlton, R., Hughes, C., Happe, F., 2003. Disentangling weak coherence and executive dysfunction: planning drawing in autism and attention-deficit/hyperactivity disorder. Philos. Trans R. Soc. Lond. B Biol. Sci. 358, 387–392.
Casanova, M., Trippe, J., 2009. Radial cytoarchitecture and patterns of cortical connectivity in autism. Philos. Trans. R Soc. Lond. B Biol. Sci. 364, 1433–1436.
Casanova, M.F., Buxhoeveden, D.P., Switala, A.E., Roy, E., 2002. Minicolumnar pathology in autism. Neurology 58, 428–432.
Casanova, M.F., Buxhoeveden, D., Gomez, J., 2003. Disruption in the inhibitory architecture of the cell minicolumn: implications for autism. Neurosci.: Rev. J. Bringing Neurobiol. Neurol. Psychiatry 9, 496–507.
Casanova, M.F., 2006. Neuropathological and genetic findings in autism: the significance of a putative minicolumnopathy. Neurosci.: Rev. J. Bringing Neurobiol. Neurol. Psychiatry 12, 435–441.
Cascio, C., McGlone, F., Folger, S., Tannan, V., Baranek, G., et al., 2008. Tactile perception in adults with autism: a multidimensional psychophysical study. J. Autism Dev. Disord. 38, 127–137.
Cascio, C.J., Moana-Filho, E.J., Guest, S., Nebel, M.B., Weisner, J., et al., 2012. Perceptual and neural response to affective tactile texture stimulation in adults with autism spectrum disorders. Autism Res. 5, 231–244.
Cascio, C.J., Lorenzi, J., Baranek, G.T., 2016. Self-reported pleasantness ratings and examiner-coded defensiveness in response to touch in children with ASD: effects of stimulus material and bodily location. J. Autism Dev. Disord. 46, 1528–1537.
Cascio, C.J., 2010. Somatosensory processing in neurodevelopmental disorders. J. Neurodev. Disord. 2, 62–69.
Cesaroni, L., Garber, M., 1991. Exploring the experience of autism through firsthand accounts. J. Autism Dev. Disord. 21, 303–313.

Chang, Y.S., Owen, J.P., Desai, S.S., Hill, S.S., Arnett, A.B., et al., 2014. Autism and sensory processing disorders: shared white matter disruption in sensory pathways but divergent connectivity in social-emotional pathways. PLoS One 9, e103038.
Coskun, M.A., Varghese, L., Reddoch, S., Castillo, E.M., Pearson, D.A., et al., 2009a. How somatic cortical maps differ in autistic and typical brains. Neuroreport 20, 175–179.
Coskun, M.A., Varghese, L., Reddoch, S., Castillo, E.M., Pearson, D.A., et al., 2009b. Increased response variability in autistic brains? Neuroreport 20, 1543–1548.
Coskun, M.A., Loveland, K.A., Pearson, D.A., Papanicolaou, A.C., Sheth, B.R., 2013. Functional assays of local connectivity in the somatosensory cortex of individuals with autism. Autism Res. 6, 190–200.
Crane, L., Goddard, L., Pring, L., 2009. Sensory processing in adults with autism spectrum disorders. Autism: Int. J. Res. Pract. 13, 215–228.
DeLorey, T.M., Sahbaie, P., Hashemi, E., Li, W.W., Salehi, A., Clark, D.J., 2011. Somatosensory and sensorimotor consequences associated with the heterozygous disruption of the autism candidate gene, Gabrb3. Behav. Brain Res. 216, 36–45.
DeLorey, T.M., 2005. GABRB3 gene deficient mice: a potential model of autism spectrum disorder. Int. Rev. Neurobiol. 71, 359–382.
Delahanty, R.J., Kang, J.Q., Brune, C.W., Kistner, E.O., Courchesne, E., et al., 2011. Maternal transmission of a rare GABRB3 signal peptide variant is associated with autism. Mol. Psychiatry 16, 86–96.
Dinstein, I., Heeger, D.J., Lorenzi, L., Minshew, N.J., Malach, R., Behrmann, M., 2012. Unreliable evoked responses in autism. Neuron 75, 981–991.
Dunn, W., Westman, K., 1997. The sensory profile: the performance of a national sample of children without disabilities. Am. J. Occup. Ther. 51, 25–34.
Dunn, W., 2001. The sensations of everyday life: empirical theoretical, and pragmatic considerations. Am. J. Occup. Therapy 55, 608–620.
Dykes, R.W., Landry, P., Metherate, R., Hicks, T.P., 1984. Functional role of GABA in cat primary somatosensory cortex: shaping receptive fields of cortical neurons. J. Neurophysiol. 52, 1066–1093.
Foss-Feig, J.H., Heacock, J.L., Cascio, C.J., 2012. Tactile responsiveness patterns and their association with core features in autism spectrum disorders. Res. Autism Spectr. Disorders 6, 337–344.
Frith, U., 1989. A new look at language and communication in autism. Br. J. Disorders Commun. 24, 123–150.
Fukuda, T., Itoh, M., Ichikawa, T., Washiyama, K., Goto, Y., 2005. Delayed maturation of neuronal architecture and synaptogenesis in cerebral cortex of Mecp2-deficient mice. J. Neuropathol. Exp. Neurol. 64, 537–544.
Gaetz, W., Bloy, L., Wang, D.J., Port, R.G., Blaskey, L., et al., 2014. GABA estimation in the brains of children on the autism spectrum: measurement precision and regional cortical variation. Neuroimage 86, 1–9.
Gescheider, G.A., 1997. Psychophysics, The Fundamentals. Lawrence Erlbaum Associates.
Goble, A.K., Hollins, M., 1993. Vibrotactile adaptation enhances amplitude discrimination. J. Acoust. Soc. Am. 93, 418–424.
Goble, A.K., Hollins, M., 1994. Vibrotactile adaptation enhances frequency discrimination. J. Acoust. Soc. Am. 96, 771–780.
Grandin, T., 1992. In: Schopler, E., Mesibov, G.B. (Eds.), An Inside View of Autism In High Functioning Individuals with Autism. Plenum, New York, pp. 105–126.
Guclu, B., Tanidir, C., Mukaddes, N.M., Unal, F., 2007. Tactile sensitivity of normal and autistic children. Somatosens. Motor Res. 24, 21–33.
Haigh, S.M., Gupta, A., Barb, S.M., Glass, S.A., Minshew, N.J., et al., 2016a. Differential sensory fMRI signatures in autism and schizophrenia: analysis of amplitude and trial-to-trial variability. Schizophr. Res. 175, 12–19.
Haigh, S.M., Minshew, N., Heeger, D.J., Dinstein, I., Behrmann, M., 2016b. Over-responsiveness and greater variability in roughness perception in autism. Autism Res 9, 393–402.
Happe, F.G., 1996. Studying weak central coherence at low levels: children with autism do not succumb to visual illusions. A research note. J. Child Psychol. Psychiatry Allied Discip. 37, 873–877.
Harada, M., Taki, M.M., Nose, A., Kubo, H., Mori, K., et al., 2011. Non-invasive evaluation of the GABAergic/glutamatergic system in autistic patients observed by MEGA-editing proton MR spectroscopy using a clinical 3 tesla instrument. J. Autism Dev. Disord. 41, 447–454.
Hashimoto, T., Tayama, M., Miyao, M., 1986. Short latency somatosensory evoked potentials in children with autism. Brain Dev. 8, 428–432.
Johansson, R.S., Vallbo, A.B., Westling, G., 1980. Thresholds of mechanosensitive afferents in the human hand as measured with von Frey hairs. Brain Res. 184, 343–351.
Juliano, S.L., Whitsel, B.L., Tommerdahl, M., Cheema, S.S., 1989. Determinants of patchy metabolic labeling in the somatosensory cortex of cats: a possible role for intrinsic inhibitory circuitry. J. Neurosci. 9, 1–12.
Kientz, M.A., Dunn, W., 1997. A comparison of the performance of children with and without autism on the Sensory Profile. Am. J. Occup. Therapy 51, 530–537.
Kohn, A., Whitsel, B.L., 2002. Sensory cortical dynamics. Behav. Brain Res. 135, 119–126.
Kohn, A., 2007. Visual adaptation: physiology, mechanisms, and functional benefits. J. Neurophysiol. 97, 3155–3164.
Kootz, J.P., Marinelli, B., Cohen, D.J., 1981. Sensory receptor sensitivity in autistic children: response times to proximal and distal stimulation. Arch. Gen. Psychiatry 38, 271–273.
LeBlanc, J.J., Fagiolini, M., 2011. Autism: a critical period disorder? Neural Plast. 2011, 921680.
Marco, E.J., Hinkley, L.B., Hill, S.S., Nagarajan, S.S., 2011. Sensory processing in autism: a review of neurophysiologic findings. Pediatr. Res. 69, 48R–54R.
Marco, E.J., Khatibi, K., Hill, S.S., Siegel, B., Arroyo, M.S., et al., 2012. Children with autism show reduced somatosensory response: an MEG study. Autism Res. 5, 340–351.
Markram, H., Toledo-Rodriguez, M., Wang, Y., Gupta, A., Silberberg, G., Wu, C., 2004. Interneurons of the neocortical inhibitory system. Nat. Rev. Neurosci. 5, 793–807.
McCormick, D.A., 1989. GABA as an inhibitory neurotransmitter in human cerebral cortex. J. Neurophysiol. 62, 1018–1027.
Miyazaki, M., Fujii, E., Saijo, T., Mori, K., Hashimoto, T., et al., 2007. Short-latency somatosensory evoked potentials in infantile autism: evidence of hyperactivity in the right primary somatosensory area. Dev. Med. Child Neurol. 49, 13–17.
O'Riordan, M., Passetti, F., 2006. Discrimination in autism within different sensory modalities. J. Autism Dev. Disord. 36, 665–675.
Paluszkiewicz, S.M., Martin, B.S., Huntsman, M.M., 2011a. Fragile X syndrome: the GABAergic system and circuit dysfunction. Dev. Neurosci. 33, 349–364.
Paluszkiewicz, S.M., Olmos-Serrano, J.L., Corbin, J.G., Huntsman, M.M., 2011b. Impaired inhibitory control of cortical synchronization in fragile X syndrome. J. Neurophysiol. 106, 2264–2272.
Plaisted, K., O'Riordan, M., Baron-Cohen, S., 1998. Enhanced discrimination of novel, highly similar stimuli by adults with autism during a perceptual learning task. J. Child Psychol. Psychiatry Allied Discip. 39, 765–775.
Ploog, B.O., Kim, N., 2007. Assessment of stimulus overselectivity with tactile compound stimuli in children with autism. J. Autism Dev. Disord. 37, 1514–1524.
Pryweller, J.R., Schauder, K.B., Anderson, A.W., Heacock, J.L., Foss-Feig, J.H., et al., 2014. White matter correlates of sensory processing in autism spectrum disorders. Neuroimage Clin. 6, 379–387.
Puts, N.A., Edden, R.A., 2012. In vivo magnetic resonance spectroscopy of GABA: a methodological review. Prog. Nucl. Magn. Reson. Spectrosc. 60, 29–41.
Puts, N.A., Edden, R.A., Wodka, E.L., Mostofsky, S.H., Tommerdahl, M., 2013. A vibrotactile behavioral battery for investigating somatosensory processing in children and adults. J. Neurosci. Methods 218, 39–47.
Puts, N.A., Wodka, E.L., Tommerdahl, M., Mostofsky, S.H., Edden, R.A., 2014. Impaired tactile processing in children with Autism Spectrum Disorder. J. Neurophysiol. 111, 1803–1811.
Puts, N.A., Wodka, E.L., Harris, A.D., Crocetti, D., Tommerdahl, M., et al., 2016. Reduced GABA and altered somatosensory function in children with autism spectrum disorder. Autism Res.
Robertson, C., Hermann, K., Ratai, E.M., Kanwisher, N., 2015. GABA measured in visual cortex using MRS predicts atypical dynamics of binocular rivalry associated with autism. J. Vis. 15, 917.
Rogers, S.J., Hepburn, S., Wehner, E., 2003. Parent reports of sensory symptoms in toddlers with autism and those with other developmental disorders. J. Autism Dev. Disord. 33, 631–642.
Rogers, S.J., Ozonoff, S., 2005. Annotation: what do we know about sensory dysfunction in autism? A critical review of the empirical evidence. J. Child Psychol. Psychiatry 46, 1255–1268.
Rojas, D.C., Singel, D., Steinmetz, S., Hepburn, S., Brown, M.S., 2014. Decreased left perisylvian GABA concentration in children with autism and unaffected siblings. Neuroimage 86, 28–34.
Royeen, C.B., Fortune, J.C., 1990. Touch inventory for elementary-school-aged children. Am. J. Occup. Ther. 44, 155–159.
Royeen, C.B., 1984. Initial profile of therapists seeking certification in sensory integrative testing. Am. J. Occup. Therapy 38, 44–45.
Rubenstein, J.L., Merzenich, M.M., 2003. Model of autism: increased ratio of excitation/inhibition in key neural systems. Genes Brain Behav. 2, 255–267.
Samaco, R.C., Hogart, A., LaSalle, J.M., 2005. Epigenetic overlap in autism-spectrum neurodevelopmental disorders: MECP2 deficiency causes reduced expression of UBE3A and GABRB3. Hum. Mol. Genet. 14, 483–492.
Selby, L., Zhang, C., Sun, Q.Q., 2007. Major defects in neocortical GABAergic inhibitory circuits in mice lacking the fragile X mental retardation protein. Neurosci. Lett. 412, 227–232.
Silva, L.M., Schalock, M., 2012. Sense and self-regulation checklist, a measure of comorbid autism symptoms: initial psychometric evidence. Am. J. Occup. Ther. 66, 177–186.
Silva, L., Schalock, M., 2013. Treatment of tactile impairment in young children with autism: results with qigong massage. Int. J. Ther. Massage Bodywork 6, 12–20.
Tannan, V., Whitsel, B.L., Tommerdahl, M.A., 2006. Vibrotactile adaptation enhances spatial localization. Brain Res. 1102, 9–16.
Tannan, V., Simons, S., Dennis, R.G., Tommerdahl, M., 2007. Effects of adaptation on the capacity to differentiate simultaneously delivered dual-site vibrotactile stimuli. Brain Res. 1186, 164–170.
Tannan, V., Holden, J.K., Zhang, Z., Baranek, G.T., Tommerdahl, M.A., 2008. Perceptual metrics of individuals with autism provide evidence for disinhibition. Autism Res. 1, 223–230.
Tavassoli, T., Auyeung, B., Murphy, L.C., Baron-Cohen, S., Chakrabarti, B., 2012. Variation in the autism candidate gene GABRB3 modulates tactile sensitivity in typically developing children. Mol. Autism 3, 6.
Tavassoli, T., Hoekstra, R.A., Baron-Cohen, S., 2014. The Sensory Perception Quotient (SPQ): development and validation of a new sensory questionnaire for adults with and without autism. Mol. Autism 5, 29.

Tavassoli, T., Bellesheim, K., Tommerdahl, M., Holden, J.M., Kolevzon, A., Buxbaum, J.D., 2016. Altered tactile processing in children with autism spectrum disorder. Autism Res. 9, 616–620.
Tommerdahl, M., Tannan, V., Cascio, C.J., Baranek, G.T., Whitsel, B.L., 2007. Vibrotactile adaptation fails to enhance spatial localization in adults with autism. Brain Res. 1154, 116–123.
Tommerdahl, M., Tannan, V., Holden, J.K., Baranek, G.T., 2008. Absence of stimulus-driven synchronization effects on sensory perception in autism: evidence for local underconnectivity? Behav. Brain Funct. 4, 19.
Wiggins, L.D., Robins, D.L., Bakeman, R., Adamson, L.B., 2009. Brief report: sensory abnormalities as distinguishing symptoms of autism spectrum disorders in young children. J. Autism Dev. Disord. 39, 1087–1091.
Wodka, E.L., Puts, N.A., Mahone, E.M., Edden, R.A.E., Mostofsky, S.H., 2016. The role of attention in somatosensory processing: a multi-trait, multi-method analysis. J. Autism Dev. Disord. 46, 3232–3241.
Zhang, Z., Sun, Q.Q., 2011. The balance between excitation and inhibition and functional sensory processing in the somatosensory cortex. Int. Rev. Neurobiol. 97, 305–333.