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ORIGINAL PAPER

Autonomic Dysregulation During Sensory Stimulation in Children with Autism Spectrum Disorder

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Abstract Autonomic nervous system (ANS) activity during sensory stimulation was measured in 59 children with autism spectrum disorder (ASD) ages 6–9 in comparison to 30 typically developing controls. Multivariate comparisons revealed significant differences between groups in the respiratory sinus arrhythmia (parasympathetic measure) vector of means across sensory stimuli ($p = 0.02$) and in change from domain to domain ($p = 0.01$). Sympathetic activity, measured by pre-ejection period, did not differ significantly between groups, although it was higher in ASD participants. Findings suggest that participants with ASD demonstrated a different pattern of parasympathetic activity during sensory stimulation. Findings are discussed in relation to the biological mechanisms of sensory processing in autism, insight into the autism phenotype, and the utility of ANS activity as an outcomes marker.

Keywords Autism spectrum disorders · Sensation · Autonomic nervous system · Parasympathetic nervous system · Sympathetic nervous system

Introduction

Sensory features, including hypo- and hyper-reactivity[1] to sensation or unusual interest in the sensory aspects of the environment, are highly prevalent in individuals with autism spectrum disorder (ASD), with estimates at 70–96 % (Baranek et al. 2006; Ben-Sasson et al. 2007; Leekman et al. 2007; Minshew et al. 2002; Rogers et al. 2003; Rogers and Ozonoff 2005; Tomchek and Dunn 2007). These sensory features are some of the most challenging obstacles for parents and children with ASD, limiting adaptive behavior, affecting participation in life activities, and reducing quality of life (Baranek et al. 2006; Baker et al. 2008; Ben-Sasson et al. 2013; O'Neill and Jones 1997; O'Riordan and Passetti 2006; Schaaf et al. 2011). Sensory features are now part of the core symptoms under the Restrictive and Stereotypic Behaviors diagnostic criteria for ASD in the DSM 5 (APA 2013). Consequently objective data specifying the type and nature of these sensory features will be an important marker for the ASD phenotype as well as for guiding the development of therapeutic interventions to target these features.

Current descriptions and categorization of sensory reactivity in ASD are mainly based on behavioral (parent report) data and lack consensus regarding the common patterns and the mechanisms of action. In an attempt to clarify this issue, Ben-Sasson et al. (2009) completed a meta-analysis of 14 descriptive studies of sensory symptoms in ASD and concluded that children with ASD show a higher frequency than typically developing controls (TDC) and other clinical groups, and that there were three common patterns: hypo-reactivity (the most prevalent pattern),

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[1] Behavioral sensory reactivity is defined based on the DSM-5 Autism Spectrum Disorder diagnostic criteria description: "hyper-or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment" such as "apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movements" (APA 2013).

hyper-reactivity, and seeking. Similarly, in an earlier review of the literature, Rogers and Ozonoff (2005) found more sensory features in children with ASD in comparison to other clinical groups and found more evidence for hypo-reactivity to sensory stimuli than hyper-reactivity in children with ASD. In fact, Baranek et al. (2007) suggests that hypo-reactivity distinguishes children with ASD from typically developing children and from those with developmental delays in young children with ASD. Similarly, Ben-Sasson et al. (2007), and Lane et al. (2010) found that hypo-reactivity was the most prevalent sensory pattern in their autism cohort (ages 18–33 and 33–115 months, respectively). Interestingly, these findings are in contrast to anecdotal information from individuals with ASD who report sensory over-reactivity as a characteristic that impacts participation in everyday activities (e.g., Grandin 1992).

In regard to hyper-reactivity, Schoen et al. (2009) reported that 29–61 % of their sample of children with ASD ages 5–15 years showed sensory hyper-reactivity to either tactile, auditory, visual, taste/smell or movement stimuli. Similarly, Baranek et al. (2006) reported that 56 % of their sample of children with ASD demonstrated hyper-reactivity, but that many of the participants had overlapping patterns. The variability in the literature suggests that sensory reactivity in ASD is pervasive and ubiquitous, underscoring the need to understand the underlying mechanisms of these sensory features to assist with diagnosis and treatment. To date, data describing the mechanisms sensory reactivity are inconclusive in terms of targeting the mechanisms of action. Marco et al. (2011) conducted a comprehensive review of the literature on the mechanisms of sensory processing in ASD in the auditory, tactile, visual and multisensory systems. They found considerable discrepancy and even contradiction in the electrophysiological data for every sensory system studied. For example, they found evidence for both hypo- and hyper-reactive auditory responses. They suggest that interpretation of the these data is complicated by the inherent heterogeneity of ASD and call for objective measurement of sensory processing in ASD as well as careful phenotyping of the samples studied—a recommendation followed in the current study.

One approach to objective measurement of sensory reactivity is the use of non-invasive measures of autonomic nervous system (ANS) activity during sensory stimulation. The ANS regulates an individual's ability to adapt to environmental changes through modulation of sensory, motor, visceral, and neuro-endocrine functions via its parasympathetic and sympathetic branches. The sympathetic branch of the ANS modulates immediate phasic responses to events, such as the fight-or-flight reaction while the parasympathetic branch modulates the visceral and the neuro-endocrine systems to maintain homeostasis and self-regulation, as well as to regulate recovery from a stressor/challenge (Nance and Hoy 1996). The sympathetic and parasympathetic ANS branches work in a coordinated fashion to control visceral functions (e.g. Berntson et al. 1991). Coordination patterns of co-activation occur when each branch of the efferent ANS (parasympathetic and sympathetic) either turns on or off (increase or decrease in neural activity), or has no change. These patterns orchestrate a wide range of ANS responses related to cardiovascular functioning, overall health as measured by the SF-36 (Berntson et al. 2008) and behavioral regulation (Calkins and Keane 2004; Porges 2005; Porges et al. 1994).

In regard to ANS activity and sensory features, the literature suggests that children with ASD demonstrate autonomic dysregulation during sensory stimulation. For example, Hirstein et al. (2001) suggest that participants with autism use stereotypic, repetitive sensory behaviors to calm hyper-reactivity of the sympathetic branch of the ANS; whereas Bal et al. (2010) suggest that they fail to engage the parasympathetic system for self-regulation. Using electrodermal activity (EDA) to measure sympathetic activity during sensory stimuli, several authors showed that children with ASD demonstrate reduced sympathetic activity during sensory stimuli (van Engeland et al. 1991; Bernal and Miller 1970); whereas others show signs of elevated EDA levels to auditory stimuli (Stevens and Gruzelier 1984); and still others show abnormal sympathetic habituation patterns to visual and auditory stimuli (Barry and James 1988). Recently, Schoen et al. (2009) showed that sympathetically mediated arousal levels in response to sensory stimuli (as measured by EDA) were lower in children with ASD in comparison to children with sensory modulation difficulties without ASD; but Woodard et al. (2012), using heart rate as a measure of sympathetic activity, showed that participants with ASD ($n = 8$) were more physiologically aroused than typical controls ($n = 8$) during sensory stimuli. Goodwin et al. (2006), also using heart rate as a measure of sympathetic activity, showed that only 1 in 5 or 22 % of their participants with autism showed significant heart rate increases to stressors. Hirstein et al. (2001) offer an interpretation of these differential findings suggesting that there are two different types of sympathetic responders within the ASD population—those that demonstrate hyper-arousal of the sympathetic system, and those that demonstrate little to no arousal of the sympathetic system during everyday activities. They suggest that these two types of sympathetic responders engage in behavioral activity such as self-stimulation or active sensory seeking behaviors to either dampen or increase sympathetic levels respectively in order to either calm or arouse themselves.

Studies on parasympathetic nervous system activity are more limited in number. In terms of resting or baseline activity, findings suggest that children with ASD display

lower resting (baseline) parasympathetic activity than TDC children (e.g. Porges et al. 2012; Ming et al. 2005; Bal et al. 2010; Toichi and Kamio 2003). Regarding parasympathetic activity during specific tasks or stimulation, the findings are variable. For example, Toichi and Kamio (2003) found differing patterns of parasympathetic activity in response to a cognitive task; whereas Porges et al. (2012) showed that parasympathetic activity, measured by change in respiratory sinus arrhythmia (RSA) during an auditory processing task, increased in the ASD participants suggesting inefficient processing of auditory stimuli. A decrease in RSA during a stress or challenge is adaptive according to the Polyvagal Theory, enabling rapid shifts in engagement and disengagement to promote behavioral regulation (Porges 2007). These studies suggest that there may be more than one type of parasympathetic response in participants with ASD and that parasympathetic responsiveness may be condition dependent.

Thus, the literature suggests that children with ASD, who demonstrate hypo- or hyper-reactivity to sensory stimuli, have atypical ANS activity; however, the exact nature of this ANS dysregulation is not clear. Further insight this autonomic dysregulation may be useful in distinguishing the sensory reactivity in ASD from other clinical groups, may serve as a biomarker for the autism phenotype, and/or be useful as an objective outcome measure for interventions designed to regulate sensory reactivity and improve adaptive behaviors.

Accordingly, the purpose of the current study was to examine parasympathetic and sympathetic activity during controlled sensory stimulation in a well-characterized sample of children diagnosed with ASD (ages 6–9 years) in comparison to a TDC group. We addressed two primary research questions:

1. Is there a significant difference between the groups in parasympathetic and sympathetic activity at baseline and across sensory stimulation?
2. Are there differences between the groups in the change in parasympathetic and sympathetic activity from one domain to the next during the sensory stimulation?

We hypothesized that children with ASD would demonstrate lower parasympathetic activity and higher sympathetic activity at baseline and in responses to sensory challenge in comparison with TDC.

Methods

Design

We utilized a quasi-experimental design to examine group differences in sympathetic and parasympathetic nervous system function at baseline and during sensory challenge. The independent variable, the 30-min Sensory Challenge Protocol (SCP), allows for controlled presentation of multiple stimulus types (auditory, visual, tactile, olfactory and vestibular), as described by McIntosh et al. (1999) and summarized in Table 1. Autonomic nervous system measures were collected continuously during the SCP, and were compared between groups.

Participants

Several recruitment approaches were used to enhance the representativeness of the sample. Targeted recruitment to solicit eligible families with children with ASD (Autism, Asperger's Syndrome or Pervasive Developmental Disorder, Not Otherwise Specified) occurred at regional autism events in both urban and suburban sites, public and private schools, and other autism programs. In order to be enrolled, children with ASD met the following inclusion criteria: previous diagnoses of an ASD, confirmed in this study using the Autism Diagnostic Interview-Revised (Lord et al. 1994); between the ages of 6.0–9.11 years; a Global Ability Index score greater than 75 confirmed using the Wechsler Intelligence Scale for Children-Fourth Edition (Wechsler 2003; Raiford et al. 2005); no significant primary uncorrected sensory impairment (blindness, hearing loss); and not taking medications that could affect heart rate or autonomic tone (dependent variables of interest)

Table 1 The Sensory Challenge Protocol

Baseline	Child sits quietly in a stationary chair mounted on a platform for 3 min
Tone	Pure tone at 84 dB
Visual	A 20 W strobe light flashed at 10 Hz
Siren	Recorded ambulance siren at 78 dB
Olfactory	Wintergreen essential oil in original bottle delivered 2 inches beneath child's nose in an arc moving from 4 inches on either side of nostrils
Tactile	Feather stimulus from mandibular angle on right to mandibular angle on left, following the line of the mandible
Vestibular	Chair tilts 30° from vertical over a 6 s period (3 s back, 3 s forward)
Recovery	Child seated in a stationary chair mounted on a platform for 3 min
Prolonged auditory	One 2-min presentation of 75 dB emergency broadcast signal

Baseline and recovery are 3 min. Each stimulus presentation lasts for 3 s and occurs 8 times in a row with a random inter-stimulus interval of 12–17 s

such as benzodiazepines or selective-serotonin reuptake inhibitors. The diagnostic confirmation and cognitive testing evaluations were conducted by doctoral-level clinicians who achieved research reliability on the Autism Diagnostic Interview-Revised to ensure an adequately diagnosed sample. In addition, ASD participants were screened for other psychiatric diagnoses using the Child Symptom Inventory 4 (Gadow and Sprafkin 2002) although participants were not excluded based these commonly co-occurring symptoms.[2] The age range for inclusion in the study was based on existing literature on ANS activity in children showing that parasympathetic activity (RSA) tends to stabilize in middle childhood (e.g. Alkon et al. 2003; Hinnant et al. 2011), thus we chose an age range where age-related changes in ANS activity were minimized.

TDC children were recruited using convenience sampling methods through distribution of study flyers at schools and at city locations where families were likely to see them. TDC were screened to ensure they did not have ASD with the Social Communication Questionnaire (Rutter et al. 2003). Additionally, the TDC's cognitive level was assessed using the Global Ability Index as described above and the Short Sensory Profile (SSP; McIntosh et al. 1999) to assure they did not have atypical sensory responsiveness.

We enrolled a total of 59 children with ASD (M = 92 mos., SD = 13), and 29 typically developing children (M = 98 mos., SD = 15). Based on the inherent heterogeneity of ASD, we enrolled more ASD subjects to assure that we captured a representative sample. There was a significant difference in mean age between the groups [$t(61) = 2.00$, $p = 0.05$], and therefore age-adjustment was utilized when comparing physiological responses. As expected, children with ASD had significantly lower mean Global Ability Index (M = 103.74, SD = 16.86, range 72–117) than TDC (M = 122.36, SD = 8.78, range 105–135), $t(59) = 3.58$, $p = 0.001$. In keeping with higher prevalence of ASD in males to females (4:1), there were significantly more males in the ASD group (93.2 %) than in the TDC group (55.2 %), $\chi^2 = 18.06$, $df = 1$, $p < 0.001$). The majority of the ASD and TDC sample were non-Hispanic (89.8 and 93.1 %, respectively) and Caucasian (80.7 and 86.2 %, respectively). Parents of children with ASD had similar education backgrounds as TDC parents, with 71 % of ASD and 76 % of TDC parents reporting a 4-year college degree or higher. Children with ASD were reported by their caregivers as having significantly greater sensory reactivity than TDC on all domains and total score of the Short Sensory Profile ($p < 0.0001$). These data are displayed in Table 2.

Procedures

The study procedures were approved by the university's institutional review board and informed consent and assent procedures were followed to ensure that all parents and children understood the study prior to participation. In order to prevent anticipatory effects from children expecting certain stimuli, and to reduce anxiety due to the application of electrodes, the laboratory used a space ship theme whereby the electrodes were described to children as a way "to prepare you for space travel." In addition, electrodes were sent home so the child could try them out prior to the study. Children were told they could stop or skip sensations during the protocol.

Sensory Challenge Protocol (SCP)

The SCP was designed to challenge a child's physiological coping mechanisms during exposure to controlled sensory stimulation (McIntosh et al. 1999) and is summarized in Table 1. E-Prime2.0 software was used for controlling stimulus presentation (Psychology Software Tools, Inc. 2012) and was triggered through the experimenter's Dell PC desktop computer running Windows XP (2000). The experimenter for the SCP followed a script with minimal interactions with the child to limit sensory stimulation. Experimenter reliability was quantified and rated by a second observer in the room. Briefly, after the child was acclimated to the electrocardiogram (ECG) electrodes (approximately 10 min), the child was instructed to sit quietly in a padded chair mounted to a platform for 3 min (baseline) in a semi-darkened room lit only with a 60 W incandescent desk light in the back of the room (10 feet behind the study participant). Participants were instructed to remain still and quiet during their pretend space ride. Once the 3 min baseline period was completed, the child was given a reward sticker and, to prevent expectation bias, told to expect to "hear, feel or see something" at the start of each sensory domain. Following the verbal instruction, the child was presented with the stimuli in the order listed in Table 1, and then rewarded with a sticker. In order to ensure comparability between groups, all children were administered the stimuli in the same order.

Measures

Quantification of ANS Measures: RSA and PEP

Non-invasive parasympathetic and sympathetic measures from the heart were collected at baseline and during

[2] Eleven subjects (19 %) screened positively for anxiety, 12 screened positively for ADHD (20 %), 11 for Oppositional Defiant Disorder (19 %), 35 for Specific Phobia (59 %), and 1 for Major Depressive Disorder (2 %).

Table 2 Age-adjusted group means for RSA

Domain	ASD			TDC			*p* value	ES
	N	Mean	95 % CI	N	Mean	95 % CI		
Baseline	50	6.84	(6.59, 7.09)	29	6.91	(6.58, 7.24)	0.74	−0.34
Tones	48	6.93	(6.69, 7.17)	28	7.05	(6.72, 7.37)	0.56	−0.58
Visual	47	6.86	(6.63, 7.10)	27	6.90	(6.59, 7.21)	0.85	−0.19
Auditory	47	6.90	(6.66, 7.15)	26	6.97	(6.64, 7.30)	0.75	−0.32
Olfactory	50	6.92	(6.68, 7.17)	29	6.67	(6.34, 6.99)	0.21	1.27
Tactile	47	6.96	(6.72, 7.20)	29	6.96	(6.64, 7.29)	0.98	−0.02
Movement	46	7.10	(6.86, 7.34)	28	7.18	(6.86, 7.50)	0.69	−0.40
Recovery	41	6.74	(6.50, 6.99)	25	6.58	(6.26, 6.90)	0.42	0.81
Pro aud	47	6.79	(6.55, 7.03)	28	7.00	(6.68, 7.32)	0.30	−1.05
Total mean[a]		6.90	(6.68, 7.12)		6.91	(6.62, 7.21)	0.92	−0.02

ES effect size

[a] Total mean across SCP

sensory stimulation. Parasympathetic output of the vagus nerve is responsible for normal variability of the heart via RSA. Respiratory sinus arrythmia, the variability in the interbeat interval of the heart period in the high frequency range of respiration, is used frequently in the literature as a measure of parasympathetic activity (Martinmaki et al. 2006; Berntson et al. 1994). Frequency domain analysis (spectral decomposition) was used to quantify RSA in accordance with the recommendations of the Society for Psychophysiological Research (Berntson et al. 1997). Specifically, the ECG signal was digitized at 1,000 Hz, and identification of R-wave peaks allowed for the quantification of inter-beat intervals for specified domain lengths corresponding to the epoch lengths of a sensory stimulation. Mismarked R-waves and periods in which movement artifact that affected the ECG signal accounted for less than 5 % of the data points. These were corrected prior to RSA calculation by either marking the correct R-wave peak (if one was present) or if movement artifacts prevented visualization of R-wave peak, through identification of an average distance between the R-waves immediately preceding and following the missing R-wave. The data were detrended using a second-order polynomial to reduce non-stationarity (Berntson et al. 1995). Respiratory sinus arrhythmia was calculated using a Fast-Fourier transformation of the resampled inter-beat interval to obtain the integral power within the frequency band of respiration, which was set to 0.15–0.50 Hz. No cases of HF spectral bands fell outside this range of respiration, ensuring that RSA captured the parasympathetic component. Respiratory signals were recorded via impedance cardiography to ensure that respiratory frequency fell within the appropriate range. Additionally, a muscle noise filter was applied using a band pass filter at 0.25–40 Hz to remove movement artifacts.

The sympathetic control of the heart was measured via the use of pre-ejection period (PEP), defined as the time interval from the beginning of electrical stimulation of the ventricles to the opening of the aortic valve (Lozano et al. 2007). PEP is a valid measure of sympathetic activity, as determined by autonomic pharmacological blockade (Berntson et al. 1994). PEP requires the identification of the QRS complex of the ECG,[3] the basal impedance signal (Z0), and first derivative of impedance (dZ/dt) signal derived from the impedance leads. Although PEP is defined as the distance in milliseconds between the Q point in the ECG and the B point in the dZ/dt wave, Q is not always present or visible, therefore the R-wave onset was utilized as the most reliably identified substitute for Q (PEPr; Berntson et al. 2004). Ensemble averaging of the ECG, Z0, and dZ/dt signals allowed for identification of the B-point on the dZ/dt wave (Lozano et al. 2007), which suggests peak left-ventricular ejection and the onset of Q, which represents the onset of ventricular depolarization. The Q wave was identified through the maximum point of slope change within a 35 ms window prior to R-wave onset (Mindware 2011). The reader is referred to Lozano et al. (2007) for a thorough description of impedance signal identification. To ensure appropriate B, Q and R-wave software identification, we performed visual inspections of the ECG, Z0 and dZ/dt signals. Because PEP is a calculated average of time from one point to another on ensemble ECG patterns for an entire domain, removing individual R-waves from the analysis due to movement improved the ability to detect true PEP. Files that showed greater than

[3] The QRS complex is the electrical signal representing ventricular depolarization on an electrocardiogram (ECG). The Q, R, and S waves occur successively, with the Q being the first negative deflection, followed by a positive inflection (R-wave), with the next negative deflection being the S wave (Das and Zipes 2012).

20 % of the data points were removed were not included for analysis.

Collection of ANS Measures

Autonomic variables used in this study were derived from the ECG and impedance cardiography as described above. Following use of a small alcohol wipe to prepare the skin, disposable spot electrodes were placed on the child's chest using a modified Lead-II configuration to maximize visualization of the R-wave of the ECG. Additionally, four spot electrodes were placed on the anterior and posterior thorax for impedance recording, with the ventral-superior (recording) electrode placed at the jugular notch, and the ventral-inferior (recording) electrode placed above the umbilicus. The dorsal-superior electrode (current) was placed along the vertebrae 2 inches above the superior-anterior electrode, approximately at C4. The dorsal-inferior electrode (current) was placed approximately at T9.

Four channels of data (ECG, basal thoracic impedance or Z0, dZ/dt, and EDA) were acquired using the Mindware System's 2-slot BioLab chassis (Gahanna, OH) and acquisition software to digitize and send signals to a Dell desktop computer. Real-time monitoring of four channels occurred prior to data collection to ensure appropriate electrode placement and maximum signal quality. ECG and impedance signals were sampled at 1,000 Hz. Occasional loss of Z0 and dZ/dt signal quality occurred in some cases due to the excessive child movements and loss of contact of the impedance electrodes on the child's back. Data were saved offline for future data checks, editing and reduction using Mindware software (HRV 3.0.5 and IMP 3.0.1 versions, Gahanna, OH).

Data Analysis

Mean RSA and PEP at baseline, each sensory domain, and recovery were measured as well as each child's change in activity from one domain to the next during the protocol. We calculated this with a change score, with the previous domain's mean subtracted from the current domain's mean (adjacent domain scores), representing change in RSA or PEP from one domain to the next.

Children with at least 95 % intact continuous RSA data were included in the analysis, as recommended in the literature (e.g. Calkins and Keane 2004) as were those with 80 % of PEP intact data. Of the 59 enrolled children with ASD, four refused electrode placement, three asked to stop testing after beginning, six asked to skip components of the testing and move on to the next sensory domain, and one exhibited premature ventricular contraction upon examination of the data. Additional intermittent loss of data occurred for some sensory domains due to movement artifacts, equipment malfunction (n = 11) or because some children requested to skip certain sensory domains. Thus, the sample size for each domain of RSA and PEP varies and these are shown in Tables 2 and 3. Behavioral characteristics of children with ASD who were able to complete the SCP (n = 41) were compared to those children with ASD who refused, stopped prematurely, or skipped portions of the SCP (n = 18)[4] using one-way ANOVA.

Chi square tests were used to examine differences between groups on categorical demographic variables, and independent samples *t* tests were used to examine differences in continuous demographic variables. All analyses were age-adjusted, and although cognitive levels were higher for the typically developing children, there is no evidence in the literature that it impacts autonomic activity and thus, was not controlled for in the analyses. Mixed effects linear regression was used to jointly model RSA or PEP scores for each condition by group. Fixed effects were included for domain, group, domain by group interaction, and age. An unstructured covariance structure was assumed to model the correlation among repeated measurement from the same subject. Within the mixed effects model, we performed two multivariate hypothesis tests. First we tested for any difference between groups in the vector of means over the course of the sensory stimulation (a 9 degree of freedom test). Second we tested for any difference between groups with respect to change in RSA and PEP from the previous domain (an 8-degree of freedom test). In addition, we tested for a difference between groups with respect to the total mean RSA/PEP score across the sensory stimulation. As an exploratory analysis, we also performed separate group comparisons of mean scores at each domain. The level of significance was set to $p < 0.05$ for all tests.

Results

Research Question 1/RSA: As shown in Table 2 and Fig. 1, a multivariate comparison of age adjusted vector of means between groups for RSA (parasympathetic activity) revealed a significant difference between the groups ($p = 0.02$). There were no differences between groups with

[4] Children with ASD who refused electrodes, requested to stop testing, or skipped a protocol domain (ASD-Stopped, n = 18) were not significantly different than ASD-Completed (n = 40) in respect to mean age [$F(1,57) = 1.07$, $p = 0.30$] or cognitive level [$F(1,48) = 0.15$, $p = 0.70$] although the ASD-Stopped were more likely to have parent-reported dysfunction on the Underresponsivity/Seek Sensation domain z-score [ASD-Stopped M = −3.7, SD = 1.6, ASD-Completed M = −2.6, SD = 2.0, $F(1,56) = 4.07$, $p = .05$] and the Visual/Auditory Sensitivity domain z-score [ASD-Stopped M = −2.0, SD = 1.2, ASD-Completed M = −1.1, SD = 1.5, $F(1,56) = 4.38$, $p = 0.04$] of the SSP.

Table 3 Age-adjusted groups means for PEP

Domain	ASD			TDC			*p* value	ES
	N	Mean	95 % CI	N	Mean	95 % CI		
Baseline	30	97.84	(93.80, 101.89)	10	97.72	(90.90, 104.53)	0.98	0.03
Tones	28	97.18	(93.19, 101.18)	11	100.02	(93.34, 106.70)	0.47	−0.74
Visual	26	97.16	(93.25, 101.07)	9	100.01	(93.46, 106.57)	0.45	−0.76
Auditory	26	96.47	(92.49, 100.44)	10	100.35	(93.71, 106.99)	0.32	−1.02
Olfactory	28	98.42	(95.10, 101.73)	11	101.84	(96.32, 107.36)	0.29	−1.08
Tactile	27	98.52	(94.72, 102.32)	11	100.02	(93.69, 106.35)	0.68	−0.41
Movement	25	97.40	(93.99, 100.82)	10	102.61	(96.94, 108.28)	0.12	−1.59
Recovery	22	96.91	(93.42, 100.40)	9	98.05	(92.26, 103.85)	0.73	−0.34
Mean[a]		97.45	(93.54, 101.04)		100.05	(94.12, 106.03)	0.45	−0.04

ES effect size

[a] Total mean across SCP

respect to the total mean RSA score ($p = 0.92$). Also shown in Table 2, when comparing means at each individual domain, no significant differences were found, although effect sizes for the group differences at olfactory (ES = 1.27), prolonged auditory (ES = −1.05) and recovery (ES = 0.81) are notable.

Research Question 1/PEP: As shown in Table 3 and Fig. 2, Multivariate analysis revealed no statistically significant difference between groups in terms of their vector of means across the sensory stimulation ($p = 0.15$). Further, there was no difference between groups with respect to the total mean PEP score across the sensory stimulation ($p = 0.45$). When comparing means at each individual domain, no significant differences were found although estimated mean PEP was lower for participants with ASD (expected direction) and effect sizes for the group differences at auditory (ES = −1.02), olfactory (ES = −1.08), and movement (ES = −1.59) are notable.

Research Question 2/domain to domain changes: Regarding domain to domain changes in parasympathetic (RSA) activity during the sensory stimulation, there was a significant difference between the groups in domain to domain change in RSA (Table 4), with the ASD group showing significantly less domain to domain change than the TDCs ($p = 0.01$). These differences were most striking in the change from siren to olfactory ($p = 0.02$), olfactory to tactile ($p = 0.02$) and recovery to prolonged auditory ($p = 0.002$). As shown in Table 5 there was not a significant difference between the groups in the multivariate consideration of domain to domain change in PEP ($p = 0.10$), however, differences in changes from baselines to tones ($p = 0.08$) and tactile to vestibular ($p = 0.07$) approached significance, and vestibular to recovery ($p = 0.03$) reached significance indicating greater sympathetic activity.

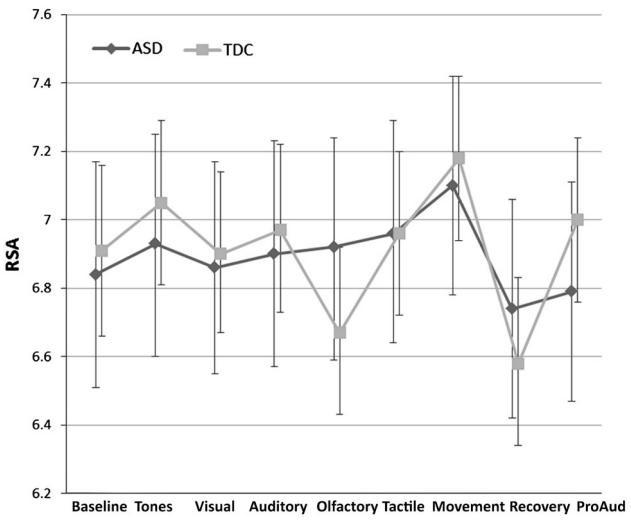

Fig. 1 Respiratory sinus arrhythmia age-adjusted means. RSA measured in ln(ms^2). *ProAud* prolonged auditory tone. Difference between groups in vector of means over course of SCP: $p = 0.02$

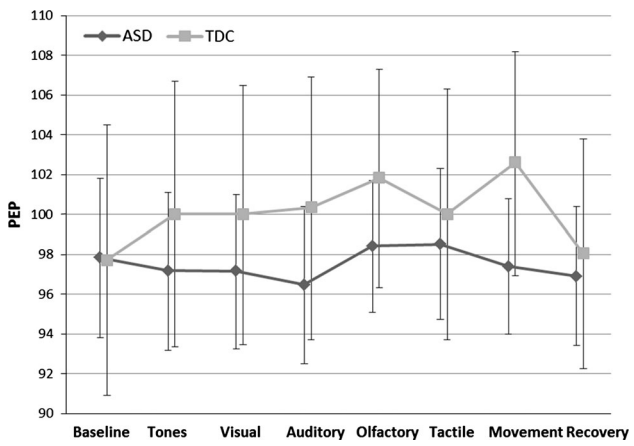

Fig. 2 Age-adjusted pre-ejection period means. PEP measured in milliseconds. Difference between groups in vector of means over course of SCP: $p = 0.15$

Table 4 Age-adjusted adjacent domain to domain changes in RSA

	Estimate	95 % CI	*p* value
ΔTones–base			0.70
ASD	0.08	(−0.06, 0.23)	
TDC	0.13	(−0.06, 0.33)	
ΔVis–tones			0.43
ASD	−0.06	(−0.19, 0.06)	
TDC	−0.15	(−0.31, 0.02)	
ΔSiren–visual			0.80
ASD	0.04	(−0.10, 0.18)	
TDC	0.07	(−0.11, 0.25)	
ΔOlf–siren			0.02
ASD	0.02	(−0.14, 0.18)	
TDC	−0.31	(−0.51, −0.10)	
ΔTact–olf			0.02
ASD	0.04	(−0.10, 0.18)	
TDC	0.3	(0.12, 0.48)	
ΔVest–tact			0.50
ASD	0.14	(0.00, 0.28)	
TDC	0.22	(0.04, 0.39)	
ΔRec–vest			0.10
ASD	−0.35	(−0.53, −0.17)	
TDC	−0.6	(−0.83, −0.37)	
ΔProlo aud–rec			0.002
ASD	0.05	(−0.10, 0.19)	
TDC	0.42	(0.24, 0.60)	

Difference between groups on domain to domain changes (multivariate test), $p = 0.01$

Table 5 Age-adjusted adjacent domain changes in PEP

	Estimate	95 % CI	*p* value
ΔTones–base			0.08
ASD	−0.66	(−2.37, 1.05)	
TYP	2.30	(−0.55, 5.16)	
ΔVis–tones			0.99
ASD	−0.02	(−1.39, 1.34)	
TYP	0.00	(−2.21, 2.20)	
ΔSiren–visual	0.45		
ASD	−0.69	(−2.10, 0.72)	
TYP	0.33	(−1.97, 2.64)	
ΔOlf–siren			0.77
ASD	1.95	(0.28, 3.62)	
TYP	1.49	(−1.22, 4.20)	
ΔTact–olf			0.24
ASD	0.10	(−1.64, 1.85)	
TYP	−1.82	(−4.59, 0.95)	
ΔVest–tact			0.07
ASD	−1.12	(−3.23, 0.99)	
TYP	2.59	(−0.76, 5.95)	
ΔRec–vest			0.03
ASD	−0.49	(−2.38, 1.39)	
TYP	−4.56	(−7.53, −1.58)	

Difference between groups on domain to domain changes (multivariate test), $p = 0.10$

Discussion

The purpose of this study was to examine parasympathetic and sympathetic activity at baseline and during controlled sensory stimulation in children with ASD ages 6–9 years in comparison to TDC. The unique contributions of the current study are that sympathetic and parasympathetic responses were assessed simultaneously in a well-characterized sample of children with ASD with a restricted age range to reduce age-related variability in ANS activity. This work has not been done and represents an innovative approach for understanding sensory reactivity in children with ASD. Our main findings were that the vector of mean scores of RSA is significantly different between the groups, and that there was significantly less change from domain to domain in RSA during the SCP for the ASD group. These findings are interesting given that the usual response to challenging stimuli is use of the vagal brake (decrease in RSA) to modulate the visceral state and promote self-regulated behaviors (Porges 2007). The TDC in our sample exhibited this response showing domain-to-domain change in HRV. In addition, the TDC's behavioral responses during the SCP suggest that they were regulating their responsiveness to the stimuli during the SCP. In contrast, the children with ASD frequently displayed signs of behavioral dysregulation and avoidance during the SCP (e.g. placing their hands over ears, rubbing at skin after touch, covering or averting eyes from visual stimuli). These observations are consistent with the physiological data (less domain to domain change and flatter vector of mean scores of RSA) and suggest that the ASD participants were not using the parasympathetic system to regulate their behavioral responsiveness to stimuli. According to the Polyvagal theory (Porges 2007) a main function of the vagal system is to inhibit and disinhibit the parasympathetic influences to the heart to allow for rapid mobilization or calming (i.e. modulating the visceral state) providing a foundation for engagement and disengagement with objects or persons—an important underpinning of flexible behavior and social engagement. The ASD participants did not exhibit this physiological response *and* they showed difficulty regulating their behavioral responses during the SCP. Difficulty engaging the vagal brake leaves the sympathetic system unchecked resulting in an "inability to attenuate the naturally occurring sympathetic reactivity to stressful stimulation… [and inability] to promote calm states" (Bal et al. 2010, p 357). Thus, individuals with

ASD's characteristics of rigid behaviors and limited social engagement may be related to this decreased autonomic (and resultant behavioral) flexibility. Goodwin et al. (2006; Woodard et al. 2012) support this idea showing that high basal heart rate, an indicator of high arousal, may contribute to lack of flexibility in response to stressful environmental stimuli; and Hoehn-Saric and McLeod (2000) suggest that individuals with chronic anxiety disorder and high arousal show limited physiological and behavioral flexibility. Thus, it is plausible that lack of parasympathetic activity during sensory stimulation may be an important mechanism of behavioral inflexibility and lack of social engagement. An important next step is to examine this potential relationship directly measuring RSA during activities that require behavioral flexibility and social engagement such as play.

In regard to sympathetic activity, although we did not find statistically significant differences in PEP during sensory stimulation between the groups, the ASD group did have lower PEP (lower PEP is indicative of greater sympathetic activity), with effect sizes for PEP during auditory (ES = −1.02), olfactory (ES = −1.08), and movement (ES = −1.59) domains reported in Table 3 supporting this suggestion. With a larger sample size this finding may reach significance. Our finding is consistent with Palkovitz and Wiesenfeld (1980), Hirstein et al. (2001), Goodwin et al. (2006), and Woodard et al. (2012) who found increased sympathetic activity in their ASD participants. For example, Hirstein et al. (2001) found that a preponderance of children with ASD in their sample demonstrated high sympathetic activity during their 35 min activity protocol suggesting that children with ASD may be in a heightened state of sympathetically-mediated arousal.

It is interesting that baseline RSA or PEP were not significantly different between the groups given that other authors have found this (Ming et al. 2005; Bal et al. 2010). Differences in findings between our study and these other studies may be related to the ages of the participants. Our mean age was 7.8 years whereas Bal et al. (2010) and Ming et al's (2005) sample mean age was 10.3 and 9.4 respectively). A second potential explanation is the difference in baseline protocol between our study and the others. Our baseline protocol is designed with a playful theme (e.g. pretend spaceship ride) and may not elicit the same level of anticipation as the participants in other studies. Replication of our finding are needed to determine if the baseline similarities we found are related to age, the experience of the protocol setting, or true physiological similarities.

This is one of the first studies that directly examined the parasympathetic and sympathetic responses simultaneously during sensory challenges in children with ASD to understand their combined actions. Given that the sympathetic and parasympathetic systems work together to regulate behavioral and systemic responses to environmental stimuli, ANS dysregulation in either or both branches of the ANS may contribute to behavioral difficulties as discussed above. Further, given that ASD is very heterogeneous, it is likely that there are specific subtypes based on autonomic activity during sensory stimuli within the population of children with ASD. Examination of subtypes may provide further insight into characterization of the autism phenotype. Berntson et al. (1991, 1994, 1993), describe four primary patterns related to autonomic regulation: (1) co-inhibition or suppression of both sympathetic and parasympathetic; (2) co-activation or activation of both sympathetic and parasympathetic, (3) reciprocal parasympathetic or suppression of sympathetic and activation of parasympathetic, and (4) reciprocal sympathetic or activation of sympathetic combined with suppression of parasympathetic. Although we found that the participants with ASD showed differential parasympathetic activity, we did not have enough power to assess whether these patterns of sympathetic and parasympathetic activity discriminated subgroups of our sample. While the sample size in this study is larger than most other physiological studies of children with ASD, a larger sample would be needed to determine if these subgroups emerge and if they are useful to categorizing responsiveness to sensory stimuli. If so, these data may provide useful data for individualizing interventions based on sensory reactivity. Given that RSA and PEP are generally stable in middle childhood (Goto et al. 1997; Salomon 2005; Salomon et al. 2000), these objective, physiological measures are ideally suited to outcome research in the autism field. This is an important next step for our program of research.

In terms of limitations of this study, our sample included participants across the autism spectrum and it is possible that autism severity impacted ANS activity. It would be important in future studies to examine the impact of autism severity on sensory reactivity and ANS. Robertson and Simmons (2013) recently found a significant positive correlation between the number of autism traits and the frequency of sensory processing problems, and thus, this is an important future direction. Further, our sample size for PEP data was greatly reduced due to movement and signal issues. It is possible that the pressure exerted on the electrodes placed on the back, as a function of sitting in the chair during the SCP, may have impacted signal quality for PEP, thus resulting in lost data. Future studies should attend to methodological approaches to improve signal quality when using impedance cardiography. Finally, given that our typically developing control sample size was smaller than our ASD group, the between group comparisons, while adjusting for different sample sizes, should be interpreted with caution. We included children with ASD who met the cut off for co-occurring conditions such as

Anxiety Disorder and Attention Deficit Hyperactivity Disorder (ADHD) on the Child Symptom Inventory 4 and it may be useful in future studies to examine these subtypes separately to examine whether ANS activity is a unique feature of these co-occurring conditions.

In summary, despite the limitations described above, our findings represent an important step forward in understanding and characterizing the physiological differences and potential patterns of reactivity to sensory challenge in a sample of school-age children with ASD. Specifically, our findings that participants with ASD showed a less variable parasympathetic response (less change from domain to domain) may reflect an inability to adjust to the changing demands of the environment. In addition, our data suggest that the sympathetic system may be functioning in an over-aroused state, possibly because it is not regulated by the parasympathetic response. Although this finding did not reach significance, there is some suggestion from other ASD literature that this might be the case. The use of valid and reliable parasympathetic and sympathetic measures from the same organ greatly enhances our understanding of autonomic responses, as does the use of a validated sensory challenge task. Future research should consider the use of larger samples to allow for further subgrouping using patterns of autonomic activity, examining older or younger children with ASD, and considering the use of ANS measures as outcome measures for interventions designed to address sensory hyper or hypo-reactivity in children with ASD.

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