SHORT REPORT

Altered Tactile Processing in Children with Autism Spectrum Disorder

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Although tactile reactivity issues are commonly reported in children with autism spectrum disorder (ASD), the underlying mechanisms are poorly understood. Less feed-forward inhibition has been proposed as a potential mechanism for some symptoms of ASD. We tested static and dynamic tactile thresholds as a behavioral proxy of feed-forward inhibition in 42 children (21 children with ASD and 21 typically developing [TD] children). Subthreshold conditioning typically raises the dynamic detection threshold, thus comparison of the dynamic to the static threshold generates a metric that predicts gamma-aminobutyric acid (GABA) mediated feed-forward inhibition. Children with ASD had marginally higher static thresholds and a significantly lower ratio between thresholds as compared with TD children. The lower ratio, only seen in children with ASD, might be indicative of less inhibition. Static thresholds were correlated with autism spectrum quotient scores, indicating the higher the tactile threshold, the more ASD traits. The amount of feed-forward inhibition (ratio between dynamic/static) was negatively correlated with autism diagnostic observation schedule repetitive behavior scores, meaning the less inhibition the more ASD symptoms. In summary, children with ASD showed altered tactile processing compared with TD children; thus measuring static and dynamic thresholds could be a potential biomarker for ASD and might be useful for prediction of treatment response with therapeutics, including those that target the GABAergic system. ***Autism Res*** *2016, 9: 616–620*. © 2015 International Society for Autism Research, Wiley Periodicals, Inc.

Keywords: tactile processing; inhibition; autism spectrum disorder; GABA

Introduction

The perception of touch is important for everyday living, and tactile reactivity may be affected in individuals with autism spectrum disorder (ASD) [Blakemore, et al., 2006; Cascio et al., 2008; Grandin, 1996; Marco, Hinkley, Hill, & Nagarajan, 2011; Tommerdahl, Tannan, Cascio, Baranek, & Whitsel, 2007]. The importance of tactile reactivity difficulties in ASD has led to the inclusion of sensory reactivity as an additional diagnostic criterion in the new Diagnostic and Statistical Manual of Mental Disorders [DSM-5 [A.P.A, 2013]]. In spite of the growing awareness of sensory reactivity in ASD, the underlying mechanisms of tactile reactivity differences are mostly unknown.

Detection Thresholds in ASD

To date, most reports have shown evidence for altered reactivity toward tactile stimulation in ASD, depending on the task used and the age group [Blakemore, et al., 2006; Cascio et al., 2008; Foss-Feig, Heacock, & Cascio, 2012; Puts, Wodka, Tommerdahl, Mostofsky, & Edden, 2014]. While a few studies suggest that tactile reactivity is unaffected in children with ASD [Guclu, Tanidir, Mukaddes, & Unal, 2007] a recent study showed that children with ASD have higher static tactile thresholds [Puts et al., 2014]. In another study, adults with ASD had lower tactile thresholds and rated supra-threshold tactile stimulation as significantly more "tickly" and intense than did the control group [Blakemore, et al., 2006]. Cascio et al. have also described increased reactivity to vibrations and thermal pain in ASD, although detection to light touch were similar in both groups [Cascio et al., 2008].

Feed-Forward Inhibition in ASD

By measuring the differences in static (single tactile stimulus) and dynamic (increasing tactile stimuli)

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tactile thresholds one can assess the amount of feed-forward inhibition [Puts, Edden, Wodka, Mostofsky, & Tommerdahl, 2013]. Feed-forward inhibition describes a major feature of cortical functional organization in which inhibitory cells receive input from incoming thalamocortical fibers and in turn suppress responses of neighboring cells, increasing tactile thresholds [Carpenter, 2003]. Using dynamic thresholds, one can assess feed-forward inhibitory mechanisms [Puts et al., 2013; Zhang, Francisco, Holden, Dennis, & Tommerdahl, 2011]. Recently, Puts et al. showed that differences between static and dynamic thresholds are related to GABAergic inhibition in the brain [Puts et al., 2013]. Some theories such as the "intense world hypothesis" suggest less cortical inhibition in ASD, possibly due to narrower GABAergic minicolumns [Markram, Rinaldi, & Markram, 2007; Markram & Markram, 2010]. Tommerdahl et al. [2007] previously showed that adults with ASD outperformed controls in tactile spatial acuity after short adaptation to a vibrotactile stimulus period [Tommerdahl et al., 2007]. Individuals with ASD do not show enhanced tactile spatial acuity after being adapted to tactile stimuli, which occurs in typical controls, and they proposed that this might be due to less GABAergic mediated inhibitory neurotransmission [Tommerdahl et al., 2007].

Suboptimal GABAergic mediated inhibition has been proposed as an underlying neural mechanism for autistic symptoms based on a diverse array of anatomical and physiological studies [Blatt & Fatemi, 2011; Casanova, Buxhoeveden, Switala, & Roy, 2002; Puts et al., 2014]. Furthermore, ASD has been associated with genetic variation within the GABAergic system [Buxbaum et al., 2002; Pizzarelli & Cherubini, 2011; Schroer et al., 1998], including association between a *GABRB3* polymorphism and ASD [Buxbaum et al., 2002]. It has also been shown that mice lacking this gene exhibit atypical tactile sensitivity [DeLorey et al., 2010]. Recent work in typically developing (TD) children has demonstrated that variations in the *GABRB3* receptor gene modulate tactile reactivity thresholds [Tavassoli, Auyeung, Murphy, Baron-Cohen, & Chakrabarti, 2012]. There is also separate evidence that GABAergic mediated feed-forward inhibition is lowered in children with ASD [Puts et al., 2014].

This study examined tactile processing in children with ASD to determine if there was a relationship between deficits in inhibition and ASD symptoms. Our current study used an easy-to-administer task, which measured tactile detection threshold as a proxy for GABAergic inhibition. We hypothesized that children with ASD will have less GABAergic inhibition compared with TD children and hence show less of a difference between static and dynamic thresholds.

Methods

Participants

Participants were recruited as part of ongoing studies in the Seaver Autism Center for Research and Treatment. All the parents of the participants consented to taking part in the study and the participants assented (as they were minors). A total of 42 participants of both sexes were recruited: 21 children with ASD (4 females/17 males) and 21 TD controls (12 females/9 males). Children with ASD (mean age = 9.8 +/−3.9 years; mean intelligence quotient (IQ) = 101.5 +/−16.6) and TD children (mean age = 10.3 +/−4.5 years; mean IQ = 110.2+/−15.7) did not differ in age ($P = 0.87$) or IQ ($P = 0.08$).

ASD Diagnoses

Regarding an ASD diagnosis, the autism diagnostic observation schedule (ADOS) and the Autism Diagnostic Interview Revised (ADI-R) were used in conjunction with DSM-5 criteria. The ADOS and ADI-R provide scores for social and communication deficits and repetitive and restricted behaviors. The Wechsler Abbreviated Scale of Intelligence (WASI) was used to measure cognitive functioning. All participants, with or without ASD, completed the autism spectrum quotient (AQ) to screen for autistic characteristics. The AQ is a short, 50-item questionnaire measuring autistic traits, with five subscales (social skills, attention switching, attention to detail, imagination, and communication). Results from the AQ have been replicated cross culturally [Hoekstra, Bartels, Cath, & Boomsma, 2008; Wakabayashi et al., 2007] and across different ages [Auyeung, Baron-Cohen, Wheelwright, & Allison, 2008]. A cut-off of above 26 is indicative of ASD. All TD participants scored below the cut-off, all ASD participants scored at or above cut-off.

Tactile Detection Thresholds

Static and dynamic tactile thresholds were measured using a vibrotactile stimulation device (Cortical Metrics, LLC; model CM3 + CM6 [Puts et al., 2013]) (see Fig. 1). Participants were instructed to rest their left hand on the stimulator. For the static detection threshold task, the participants felt a weak vibration on either their index or middle finger. The instructions for the two-alternative-forced-choice paradigm were: "*You will feel one weak vibration. Choose which finger you felt it on.*" Tests were started only after training, where the participants had to get three consecutive trials correct to establish that the instructions were understood. The static threshold task began with a trial of a suprathreshold vibration (starting amplitude 25 μm, frequency 25 Hz, duration 500 ms) followed by a lower amplitude (i.e., more difficult to detect) vibration. The 1up/1down staircase paradigm decreased the amplitude of the

Figure 1. The figure represents the Cortical Metrics tactile stimulator used.

stimulus after correct identification, and increased the amplitude after incorrect identification. The second threshold task was a dynamic detection task using a different stimulus presentation. Participants had to identify on which finger they felt a vibration, again using a mouse click with their right hand. The amplitude started at zero and was increased until the participant could detect it (frequency 25 Hz, duration 500 ms). The dynamic threshold task, therefore, consists of a predetection subthreshold stimulation, which activates local feed-forward inhibitory mechanisms and thus raises the threshold [Puts et al., 2014]. As there is a reaction time component in the dynamic threshold task, which slightly increased the threshold the dynamic threshold was corrected using mean reaction time and the rate of amplitude increase [Puts et al., 2014]. Ratio between dynamic and static thresholds was conducted as a proxy measure for the amount of feed-forward inhibition. The larger the difference between dynamic and static threshold the more feed-forward inhibition takes place. All tactile detection thresholds were measured in μm. Finally, we measured reaction time by applying suprathreshold stimulus to the middle finger and asking participants to respond as soon as they felt a vibration.

Statistical Analyses

Tactile static and dynamic thresholds were analyzed using SPSS 20. Static threshold (Kolmogorov-Smirnoff statistic = 0.10, $P > 0.20$) and dynamic threshold (Kolmogorov-Smirnoff statistic = 0.08, $P > 0.20$) were both normally distributed. Paired-sample *t*-tests were conducted to investigate if there were significant differences between static and dynamic thresholds in the ASD and TD group. Analysis of variance was conducted with group as fixed factor and static, dynamic, ratio of dynamic to static, and reaction time as dependent variables. In addition, Spearman correlations between tactile thresholds and AQ, ADOS, and ADI-R scores were conducted.

Results

Group Comparison

Paired-sample *t*-tests showed that the there was a significant difference between static and dynamic thresholds in the TD group ($P = 0.0001$), which is thought to reflect feed-forward inhibition. In contrast, children with ASD showed no difference between static and dynamic thresholds ($P = 0.29$) (Fig. 2).

Tests of between subject effects showed that dynamic thresholds were not different across groups ($F(1) = 0.1.22$, $P = 0.27$. However, groups showed marginal differences for static thresholds ($F = 3.60$, $P = 0.06$) (Fig. 2). The ratio between dynamic and static thresholds differed between groups ($F = 5.42$, $P = 0.02$). There were no group differences on reaction time measures ($F = 0.07$, $P = 0.79$).

Correlations Between Tactile Thresholds and ASD Dimensions

Within the ASD group, the ratio of dynamic to static thresholds correlated with ADOS repetitive behavior domain scores ($r = -0.49$, $P = 0.03$), demonstrating that the lower the ratio—or the lower the inhibition detected with the paired threshold metrics—the more repetitive behaviors. There were no correlations between ratio and scores from the ADOS total ($r = -0.36$, $P = 0.11$) or ADI-R ($r = -0.04$, $P = 0.85$). Static threshold was correlated to AQ score ($r = 0.43$, $P = 0.04$) within the ASD group, showing the higher the static threshold the more autistic traits.

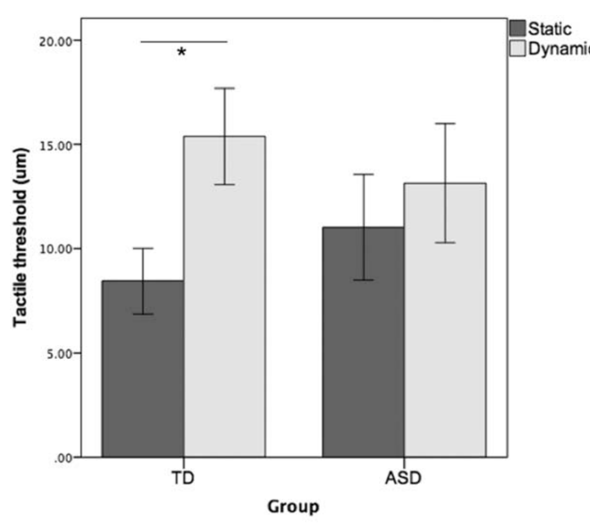

Figure 2. Static and dynamic tactile thresholds in individuals with ASD and TD individuals. Bars represent tactile detection thresholds (in micrometers; μm) for children with ASD and TD children.

Discussion

Processing touch is essential to daily functioning and tactile processing may be affected in some individuals with ASD [Blakemore, et al., 2006; Grandin, 1996]. We observed that children with ASD have higher static thresholds and a lower ratio between dynamic and static thresholds as compared with a TD group. We independently replicated previous studies showing that dynamic thresholds are higher than static thresholds in healthy controls and, importantly, found that this difference was not observed in children with ASD [Puts et al., 2014; Zhang et al., 2011].

The effect of a higher dynamic threshold compared with static threshold might be due to predetection subthreshold stimulation, which activates local feed-forward inhibition and raises the dynamic threshold [Puts et al., 2014; Zhang et al., 2011]. Hence, our results indicate less GABAergic mediated feed-forward inhibition in children with ASD. We also found a relationship between the dynamic and static ratio and ASD symptoms as measured by the ADOS, suggesting that a reduced ratio between dynamic and static thresholds, likely indicating reduced GABAergic inhibition, is associated with increased ASD symptoms in children with ASD. Interestingly, altered tactile processing was only correlated with repetitive behaviors, suggesting that the new DSM-5 Symptom B category, including repetitive behaviors and sensory reactivity issued, might share overlapping underlying mechanism.

Static Thresholds

Our finding of marginally higher static thresholds in children with ASD is consistent with previous studies [Blakemore, et al., 2006; Puts et al., 2014]. Here, we showed marginally lower vibrotactile detection thresholds (at 25 Hz), which has also been recently shown by Puts et al. [2014]. Moreover, previously Blakemore et al. [2006] have shown a trend toward lower thresholds at 30 Hz. Other studies using different tactile stimuli such as sandpaper, could not find any differences in tactile processing between children with and without ASD [Guclu et al., 2007; O'Riordan & Passetti, 2006]. However, the tactile discrimination tasks used in these studies might not have been sensitive enough to show differences, and the sample size might have been too small to draw the conclusion of intact tactile processing in ASD [Guclu et al., 2007]. Our study confirms higher static thresholds to low frequency vibrations in ASD and likely impaired tactile processing. Future studies need to explore this finding in a larger sample size with a broader range of cognitive functioning.

Lower Ratio Between Dynamic and Static Thresholds: Less Inhibition

Our findings of lower ratio between dynamic and static thresholds indicate potentially less GABAergic inhibition and are consistent with previous work linking GABAergic mediated inhibition to ASD symptoms [DiCristo, 2007; Tommerdahl et al., 2007]. Past research using vibrotactile detection thresholds and adaptation found differences between individuals with and without ASD, also suggesting less GABAergic mediated inhibition [Tommerdahl et al., 2007]. GABAergic mediated inhibition is critical for cortical circuits and modulating excitation: an imbalance between excitation and inhibition can result in deficits in sensory processing, memory, and emotional processing [Pizzarelli & Cherubini, 2011]. Our findings are consistent with the idea that an imbalance between excitatory and inhibitory processing can result in basic sensory and higher order processing deficits.

Correlation with ASD Traits

Our study showed that static thresholds were correlated with the AQ score in the ASD group, indicating that the higher the tactile threshold, the more ASD traits. The amount of feed-forward inhibition as indicated by the ratio between static and dynamic thresholds was also negatively correlated with the ADOS repetitive behavior domain, showing that the less inhibition the more ASD symptoms the individual had. Although, these findings are interesting and suggest that sensory and other ASD symptoms such as repetitive behaviors may share similar underlying mechanisms, larger sample sizes and a group with lower cognitive functioning are needed to confirm these findings.

Conclusions

Our current study used tactile threshold detection tasks, which are easy to administer and take about 5 to 10 min to complete. Comparing static and dynamic thresholds may be useful to provide clinicians and researchers with an idea about possible sensory impairments. The amount of feed-forward inhibition in children with ASD may also be a potential biomarker for future studies. Exploring the utility of threshold detection tasks to identify subgroups of children with ASD who show deficits in feed-forward GABAergic-mediated inhibition may help identify individuals who may respond selectively to GABAergic medications. Vibrotactile detection threshold tests may also be used to track treatment effects. Objective measures of ASD-related deficits in sensory processing are critical for understanding phenotypic differences across affected individuals and developing targeted therapeutics.

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