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Impaired tactile processing in children with autism spectrum disorder

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[1]*Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, Maryland;* [2]*F. M. Kirby Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, Maryland;* [3]*Laboratory for Neurocognitive and Imaging Research, Kennedy Krieger Institute, Baltimore, Maryland;* [4]*Center for Autism and Related Disorders, Kennedy Krieger Institute, Baltimore, Maryland;* [5]*Department of Neurology, Johns Hopkins University, School of Medicine, Baltimore, Maryland;* [6]*Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, Maryland; and* [7]*Department of Biomedical Engineering, University of North Carolina, Chapel Hill, North Carolina*

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Puts NA, Wodka EL, Tommerdahl M, Mostofsky SH, Edden RA. Impaired tactile processing in children with autism spectrum disorder. *J Neurophysiol* 111: 1803–1811, 2014. First published February 12, 2014; doi:10.1152/jn.00890.2013.—Impaired responses to tactile stimulation are a commonly reported symptom among children with autism spectrum disorder (ASD). Furthermore, impairments in filtering or habituation to tactile input have been described in ASD. This study measured different aspects of tactile processing to investigate atypical touch sensitivity in children with ASD, methodology that has not been previously used in this population. Sixty-seven typically developing children (TDC) and 32 children with ASD (ages 8–12) completed vibrotactile tasks assessing: reaction time (RT); static and dynamic detection threshold (DT); amplitude discrimination with and without single-site adaptation; frequency discrimination; and temporal order judgment (TOJ) with and without concurrent stimulation. Children with ASD showed raised static detection thresholds and an absence of the effect of a dynamically increasing subthreshold stimulus on static detection threshold. Children with ASD also showed poorer amplitude discrimination than TDC, as well as decreased adaptation. There were no significant differences in frequency discrimination or TOJ performance between the groups. Differences in the effect of dynamic stimulation on detection threshold suggest impaired feed-forward inhibition in autism, which may be linked to poor sensory filtering. Increased baseline amplitude discrimination thresholds in ASD suggest that lateral inhibitory connections are weaker in ASD, and an absence of the effect of adaptation suggests impaired modulation of lateral inhibitory connections in ASD, which may relate to aberrant habituation. These results suggest a functional deficit in the somatosensory inhibitory system in autism. Understanding the specific mechanisms underlying sensory symptoms in autism may allow for more specific therapeutic or drug targeting in the near future.

autism; inhibition; tactile; somatosensory; psychophysics

AUTISM SPECTRUM DISORDER (ASD) is defined by impairments in both social and communicative interactions as well as repetitive, stereotypical patterns of behavior. Difficulties with sensory perception are a long recognized feature of autism. Impairments in the response to sensory stimulation were reported in Kanner's original account of the disorder, are described as phenotypically characteristic of ASD, and have been added to Diagnostic and Statistical Manual of Mental Disorders V criteria for ASD. Abnormalities in the response to sensory, particularly tactile, stimulation (e.g., tags in shirts, food textures) are among the most common behavioral concerns of parents of children with ASD, with up to 95% of parents reporting differences in sensory processing for their child with autism (Rogers and Ozonoff 2005) and may involve hyper/hypo-sensitivity to textures or structures and the inability to habituate to prior sensory experiences.

Most studies of sensory impairments in children with ASD have thus far reported on findings derived from subjective measures such as parent and teacher questionnaires. In recent years, advances in psychophysical methods for tactile assessments have allowed for less biased and more objective assessments of tactile sensitivity. The methods are further advantageous in that they allow for investigation of cortical mechanisms underlying sensory behavior. These measures have recently been validated in children (e.g., Puts et al. 2013) and are therefore well suited to studying sensory dysfunction in autism.

Several studies have attempted to characterize tactile impairments in autism using psychophysical assessment. An inability to filter irrelevant sensory information, as often seen in autism, may relate to hyper/hypo-sensitivity to tactile stimulation, as evaluated by measuring tactile detection threshold. While some studies have shown that detection of tactile stimuli is altered in both adults and children with ASD (e.g., in vibration detection; Blakemore et al. 2006), there is substantial inconsistency in findings across studies with other work showing that tactile detection is normal in autism (Cascio et al. 2008; Guclu et al. 2007; O′Riordan and Passetti 2006). This is in part attributable to differences in the of tactile stimulation used [i.e., flutter or vibration (Blakemore et al. 2006; Cascio et al. 2008) or sinusoidal or constant] as well as cohort characteristics and stimulus location (Blakemore et al. 2006). It therefore remains unclear what sensory mechanisms underlying detection are altered or whether it is the emotional response that leads to issues filtering sensory input and hyper/hypo-responsiveness. Recently, we have shown in healthy adults and typically developing children (TDC) that a detection threshold is raised after application of subthreshold stimulation, compared with a static stimulus (Puts et al. 2013). Subthreshold stimulation is thought to act through feed-forward inhibitory mechanisms (Favorov and Kursun 2011; Zhang et al. 2011), a mechanism important in filtering sensory information that is thought to be

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altered in autism. Measuring near-threshold perception in TDC and children with autism by contrasting the static and dynamic threshold might elucidate some of the somatosensory mechanisms underlying altered sensitivity to tactile stimuli.

Processes underlying tactile adaptation, the ability to adjust one's sense to prior sensory experiences (Kohn 2007), may be particularly relevant to autism. Altered ability of the nervous system to integrate prior information for future reference may contribute to difficulty habituating to sensory stimuli as is commonly reported in autism. The effect of adaptation is typically explained as inducing an "increase of contrast" around a stimulus of interest, by "sharpening" the spatiotemporal patterns of neuronal activity representing the stimulus (Kohn 2007; Kohn and Whitsel 2002) but also leading to a decrease in neuronal firing (Whitsel et al. 1989; Whitsel et al. 2003), potentially reducing the perceived intensity of stimuli after adaptation. Work by Tommerdahl and colleagues (2007, 2008) have shown that adaptation is altered in adults with ASD. Tannan et al. (2008) showed that the while healthy adults' performance on an amplitude discrimination task worsens after being exposed to adapting stimuli (thought to occur through a reduction of the perceived intensity of one of the test-stimuli), the effect of adaptation was absent in the adults with ASD. The absence of the effect of adaptation in autism has also been shown on spatial discrimination (Tommerdahl et al. 2007) and on temporal order judgment (Tommerdahl et al. 2008). The findings of impaired adaptation in adults with ASD thereby suggest that modulation of patterns of neuronal activity are altered in autism and are potentially inhibition-related. Both amplitude discrimination and adaptation are under the influence of lateral inhibitory connections; contrasting amplitude discrimination with and without adaptation will probe whether the overall lateral inhibitory mechanism is affected or whether it is the effect of adaptation that is specifically altered in autism.

Autism has been linked to inhibitory (dys)-function as shown by abnormal cortical structure (Casanova 2004) and GABA-system genetic variants have been proposed as models for autism (e.g. DeLorey 2005). Different aspects of tactile perception have been closely linked to different types of neuronal inhibitory function. Under the assumption that inhibition is indeed altered in ASD, it is expected that tasks where inhibitory mechanisms are important are altered in children with autism. Prior subthreshold stimulation in a detection threshold task has been linked to feed-forward inhibitory mechanisms. Contrasting this dynamic stimulation with a static threshold task allows us to probe the effect of feed-forward inhibition. Separation of signals through lateral inhibition is important in tactile discrimination; inhibition has also been shown to play an important role in driving tactile adaptation (Tommerdahl et al. 2010). Contrasting an amplitude discrimination task with and without adaptation allows for probing of lateral inhibitory mechanisms. Furthermore, synchronous firing (under the influence of inhibitory mechanisms) of neuronal ensembles plays an important role in the encoding of tactile frequency (McLaughlin and Juliano 2005) as well as separation of temporal stimulus order (Tommerdahl et al. 2008), the latter of which is altered in adults with autism. Given the central role of inhibition in tactile processing, we hypothesize that inhibitory mechanisms underlying vibrotactile function may be impaired in ASD.

While previous studies show differences in tactile perception and adaptation between ASD and healthy adults/TDC, it is difficult to compare findings across studies due to the variability in cohorts tested, as well as differences between stimulus characteristics. Moreover, many of the studies investigating sensory impairments in autism do not relate their findings to potential underlying physiological mechanisms. Recently, we proposed a battery of vibrotactile tasks to examine different aspects of inhibitory cortical function underlying vibrotactile processing within the same cohort. By applying a number of different vibrotactile tasks within the same cohorts of TDC and children with ASD, the scope of tactile impairments in autism can be addressed more specifically in terms of separation of the inhibitory mechanisms involved. We hypothesize that children with ASD have impairments related to modulation of perception, such as through subthreshold activity and adaptation mechanisms. Identifying the overall pattern of differences in tactile processing between TDC and children with ASD may allow for a better understanding of mechanisms of cortical dysfunction in autism. Understanding the underlying dynamics may provide direction for future work developing novel therapies, both behavioral and pharmacologic.

MATERIALS AND METHODS

Participants

Two cohorts of children, ages 8–12 yr, were tested on a tactile battery consisting of 10 tasks: 67 TDC (age: 10.08 ± 1.28 yr; 13 female) and 32 children with ASD (age 10.70 ± 1.15 yr; 5 female). There were no group differences in age or sex. A subset of these TDC (22) was included in a previous study reporting validity of these tasks between adults and TDC (Puts et al. 2013). Informed consent was obtained from a parent of each child (who also assented to testing themselves), under the approval of the Kennedy Krieger Institute and Johns Hopkins School of Medicine Institutional Review Boards.

Criteria. Participants in the ASD cohort met the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for ASD, and this was confirmed with the Autism Diagnostic Observation Schedule-Generic (ADOS-G) (Lord et al. 2000) and Autism Diagnostic Interview-Revised (ADI-R) (Lord et al. 1994). Children with identifiable causes of autism (e.g., Fragile X syndrome) and neurological disorders including epilepsy were excluded. Standard intellectual functioning was assessed using the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) (Wechsler 2003). Children with full-scale IQ scores below 80 were excluded from participation in all studies unless there was a 12-point or greater index discrepancy, in which case either the Verbal Comprehension Index or Perceptual Reasoning Index (PRI) was required to be $\geq$80 and the lower of the two was required to be $\geq$ 65.

Data. While there was a group difference in full-scale IQ (FSIQ TD: 117.33 ± 12.24; FSIQ ASD: 103.14 ± 14.93; $P < 0.001$), there were no group differences on the PRI, which is thought to be a more valid measure of intellectual functioning in children with ASD (TDC: 113.25 ± 13.91; ASD: 109.73 ± 12.75; $P > 0.2$). All children in the TDC cohort were free of criteria for psychiatric disorders as assessed using the Diagnostic Interview for Children and Adolescents-Fourth Edition (DICA-IV), and none of the children in the TDC cohort were prescribed psychoactive medications. Twelve children with ASD had comorbidity for attention-deficit/hyperactive disorder (ADHD) combined-type, four had ADHD inattentive-type, three had obsessive compulsive disorder (OCD), one had oppositional defiance disorder (ODD), and two had generalized anxiety disorder. Psychotropic medication was allowed, but children were removed from stimulant medication 1 day before and on the day of onsite visits. All other

medication was taken as prescribed. Handedness was evaluated using the Edinburgh Handedness Inventory (Oldfield 1971). Two ASD and five TDC were left-handed.

Stimulus Delivery

A CM4 four-digit tactile stimulator (Cortical Metrics) was used for stimulation (Holden et al. 2012). All stimuli were delivered to the glabrous skin of the left hand on digit 2 (LD2) and digit 3 (LD3) using a cylindrical probe (5 mm in diameter). All stimuli were presented within the flutter range (25–50 Hz). Visual feedback, task responses, and data collection were performed on an Acer Onebook Netbook computer, running CM4 software (Holden et al. 2012).

Experimental Design

The vibrotactile testing battery consisted of 10 separate tests (these are grouped as 5 *tasks*, each task having 2 *conditions*), shown in schematic form in Fig. 1 and was performed in between 30–40 min per individual. A break was given halfway through testing. Each task condition was preceded by three consecutive practice trials that required correct response to proceed, to confirm that the participant understood the specific task instructions. Feedback was given during practice trials but not during test trials. In all tasks, stimulus delivery was pseudorandomized between LD2 and LD3. Responses were obtained via a mouse click on the participants' right hand. The left mouse button corresponded to LD3 and the right mouse button to LD2. For all conditions except reaction time and dynamic detection threshold, stepwise tracking was used. The tested parameter was modulated with 1 up/1 down tracking for the first 10 trials and a 2 up/1 down tracking for the remainder of the task (difficulty was increased for correct answers and decreased for incorrect answers).

Reaction time: simple and choice reaction time. A suprathreshold stimulus (25 Hz, 300 μm, 40 ms) was delivered on LD2 or LD3, and participants were asked to respond when they felt the stimulus and as quickly as possible as shown in Fig. 1*A*. In the simple reaction time (sRT) condition, a mouse click was sufficient. In the choice reaction time (cRT) condition, participants additionally had to determine on which finger they felt the stimulus [intertrial interval (ITI) 3 s; 20 trials]. For each individual, a truncated mean was calculated by sorting the reaction times (for correct trials only in the cRT condition) in order, and averaging the median 6 values (to exclude the effect of extreme outliers on mean reaction time). The standard deviation across all 20 trials was also determined for each participant to probe variability.

Detection threshold: static and dynamic detection threshold. In the static detection (sD) condition, a static suprathreshold stimulus (starting amplitude 25 μm, 25 Hz, 500 ms) was delivered to either LD2 or LD3 and participants were asked to determine on which finger they felt the stimulus (ITI = 5 s; 24 trials). The sD threshold was determined as the mean amplitude of the final five trials. In the dynamic detection (dD) condition, after a variable delay (0–2,500 ms) a 25-Hz stimulus increased from zero amplitude for each trial, (rate of amplitude increase: 2 μm/s). Participants were asked to respond as soon as they felt the stimulus and indicate the finger on which the stimulus was felt (ITI 10 s; 7 trials). dD threshold was determined as the mean stimulus amplitude at the time of pressing the button for correct trials only. Both conditions are shown in Fig. 1*B*.

Amplitude discrimination threshold with no-adaptation and with single-site adaptation. In the no-adaptation (nAD) condition, two stimuli were simultaneously delivered on LD2 and LD3. One of the stimuli had a higher amplitude (both stimuli were 25 Hz; 500 ms; Standard stimulus amplitude: 100 μm; initial comparison stimulus amplitude: 200 μm; ITI 5 s; 20 trials), and participants were asked to determine which of the two stimuli had the higher amplitude. In the single-site adaptation (sAD) condition, each trial was preceded by an adapting stimulus (duration: 1 s; amplitude: 100 μm) delivered to a single site before the comparison stimulus as shown in Fig. 1*C*. Participants were told to ignore the adapting stimulus. Amplitude discrimination thresholds were taken as the mean amplitude of the last five trials.

Frequency discrimination threshold: sequential and simultaneous. In the sequential frequency discrimination (sqFD) condition, two tactile stimuli (500 ms; 200 μm) were delivered to LD2 and LD3 sequentially [interstimulus interval (ISI) 500 ms]. In the simultaneous frequency discrimination (smFD) condition, the two stimuli were delivered to both LD2 and LD3 simultaneously as shown in Fig. 1*D*. One finger received the standard stimulus (30 Hz) and the other the comparison stimulus (initial frequency 40 Hz) in a pseudorandom allocation. In both conditions, participants were asked to determine which finger received the higher frequency stimulus (ITI 5 s; 20 trials). Frequency discrimination thresholds were taken as the mean of the frequency of the final five trials. In this task, amplitude is constant for both standard and comparison stimulus, in line with the report of Harris et al. (2001) that "subject's accuracy at comparing frequency was not affected by shifts in vibration amplitude that causes the two vibrations to have equivalent intensity," and order of higher/lower is randomized across digits.

Temporal order judgment: without and with carrier stimulus. Most, but not all participants (54 TDC, 27 ASD) also received the Temporal Order Judgment (TOJ) tasks. In this task, two single vibrotactile pulses (40 ms, 25 Hz, 200 μm) were delivered on LD2 and LD3 separated temporally by a starting ISI of 150 ms (the first pulse was assigned pseudorandomly) within a 1-s interval as shown in Fig. 1*E*. Participants were asked to respond to the digit that received the first pulse. TOJ thresholds were taken as the mean of the ISI of the final five trials. In one condition, there was no concurrent stimulation (TOJs) and in the second condition (TOJc), a 25 Hz concurrent carrier (20 μm) stimulus was delivered throughout each 1-s trial interval.

Analysis

All data were visually inspected before analysis. Participants' data for individual conditions were excluded when it was reported, orally by the experimenter, that the participant was unable to execute the condition properly (e.g., not understanding the instructions, or randomly pressing buttons as to proceed as quickly as possible without regard for the test). Children were also excluded when inspection of the tracking-profile showed deviations in stimulus value over the last five trials greater than four times the starting value, divided by the number of trials (which also reflected random button presses). For each task, a univariate model analysis was performed with condition as the dependent measure (e.g., simple and choice reaction time) and diagnosis as between-subjects factor, using SPSS 17 (SPSS, Chicago, IL). The main effects of condition and diagnosis, as well as interactions, are reported for each task. Further post hoc testing was performed to determine differences in individual tasks between the two cohorts using *t*-tests. To examine whether performance correlated between different task conditions, and with IQ and PRI, Pearson *R* values were calculated for both cohorts separately. A principal component analysis (PCA) was used to investigate components attributing to diagnosis for 11 variables: sRT; variability in sRT; difference between cRT and sRT; sD; difference between sD and RT-corrected dD; Baseline nAD; difference between sAD and nAD; sqFD; difference between smFD and sqFD; TOJs; and difference between TOJs and TOJc. Z-scores were input to the "pca" function in Matlab (The MathWorks, Natick, MA) for computation of principal components.

RESULTS

Reaction Time

Results for the sRT condition for three ASD and for the cRT condition for one TDC were excluded due to poor understanding of the task. There was a main effect of condition (F =

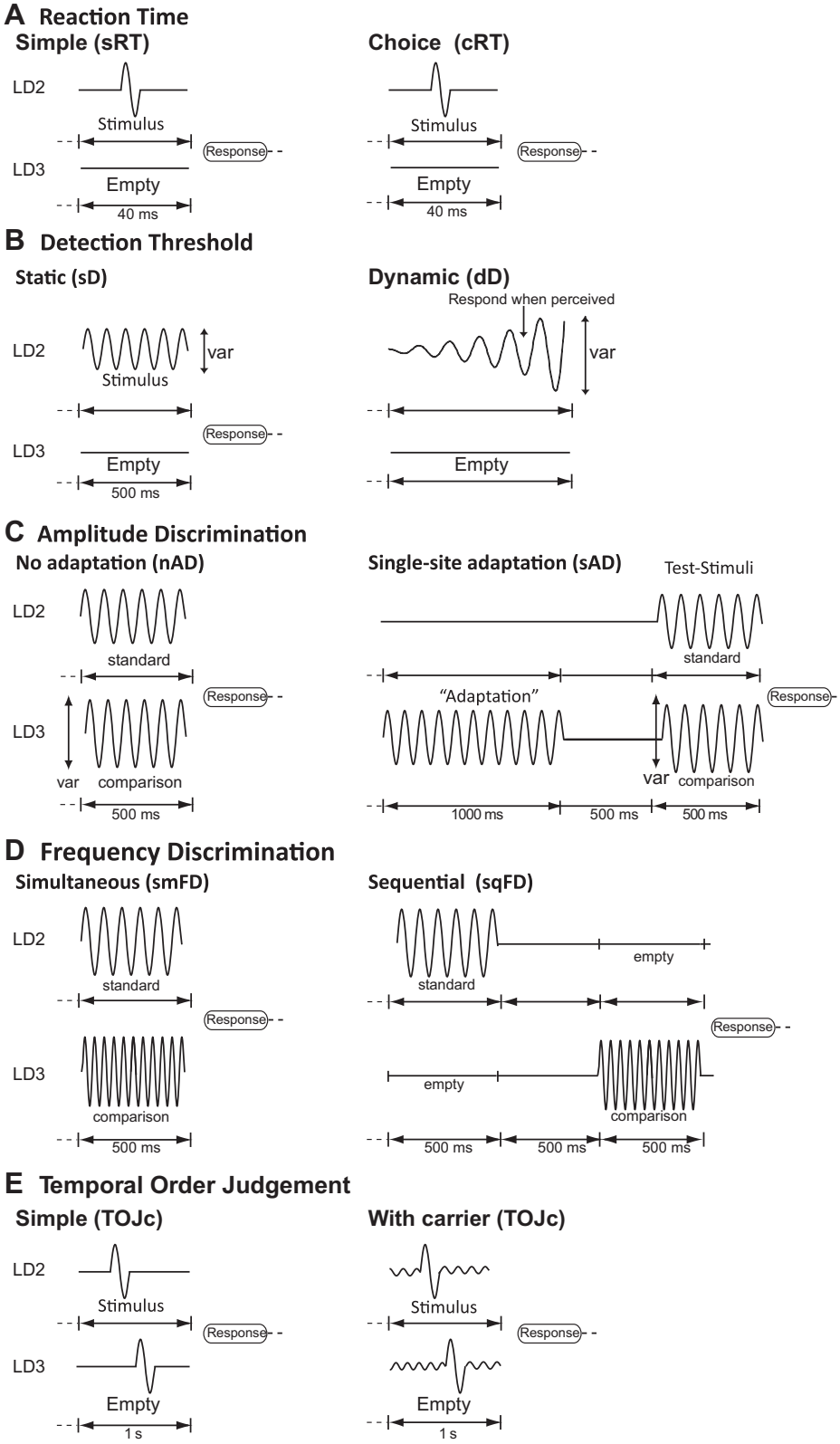

Fig. 1. Vibrotactile testing battery, trial examples. *A*: simple (sRT) and choice (cRT) reaction time. *B*: static (sD) and dynamic (dD) detection threshold. *C*: amplitude discrimination without adaptation (nAD) and with single-site adaptation (sAD). *D*: sequential (sqFD) and simultaneous (smFD) frequency discrimination. *E*: simple (TOJs) and carrier (TOJc) temporal order judgment. LD2 and LD3, left hand on digit 2 and digit 3.

143.9; $P < 0.0001$), and of diagnosis ($F = 7.01$; $P < 0.001$) but no significant interaction ($F = 1.27$; $P = 0.26$). Mean reaction time increased 107% between sRT and cRT conditions for TDC ($t = -17.30$; $P < 0.0001$) and 112% for ASD ($t = -11.01$; $P < 0.0001$) as shown in Table 1 and visualized in Fig. 2*A*. Post hoc analysis showed no significant differences in sRT between the two cohorts ($t = -1.90$; $P = 0.06$) although ASD were slower, and this effect was significant for cRT ($t = -2.09$; $P = 0.03$). Subsequently, intrasubject variability (ISV) in reaction times across all trials was investigated. There was a

Table 1. *Descriptive statistics*

Task Group/Task Single	TDC (*n*)	ASD (*n*)	Average ± SD TDC	Average ± SD ASD	Main Effects: Condition	Main Effects: Diagnosis	Task × Diagnosis Interaction (*P* Values)	Posthoc Between Task–Within Cohort (*P* Values): TDC	Posthoc Between Task–Within Cohort (*P* Values): ASD	Post Hoc Within-Task Between Cohorts (*P* Values)
Reaction time, ms										
sRT	67	29	310.79 ± 89.47	357.42 ± 148.83	<0.0001	<0.01	0.26	<0.001	<0.001	0.06
cRT	66	32	644.13 ± 179.32	759.92 ± 372.12						0.03
Detection threshold, μm										
sD	67	32	6.59 ± 2.81	9.13 ± 4.81	0.6	0.03	0.03	<0.001	0.63	0.001
dD	64	31	9.37 ± 3.54	9.69 ± 4.21				0.008	0.24	0.70
dD-RT corrected	64	31	8.13 ± 3.77	7.69 ± 4.62						0.63
Amplitude discrimination, μm										
nAD	66	30	49.05 ± 28.34	66.97 ± 37.31	0.01	0.03	0.23	<0.001	0.51	0.01
sAD	64	30	68.90 ± 36.63	73.76 ± 43.32						0.58
Frequency discrimination, hz										
sqFD	66	29	8.83 ± 4.2	9.65 ± 3.87	0.08	0.28	0.80	0.07	0.32	0.37
smFD	66	29	10.08 ± 3.82	10.59 ± 3.39						0.54
Temporal order judgement,ms										
TOJs	54	27	65.07 ± 44.97	73.09 ± 38.46	<0.0001	0.15	0.45	0.005	0.005	0.44
TOJc	54	27	102.87 ± 86.05	128.17 ± 83.05						0.22

Cohort averages for all tasks for both typically developing children (TDC) and autism spectrum disorder (ASD), main effects of task condition, and diagnosis as well as interactions. Further post hoc tests were performed to test differences between individual tasks within a task group for both cohorts separately, as well as between cohorts for individual tasks. sRT, simple reaction time task; cRT, choice reaction time task; sD, static detection threshold task; dD, dynamic detection threshold task; nAD, amplitude discrimination–no adaptation; sAD, amplitude discrimination–single-site adaptation; sqFD, sequential frequency discrimination; smFD, simultaneous frequency discrimination; TOJs, simple temporal order judgment; TOJc, temporal order judgment with a carrier stimulus.

significant main effect of condition ($P = 0.02$) and of diagnosis ($P < 0.01$) and no significant interaction. Post hoc testing showed higher variability for ASD than for TDC for both conditions (*F*-tests: $F = 0.03$ and $P < 0.001$ for sRT; $F = 0.54$ and $P = 0.02$ for cRT). There were no group differences in error-rate.

Detection Threshold

Results for the dD condition for three TDC and one ASD participant were excluded due to poor execution of the task, poor compliance and large deviations in the final trials. One ASD participant was excluded from both conditions. As the stimulus amplitude continues to increase between stimulus perception and response, the dD condition contains a reaction time component that contributes to increases in threshold values; therefore, the dD threshold for each individual was corrected using their mean cRT and the rate of amplitude increase (Puts et al. 2013) and reaction time-corrected dD is used for further analysis.

There was no significant main effect of condition ($F = 0.22$; $P < 0.6$), a significant main effect of diagnosis ($F = 4.74$; $P = 0.031$), and a significant interaction between condition and diagnosis ($F = -4.73$; $P = 0.031$). Post hoc analysis showed that both mean dD and reaction time-corrected dD threshold were significantly higher than sD threshold ($t = -5.43$ and $P < 0.001$; $t = -2.68$ and $P = 0.008$, respectively) in TDC, but this effect was not observed for children with ASD (see Fig. 2*B*). sD was significantly higher in ASD compared with TDC ($t = -2.96$; $P < 0.005$), but dD and reaction time-corrected dD did not differ between cohorts (see Table 1 for details).

Amplitude Discrimination

One TDC and one ASD participants were excluded from the nAD condition and one TDC and one ASD participant were excluded from the sAD condition due to poor execution of the test and large variability in threshold tracking. There was a significant main effect of condition ($F = 5.97$; $P = 0.01$) and of diagnosis ($F = 4.37$; $P < 0.05$) but no significant interaction between task and diagnosis ($F = 1.424$; $P = 0.234$). Post hoc analysis revealed that for TDC group, performance significantly worsened 39% after single-site adaptation compared with no adaptation ($t = -3.55$; $P < 0.001$) and this effect was not observed in the ASD group (10% worsening of performance; $t = -0.65$; $P = 0.51$) as seen in Fig. 2*C*. nAD was significantly worse in children with ASD compared with TDC ($t = -2.58$; $P = 0.0$; Table 1), but there were no significant differences in performance after single-site adaptation (sAD).

Frequency Discrimination

One TDC and three ASD participants were excluded for both conditions due to poor execution. There was no significant main effect of condition or diagnosis or a significant interaction. Indeed, post hoc analysis showed that sequential and simultaneous frequency discrimination did not differ significantly from one another in either TDC or ASD as seen in Table 1.

Temporal Order Judgment

There was a significant main effect of condition ($F = 16.39$; $P < 0.0001$) and post hoc analysis showed that in both ASD and TDC, TOJ performance worsened when a carrier stimulus

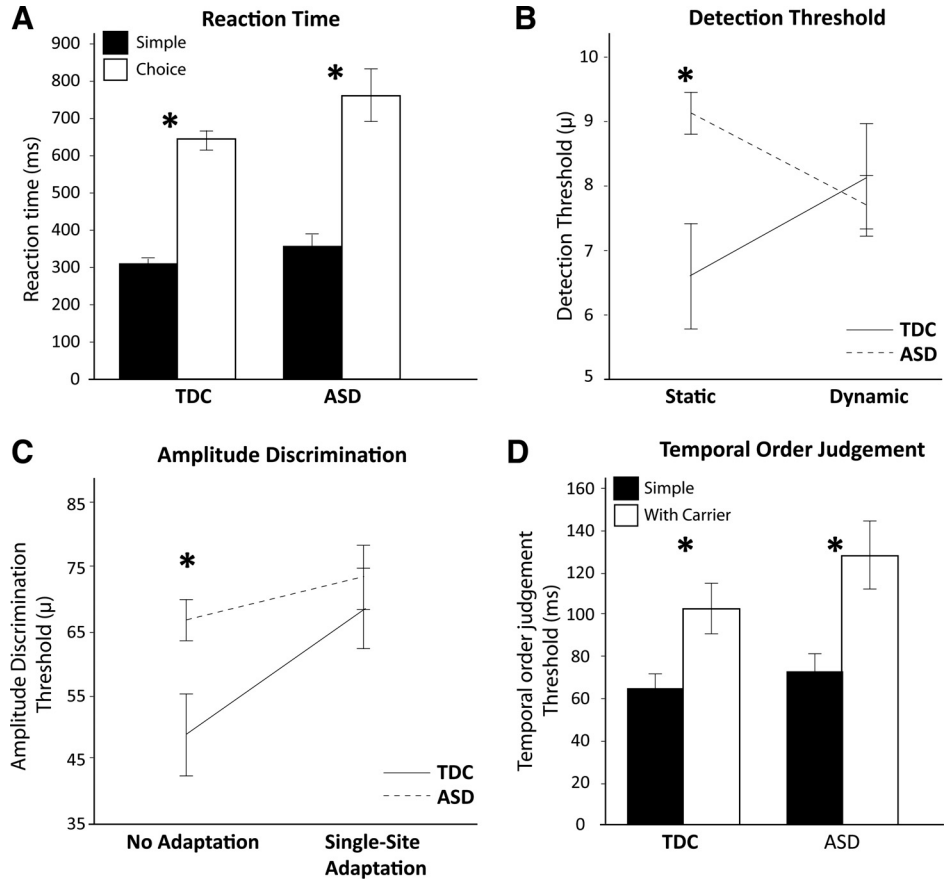

Fig. 2. Individual results. *A*: reaction time. RT is faster in the sRT condition than in the cRT condition in both cohorts. Autism spectrum disorder (ASD) children are significantly slower ($P < 0.01$) than typically developing children (TDC) in the cRT condition. *B*: detection threshold. sD is significantly lower than dD in TDC ($P < 0.001$) but not in ASD. sD is significantly higher in ASD than in TDC. *C*: amplitude discrimination. In TDC, sAD threshold is significantly worse than nAD but not in ASD. nAD is significantly worse in ASD compared with in TDC. *D*: TOJ with a carrier stimulus is significantly worse compared with the simple condition in both ASD and TDC. There are no differences between cohorts.

was present compared with TOJ without carrier stimulation ($t = -3.76$ and $t = -4.08$; $P < 0.005$ for both) as seen in Table 1. There was no main effect of diagnosis or a significant interaction. Post hoc analysis showed no significant differences between these conditions between the cohorts as shown in Fig. 2*D*.

Correlations and PCA Analyses

Figure 3 shows correlation matrices between task conditions for TDC and ASD separately. In both ASD and TDC, correlations within task groupings are visible. In TDC and ASD, correlations appear between TOJ and reaction time. It appears

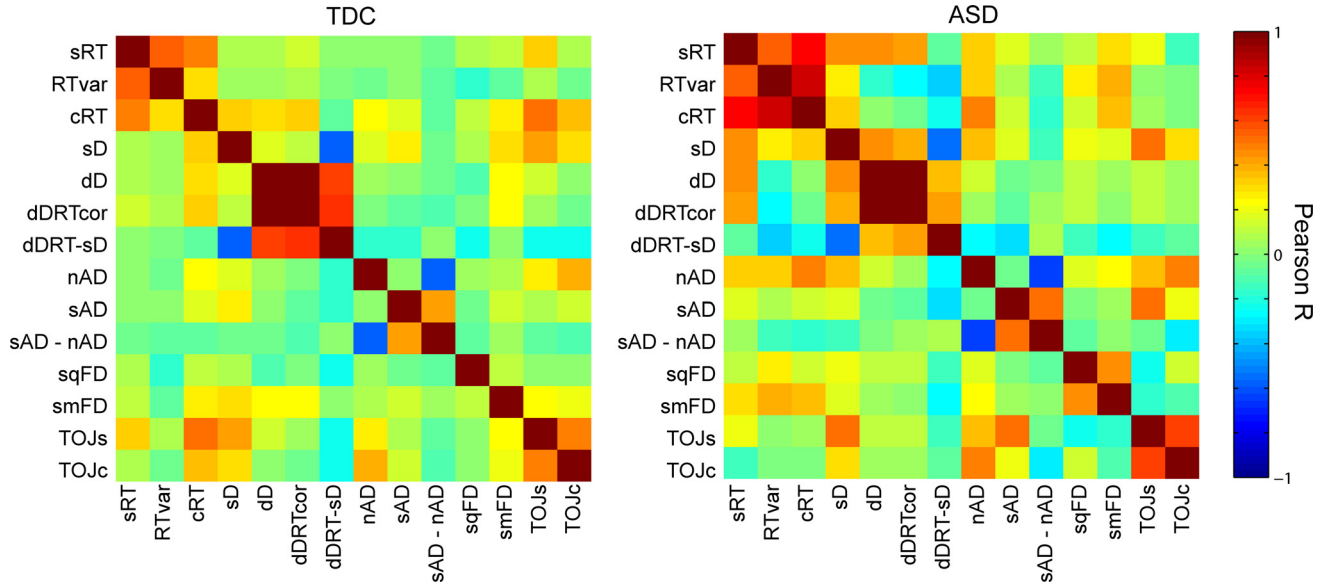

Fig. 3. Correlation matrices between task conditions for TDC and ASD separately. In both ASD and TDC, correlations within task groupings are visible. In TDC and ASD, correlations appear between TOJ and RT. It appears that in ASD there are more and stronger correlations between different task-groups, particularly between reaction time and detection threshold tasks, between TOJ and detection threshold and between amplitude discrimination and detection threshold. Finally, RT tasks appear more strongly correlated in ASD.

that in ASD the correlations are greater in strength and number, with significant correlations observed between reaction time and detection threshold tasks, TOJ and detection threshold, and amplitude discrimination and detection threshold. None of the vibrotactile measures correlated with IQ or PRI in either group. Principal component analysis did not lead to separation of ASD and TDC cohorts. The first five principal components represent 85% of the variability found in this cohort, but do not show clear separation of groups. However, the five parameters that contribute most to the total variance were as follows: sRT ISV; sD; difference between sD and corrected reaction time; nAD; and the difference between sAD and dAD, those parameters that showed the largest group differences.

DISCUSSION

The goal of this study was to compare vibrotactile sensitivity across a number of different tasks and conditions between children with ASD and TDC. By applying a broad assessment of sensory function within the same cohort, it is possible to better identify specific neurophysiological mechanisms and thereby differentiate cortical mechanisms underlying abnormal tactile processing. The results of this study show significant differences in tactile sensitivity between children with ASD and TDC on a number of vibrotactile measures, which may reflect impairments in specific inhibition-related cortical processing in autism.

Our results showed that reaction time was affected by a choice-component similarly between cohorts. TDC showed a higher detection threshold after subthreshold stimulation compared with a static threshold, but this effect was not seen in ASD, although static dynamic detection threshold was significantly higher in ASD. Similarly, TDC showed a worse amplitude discrimination threshold after adaptation compared with a baseline task, but the effect of adaptation was not visible in ASD. Finally, ASD and TDC showed similar results on frequency discrimination and TOJ tasks.

Although the ASD group showed greater variability in reaction times, mean simple reaction time did not differ significantly between cohorts although ASD were slightly slower. Greater variability in reaction times might reflect greater variability in neural signals, as shown in autism before (Dinstein et al. 2012; Milne 2011), or may indicate difficulty in orienting and executing attention to task for the ASD group. However, the specificity of differences in performance (i.e., no differences in frequency discrimination or TOJ) on various tasks suggests that while attention deficits may contribute to group differences in vibrotactile performance, they cannot fully account for these differences, and thus the role of attention in tactile response in ASD warrants further examination.

Static detection threshold was significantly worse in children with ASD. As detection threshold has been linked to expression of the GABRB3 gene (Tavassoli et al. 2012) and deficiencies in this gene have been shown in autism (DeLorey 2005; DeLorey et al. 2011), reduced static detection threshold may indeed be expected in some children with autism. It has been shown that subthreshold stimulation probes feed-forward inhibitory mechanisms (Favorov and Kursun 2011; Zhang et al. 2011), and this subthreshold inhibitory drive is expected to raise detection threshold. Indeed, in TDC a dynamic subthreshold stimulus raised detection threshold significantly, consistent with previous studies (Puts et al. 2013; Zhang et al. 2011) but we show for the first time that children with ASD are unaffected by a dynamically increasing subthreshold stimulus. The observation that subthreshold stimulation does not increase detection threshold in autism suggests impairments in feed-forward inhibitory mechanisms. Impaired inhibition could account for both increased threshold in the static condition and the lack of effect of subthreshold activation in the dynamic condition. Given the role of feed-forward inhibition in filtering of sensory input (Blankenburg et al. 2003), it is possible that an inability to filter sensory information and therefore suppress responses to stimuli that would otherwise be ignored (leading to adverse responses to sensory input in ASD) may arise from inhibitory impairment. While these findings implicate abnormal feed-forward inhibition mechanisms in ASD, further study is necessary to clarify this relationship.

Previous research has documented that a single-site delivered adapting stimulus increases amplitude discrimination threshold compared with a baseline condition in healthy adults and in TDC (Puts et al. 2013; Tannan et al. 2007, 2008). In this study we show that single-site adaptation has no such effect on amplitude discrimination threshold in children with ASD, confirming and extending findings by Tannan et al. (2008) who observed this in adults with ASD. Investigators found tighter minicolumnar organization in postmortem analysis adults with autism (Casanova et al. 2002, 2003) and also found that fewer inhibitory lateral connections were present in these brains. Fewer lateral inhibitory connections between minicolumns would reduce the contrast between areas of the brain representing different digits, therefore reducing the capacity to discriminate amplitudes, and, indeed, baseline amplitude discrimination threshold is worse in ASD than in TDC. In TDC, the presence of an adapting stimulus increases amplitude discrimination threshold, and it is thought that adaptation modulates the spatial patterns of neuronal activity between areas of the brain representing the two digits (Tommerdahl et al. 2010; Whitsel et al. 1989). In ASD, an adapting stimulus does not raise discrimination threshold, which suggests that there is also impaired modulation of the spatiotemporal pattern of activity through lateral connections, although this might be due to a ceiling effect. While these results show significant mean differences in task performance between a cohort with ASD and TDC, further analysis did not show significant effects of diagnosis on condition differences in the amplitude discrimination task. This is likely due to the relatively large variability in individual responses and possibly due to the finding that while children with ASD have a significantly worse baseline responses, modulation does not further change the threshold, so differences between cohorts for the adaptation condition are relatively small.

In this current study, TOJ performance was affected by a carrier stimulus in both TDC and children with ASD. This differs from findings reported by Tommerdahl et al. (2008), who showed in adults with ASD that TOJ threshold was not increased by a carrier stimulus, in contrast to healthy adults. Compared with Tommerdahl et al. (2008), TOJ thresholds in children as found in our study appear to be higher than those found in adults in the study of Tommerdahl study. In the current study, no differences in frequency discrimination performance were observed between cohorts either. Both frequency discrimination (McLaughlin and Juliano 2005) and

TOJ probe similar mechanisms involved in temporal encoding and the consistency of results between these tasks reinforces this link. Moreover, similarities in performance between TDC and ASD show that group differences in other tasks are not likely due to differences in task understanding or compliance. It is possible that impairments in temporal encoding or local synchrony leading to impaired TOJ in ASD are more apparent in adults.

Puts et al. (2013) showed that correlations between conditions (but "within-task groups") were weaker in TDC than in healthy adults. In the current study, a larger number of participants were used. Given the diversity of symptoms in autism, it might be expected that some children with autism show impaired responses in some tasks while other children show impaired responses in other tasks as children with ASD may have an impaired sensory response in one domain (e.g., detection) but not in other domains (e.g., discrimination). This would make correlating performance between tasks difficult. However, even though the correlation matrices shown here show weaker correlations than shown for adults in Puts et al. (2013), Fig. 3 shows that similar between-condition but within-task-group correlations are visible for both ASD and TDC. This is interesting because it shows that despite differences in behavioral performance between ASD and TDC, individual measures at the task-group level still correlate. This may suggest a change in the general "level" of inhibitory drive leading to worse responses, rather than different underlying mechanisms between ASD and TDC. Although only suggestive, Fig. 3 shows stronger correlations for ASD between, e.g., detection threshold and reaction time, detection threshold and TOJ, and amplitude discrimination and TOJ, as well as a correlation between the two frequency discrimination conditions (which is not visible in TDC). As groupings appear more separate and restricted to within-task group in TDC and healthy adults, and these task groups are thought to underlie different mechanisms, these data may suggest that children with ASD try to rely more on similar strategies across tasks than TDC do, perhaps on timing information as both frequency discrimination and TOJ are intact.

The PCA analysis, which is performed blind to diagnosis, seeks linear combinations of task results that account for variance across the cohort. Although there are individual tasks that show significant group differences, the variance within groups is substantial, such that the principal components derived do not themselves differentiate between groups. This suggests that impairments in individuals with ASD are task specific, i.e., some children are impaired in one task/condition and other children another. In 11-parameter space, the 5 parameters that contribute most strongly to the total variability between cohorts were indeed the measures that were found to be different between ASD and TDC. Here lies both the strength and weakness of the vibrotactile battery designed. It is possible to probe a number of different cortical mechanisms using this battery of tasks, and the results show mean differences between ASD and TDC in individual conditions, while assessments on an individual basis is difficult to achieve. This reflects the large heterogeneity of sensory symptoms in ASD and of ASD in general. In addition, while the relatively short testing time of our battery allows for application in pediatric and neurodevelopmental cohorts, psychophysical examinations are typically more lengthy and it remains unclear what effect our shorter protocols have on the accuracy of the measurements. Applying these tasks to neurodevelopmental cohorts is challenging and increasing the number of trials would be expected to adversely affect compliance, fatigue, and ultimately threshold measurements.

In summary, our results are consistent with the theory that impaired inhibitory processing, at least in part, underlies some of the sensory symptoms seen in autism. It has been found that the minicolumnar organization of the cortex is tighter in people with autism, and based on this finding it might be predicted that lateral (primarily) inhibitory connections are altered. Under the assumption that lateral inhibitory connections are altered in autism, a higher amplitude discrimination threshold is expected (as signals cannot be separated as well, see also Whitsel et al. 1989). Furthermore, this might also explain the lack of further adaptation in autism. On the basis of earlier studies, a higher detection threshold might be expected in autism due to altered GABAergic function (DeLorey 2005; DeLorey et al. 2011; Tavassoli et al. 2012), and our results show no further modulation due to subthreshold modulation, which may also indicate impaired feed-forward inhibitory function although no absolute differences in the dynamic condition are seen. Interestingly, temporal encoding and tasks probing neuronal synchrony appear intact in autism, even though inhibition is known to play a large role in temporal synchronicity and frequency (McLaughlin and Juliano 2005; Puts et al. 2011). Previous studies have shown reduced GABA concentration in children with autism in the sensory domains (Gaetz et al. 2013; Rojas et al. 2013) as well as reduced synchronicity as measured with MEG (Rojas et al. 2011). Our results suggest that the inhibitory deficit in ASD may be functionally specific in terms of cortical processing, rather than a broad loss of inhibitory function.

It remains unclear what the effect of medication use on these measures is, and it is possible that some medications might alter the inhibitory system and/or behavioral sensitivity, although the evidence for direct interactions is limited. As task-specific differences are seen in this study, while other measures are intact in ASD, it seems unlikely that medications drive the group differences seen. This needs further investigation in larger studies statistically powered to investigate effects of medication.

We have demonstrated that children with autism have possibly reduced inhibitory drive in specific mechanisms as measured with a battery of vibrotactile tasks. The battery is suitable for pediatric populations and acquired in 30–40 min. Our results support previous theories that inhibitory dysfunction could be one of the factors driving abnormal sensory processing in autism. The results described in this study help probe the contribution of different aspects of inhibitory (dys)-function to impaired sensory processing in autism. Understanding these mechanisms may provide a potential target for future therapies to address sensory symptoms, by both pharmacological and behavioral intervention.

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DISCLOSURES

Dr. M. Tommerdahl is cofounder of Cortical Metrics that built and provided the stimulator.

AUTHOR CONTRIBUTIONS

Author contributions: N.A.P., E.L.W., M.T., S.H.M., and R.A.E. conception and design of research; N.A.P. performed experiments; N.A.P. analyzed data; N.A.P., E.L.W., M.T., S.H.M., and R.A.E. interpreted results of experiments; N.A.P. and R.A.E. prepared figures; N.A.P. drafted manuscript; N.A.P., E.L.W., M.T., S.H.M., and R.A.E. edited and revised manuscript; N.A.P., E.L.W., M.T., S.H.M., and R.A.E. approved final version of manuscript.

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