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Unusual sensory features are related to resting-state cardiac vagus nerve activity in autism spectrum disorders (自閉症スペクトラム障害児の非定型的な感覚特性は安静時の迷走神経活動と関連する)

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ABSTRACT

The relationship between unusual sensory features (hyper-reactivity, hypo-reactivity, and unusual sensory interests) and the parasympathetic nervous system in autism spectrum disorder (ASD) has recently garnered interest. The purpose of this study was to investigate whether unusual sensory features are associated with resting-state cardiac vagus nerve activity in ASD children. Electrocardiogram signals were recorded during three 2-min resting periods to quantify the high frequency (HF) component of heart rate variability (HRV) in 37 children with ASD aged 6-12 and 32 typically developing children. Parent-reported questionnaires (Short Sensory Profile, SSP; Social Responsiveness Scale-2, SRS-2) assessed atypical sensory behaviors in daily life and autistic traits. Children with ASD consistently showed lower HF-HRV than typically developing children across the three resting periods. The SSP *"Visual/Auditory Sensitivity"* score was correlated with resting-state HF-HRV in the ASD group, indicating that ASD children with more severe visual/auditory hyper-reactivity in daily life have lower vagus nerve activity. The SRS-2 "*Restricted Interests and Repetitive Behavior*" score was also correlated with resting-state HF-HRV in the ASD group. These findings suggest that ASD children with lower vagus nerve activity may have inadequate self-regulatory capacity and difficulty regulating behavioral responses to unpredictable and unavoidable visual/auditory stimuli in daily life.

Keywords:

Autism spectrum disorders; sensory features; parasympathetic nervous system; resting state; heart rate variability

1. Introduction

Autism spectrum disorder (ASD) is characterized by deficits in social communication and social interaction, and restricted and repetitive patterns of behavior, interests, or activities (American Psychiatric Association, 2013). Unusual sensory features (hyper-reactivity, hypo-reactivity, and unusual sensory interests) are common symptoms in children with ASD (for review, see Ben-Sasson et al., 2009; Caminha & Lanpreia, 2012), and are related to temperament, adaptive behaviors, and activity participation (Ashburner, Ziviani, & Rodger, 2008; Brock et al., 2012; Lane, Young, Baker, & Angley, 2010; Little, Ausderau, Sideris, & Baranek, 2015). The association between unusual sensory features and autonomic nervous system activity in ASD children has recently gained interest; previous studies have reported that autonomic nervous system activity during sensory stimulation differed between ASD and typically developing children (Chang et al., 2012; Porges et al., 2013; Schaaf, Benevides, Leiby, & Sendecki, 2015; Schoen, Miller, Brett-Green, & Nielsen, 2009) Schaaf et al. (2015) reported that children with ASD showed less variable parasympathetic nerve activity in response to different sensory stimuli. In addition, recent studies have found an association between behavioral response to sensory stimuli and heart rate (Woodard et al., 2012), and an association between parent-reported unusual sensory behaviors and pupillary light reflex constriction amplitude (Daluwatte, Miles, Sun, & Yao, 2015). These studies have suggested that atypical autonomic nervous system function may underlie unusual sensory features in children with ASD. Recent investigations of the autonomic nervous system have proposed that the parasympathetic nervous system, particularly the vagus nerve, is associated with self-regulatory capacity (Porges, 2007, 2011). ASD children with unusual sensory features may have difficulties in regulating behavioral responses to sensory stimuli in the external environment and accordingly show hyper-reactivity or hypo-reactivity in daily life (Daluwatte et al., 2015; Schaaf et al., 2015).

Resting-state vagus nerve activity has been thought to represent a person's general responsiveness to the external environment (for review, see Graziano & Derefinko, 2013). Many previous studies have reported that children with ASD had significantly lower vagus nerve activity during rest than typically developing children (Bal et al., 2010; Guy, Souders, Bradstreet, DeLussey, & Herringto, 2014; Ming, Julu, Brimacombe, Connor, & Daniels, 2005; Porges et al., 2013; Van Hecke et al., 2009); although, some other studies have reported that there were no such differences (Levine et al., 2012; Schaaf et al., 2015). Atypical developmental trajectories of resting-state vagus nerve activity were also found in children at risk for ASD (Patriquin, Lorenzi, Scarpa, & Bell, 2014). In addition, children with unusual sensory features showed a tendency for lower vagus nerve activity during rest than typically developing children, although the subjects were not ASD (Schaaf et al., 2010). Therefore, it may be important to investigate the relationship between unusual sensory features and resting-state vagus nerve activity in children with ASD; however, there are no published studies clarifying this relationship.

Therefore, the purpose of the present study was to investigate whether unusual sensory features are associated with resting-state vagus nerve activity in children with ASD.

Electrocardiogram (ECG) was used to quantify heart rate variability (HRV), a physiological indicator of cardiac vagus nerve activity. HRV is defined as the fluctuation in the length of adjacent R-R intervals (*i.e.*, the variability in the inter beat intervals of the heart). The high frequency (HF) component of the HRV reflects parasympathetic cardiac control related to respiratory sinus arrhythmia, providing a relatively pure index of vagus nerve activity (Berntson et al., 1997; Berntson, 2008). To date, most studies have measured resting-state parasympathetic activity before a task (baseline period). Although these studies certainly considered participants' acclimation to the laboratory environment, the participants may have anticipated the next experimental task during the baseline period and therefore might have felt some anxiety. Anxiety is common in children with ASD (van Steensel, Bögels, & Perrin, 2011; White, Oswald, Ollendick, & Scahill, 2009), and affects vagus nerve activity (Guy et al., 2014). Children with ASD who are faced with an uncertain situation may feel higher anxiety than typically developing children do (Boulter, Freeston, South, & Rodgers, 2014). Uncertainty may be high at the beginning of the experimentation (including baseline period), but may decrease as the experiment progresses. Therefore, the present study measured HF-HRV during three 2-min resting periods (baseline, intermediate, and recovery) in the whole experiment, whose procedure is described below. The Short Sensory Profile (SSP; McIntosh, Miller, Shyu, & Dunn, 1999) was used to assess atypical sensory responses in each subject. The Social Responsiveness Scale-2 (SRS-2) was also used to assess autistic behavioral features including restrictive and stereotypic behaviors, which are core symptoms of ASD (Boyd et al., 2010; Mandy, Charman, & Skuse, 2012), because previous studies have shown that unusual sensory features are associated with such behaviors (Joosten & Bundy, 2010; Lidstone et al., 2014;Wigham, Rodgers, South, McConachie, & Freeston, 2015).

This study is part of a larger study program that was designed to examine physiological activity during rest and sensory tasks in children with ASD, with two different purposes. The first purpose was to examine the association between unusual sensory features and resting-state HF-HRV in ASD children. The second purpose was to investigate whether the way of presenting sensory stimuli affected HF-HRV differently in ASD children and typically developing children. We used tactile and auditory stimuli in sensory tasks and two different means of presentation of stimuli were included in each sensory task. Thus, only the resting-state HF-HRV is reported in this article.

2. Methods

2.1 Participants

2.1.1 Children with ASD (ASD group)

Forty-seven children with ASD, aged 6 to 12 years, were recruited at Kyoto University Hospital and the clinic of the Prefectural University of Hiroshima. The diagnoses were autistic disorder (n = 23), pervasive developmental disorder not otherwise specified (n = 21), and Asperger's Disorder (n = 3) (the Diagnostic and Statistical Manual of Mental Disorders; DSM-IV-TR, 2000). All children with ASD have social communication problems at school and/or at home. These diagnoses were independently established by licensed pediatricians and child psychiatrists who have extensive experience working with children with ASD. Potential participants were screened on the following five criteria: (i) no primary uncorrected sensory impairment, such as blindness and deafness; (ii) full-scale Intelligence Quotients (IQs) of 70 and over as assessed using the Japanese version of the Wechsler Intelligence Scale for Children-Fourth Edition (Japanese WISC-IV Publication Committee, 2010) The Japanese version of the WISC-IV used in this study was standardized among 1293 Japanese children aged 5-16 years, and was found to have good reliability and validity

(Japanese WISC-IV Publication Committee, 2010);(iii) no history of cerebral palsy, epilepsy, or any other major neurological condition; (iv) no history of cardiovascular disease; and (v) a score of ≥13 on the Pervasive Developmental Disorders Autism Spectrum Disorders Rating Scale-Text Revision (PARS-TR, Adachi et al., 2006; Ito et al., 2012; Tsujii et al., 2006). The PARS-TR is widely used in Japan as an instrument for evaluating ASD. This scale uses an interview format similar to the Autism Diagnostic Interview-Revised (ADI-R, Le Couteur, Lord, & Rutter, 2003), and the procedures, which are briefly summarized in the manual, can be implemented after simple training. The criteria for rating each item are clearly defined in the PARS-TR, and the evaluator assigns values at one of three levels: none (0 points), somewhat apparent (1 point), or apparent (2 points), for the items listed as typical behavioral symptoms of pervasive developmental disorders. The total score on the PARS (the former version of the PARS-TR, for which the items and scoring are identical to those of the PARS-TR) showed a correlation with ADI-R total score, and the inter-rater reliability was sufficient (Ito et al., 2012).

Before this screening, participants did not take any medication that might influence autonomic function, with the exception of two children with ASD who were taking methylphenidate for their attention deficit-hyperactivity disorder (ADHD) symptoms.

2.1.2 Typically developing children (TD group)

Forty-two typically developing (TD) children, aged 6 to 12 years, were recruited using a convenience sampling method through the distribution of study flyers at elementary schools in Kyoto city. Potential participants were screened on the following five criteria: (i) not receiving any special education services;(ii) not taking any form of medication; (iii) did not have siblings with developmental disorders including ASD; (iv) had never exhibited any developmental delays during the infant medical examination based on individual interviews with parents; and (v) total T-score of < 60 on the SRS-2; additional parent interviews confirmed eligibility for this study based on the results of the SRS-2.

2.1.3 Ethical considerations

Ethical approval was granted by the Medical Ethics Committee of the Faculty of Medicine, Kyoto University. Prior to participation, informed consent and assent were obtained from parents and children, respectively.

2.2 ECG recording

All parents and children understood the purpose of this study prior to participation, and the children were given an opportunity to talk with the experimenter (the first author) before the experiment in order to acclimate them to the laboratory environment and reduce their anxiety. The experiment was carried out between 10:00 and12:00 h or between 14:00 and16:00 h, which was designed to limit the influence of meals and circadian rhythm. In the 2 h prior to the experiment, the children were not allowed to eat (but were permitted to drink fluids). Data were collected under a controlled temperature (22–26°C) in a quiet room with a white wall and a fluorescent light. Parents waited in the next room of the laboratory during testing.The children were instructed not to speak or move during the recording periods of resting-state. They sat on a chair without a back facing an iPad. ECG signals were recorded using the

PowerLab system (ADInstruments Japan Inc., Japan) and disposable electrodes (Vitrode F150M, Nihon Kohden Corporation, Japan) with a standard lead II configuration. ECG signals were sampled at a rate of 1 kHz using a 1 Hz high-pass filter. A schematic of the recording protocol is shown in Figure 1.

Three 2-min resting periods (a baseline period, an intermediate period between sensory tasks, and a recovery period) were recorded. The children watched a timer on the iPad during these resting periods. In the two 6-min task periods, tactile stimuli of 3-s duration were presented to the children with a feather 30 times, and auditory stimuli with an 84 dB pure tone of 1-s duration were presented 33 times. The intervals between tasks were 30-s. The whole experiment was recorded with a video camera.

2.3 ECG data analysis

MATLAB (The MathWorks Inc., USA) was employed to process the ECG data. The peak of the ECG R-wave and the inter beat intervals were automatically detected from each sequential heartbeat using the Pan Tompkins algorithm (Sedghamiz, 2014). After this automatic detection, the ECG signals were visually inspected, and if incorrect detection or a movement artifact was found, the correct peak was detected manually. If an arrhythmia was found, the ECG segments with a regular pulse were extracted before inter beat interval calculation. The frequency-domain analysis was used to quantify HRV. Power spectral density at each frequency of HRV was calculated on the basis of the Welch power spectral density method, implemented by the analysis software HRVAS (Ramshur, 2010). The frequency band for an HF component was 0.15 -1.04 Hz. The HF component is related to respiratory patterns; the frequency band of respiration is considered to range from 0.15 - 0.40 Hz in adults, but may be extended in infants

(Berntson et al., 1997). Since it was possible that children with ASD might have a higher respiration rate, the frequency band for the HF component was set from 0.15 to 1.04 Hz in the present study. The power values of the HF were log normalized and expressed as $\ln(ms^2)$ according to the standard procedure (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

2.4 Parent-reported questionnaires

Parents were asked to complete two questionnaires (SSP and SRS-2) before visiting the laboratory or while waiting for their children in the next room.

2.4.1 Short sensory profile—Japanese version (SSP)

The SSP is a 38-item measure of behaviors associated with responses to sensory stimuli (McIntosh et al., 1999). Items on this questionnaire are drawn from the Sensory Profile (Dunn, 1999). Parents indicate their perception of the frequency with which their child exhibits unusual behavior in response to sensory stimuli. Item response scores range from 1 (always) to 5 (never) (total score from 38 to 190). A lower total score indicates a greater severity of sensory processing difficulties. There are seven sections of the SSP: *Tactile Sensitivity, Taste/Smell Sensitivity, Movement Sensitivity, Underresponsive/Seeks Sensation, Auditory Filtering, Low Energy/Weak, and Visual/Auditory Sensitivity*. The SSP-Japanese version adopted in this study was translated from the SSP (Tsujii, 2015). Internal consistency for each section of the SSP-Japanese version was reported as ranging from 0.54 to 0.88, along with acceptable discriminative validity (between ASD children and typically developing children)

(Tsujii, 2015). The Japanese version item response scores are reversed (1 = never and 5 = always), but we adopted the original scoring in this article to prevent readers' confusion.

2.4.2 Social responsiveness scale-2 (SRS-2 school-age form)

The SRS-2 school-age form (Constantino & Gruber, 2007, 2012) is a 65-item rating scale questionnaire to measure the severity of ASD symptoms. It is completed by a parent, teacher, or caregiver who has routinely observed the child in his/her natural social settings. The five SRS-2 subscales were developed to provide a differentiated approach and include *Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behavior*. Item response scores range from 1 (not true) to 4 (almost always true). The SRS-2 School-Age Form assesses the behavior of children or adolescents aged between 4 and 18 years. SRS-2 total score and subscale scores are expressed in two ways: SRS-2 raw scores (from 0 to 195) and normalized SRS-2 T-scores (mean = 50, SD = 10). In both cases, higher scores indicate a greater severity of social impairment. We used raw scores in this study. The total raw score of the SRS-Japanese version (the former version of SRS-2 School-Age Form, with item contents and scoring identical with those of the SRS) correlated with the PARS total score (Kamio et al., 2009). Permission to use the author-approved Japanese research translation of the SRS-2 was granted by Nihon Bunka Kagakusha.

2.5 Statistical analysis

Statistical analyses were performed with IBM SPSS version 22.0 (IBM Japan, Ltd., Tokyo). In order to examine group differences in resting-state HF-HRV, two-way repeated measures ANOVA was used. The following two factors were studied: the group factor (ASD and TD) and the period factor (baseline period, intermediate period, and recovery period). Greenhouse-Geisser corrections were applied when appropriate. Spearman rank correlation coefficients were calculated in order to examine the relationship between the scores of each parent-reported questionnaire and the resting-state HF-HRV, and the significance of correlation coefficients was tested. When calculating correlation coefficients, the HF-HRV at three resting periods were averaged. The level of significance was set to $p < 0.05$ for all tests.

3 Results

3.1 Participant characteristics

Out of 47 potential participants with ASD, eight children were excluded for the following reasons: they did not meet inclusion criteria on the PARS-TR (n = 4), or they had diagnoses related to cardiovascular disease (Kawasaki disease, ventricular septal defect, Wolff-Parkinson-White syndrome) (n = 4). In addition, two children with ASD were excluded from the analysis because they could not sit quietly during ECG recording. Out of 42 possible TD participants, 10 children were excluded for the following reasons: they had been born prematurely (n = 3), were discovered to have a sibling with a developmental disorder (n = 3), had shown developmental delays during the infant medical examination (n = 3), or had anamnesis of encephalitis (n = 1). All children in the TD group could sit quietly during ECG recording.

The characteristics of the participants (ASD group, n = 37; TD group, n = 32) are reported in Table 1. They were about average in height and weight for their age group. The two groups did not differ significantly in age (t = 0.52, p =0.60) or gender (p

= 0.32). The ASD group had a significantly lower full scale IQ (t = 5.08, $p < 0.001$). SSP and SRS-2 scores differed significantly between the two groups (Table 2). Total SSP scores indicated that 91.9% of the ASD group and 21.9% of the TD group obtained a score of below the mean -1 SD of the normative samples in Japan. The ASD group had significantly more severe social behavioral deficits and restricted and stereotypic behaviors ($p < 0.001$).

Of the 69 participants, six children (five with ASD and one typically developing child) did not complete the entire experiment due to refusal to complete the auditory task, and therefore only two resting periods (baseline period and recovery period) were recorded for these children. For this reason, we included data from 63 participants (ASD group, n = 32; TD group, n = 31) in the final analysis, for which a two-way repeated measures ANOVA was carried out. The correlation analysis included data from all 69 participants, for which the average of the HF-HRV of two or three resting periods was used.

3.2 Group differences in resting-state HF-HRV

Figure 2 and Table 3 show resting-state HF-HRV in the ASD and TD groups. The ASD group had significantly lower resting-state HF-HRV across the three resting periods: there was a significant main effect of the group factor (ASD and TD) [$F(1, 61) = 47.94$, $p < 0.001$]. HF-HRV maintained a stable value across the three resting periods in both groups: there was no main effect of the period factor (baseline, intermediate, and recovery) [$F(2, 122) = 0.10$, $p = 0.90$]. There was no significant interaction between the group and period factors [$F(2, 122) = 1.76$, $p = 0.18$].

3.3 Relationship between parent-reported questionnaires and resting-state HF-HRV in ASD

Table 4 shows the relationship between SSP scores and resting-state HF-HRV. The total SSP score was not significantly correlated with the resting-state HF-HRV in the ASD group. Of the seven SSP sections, the "*Visual/Auditory Sensitivity*" section was significantly and positively correlated with resting-state HF-HRV in the ASD group (ρ = 0.38, p = 0.019) (Figure 3), while the remaining six sections (*Tactile Sensitivity, Taste/Smell Sensitivity, Movement Sensitivity, Underresponsive/Seeks Sensation, Auditory Filtering, and Low Energy/Weak*) were not. A significant correlation between the "*Visual/Auditory Sensitivity*" score and HF-HRV was still observed (ρ = 0.33, p = 0.049) even when the sample showing the lowest score for "*Visual/Auditory Sensitivity*" was excluded.

Table 5 shows the relationship between SRS-2 scores and resting-state HF-HRV. The total SRS-2 score was not significantly correlated with resting-state HF-HRV in the ASD group. Of the five SRS-2 subscales, the "*Restricted Interests and Repetitive Behavior*" subscale was significantly and negatively correlated with resting-state HF-HRV in the ASD group (ρ = - 0.33, p = 0.047) (Figure 4). In the TD group, the "*Social Motivation*" subscale was significantly and positively correlated with resting-state HF-HRV (ρ = 0.39, p = 0.029).

4 Discussion

The purpose of this study was to investigate the relationship between unusual sensory features and resting-state cardiac vagus nerve activity in children with ASD. We found that the ASD group consistently showed significantly lower HF-HRV than the typically developing children across the three resting periods (baseline, intermediate, and recovery). ASD children who showed more severe visual/auditory hyper-reactivity in daily life had lower HF-HRV. ASD children with more severe restricted and stereotypic behaviors also showed lower HF-HRV.

The correlation between "*Visual/Auditory Sensitivity*" scores and resting-state HF-HRV was significant in the ASD group. This finding reveals that ASD children with more severe visual/auditory hyper-reactivity in daily life have lower vagus nerve activity. Atypical visual/auditory processing in ASD has been reported (Demopoulos et al., 2015; Green et al., 2013; for review, see Marco, Hinkley, Hill, & Nagarajan, 2011), and the literature has reported a difference in vagus nerve activity during sensory stimulation in a laboratory environment between ASD children and typically developing children (Schaaf et al., 2015). The present study showed a relationship between visual/auditory hyper-reactivity in daily life and resting-state vagus nerve activity in ASD children. Myelinated vagus function plays an important role in autonomic self-regulation processes; it fosters calm behavioral states by inhibiting the influence of the sympathetic nervous system (Porges, 2007, 2011). Visual/auditory stimuli in the "*Visual/Auditory Sensitivity*" items, such as light and sound arising from the surrounding environment, are more unpredictable than the sensory stimuli of other SSP sections (e.g. *Tactile Sensitivity, Taste/Smell Sensitivity, and Movement Sensitivity*). Children with lower vagus nerve activity may have difficulty regulating their response to unpredictable and unavoidable sensory stimuli in daily life. Chang et al. (2012) reported an association between stronger sympathetic activation to auditory stimuli in the laboratory and parent-reported unusual sensory behaviors in the natural environment in ASD children. It is possible that the parasympathetic system in ASD children is unable to modulate immediate phasic responses, such as the fight-or-flight reaction (sympathetic response) effectively. Daluwatte et al. (2015) also reported an association between unusual sensory features and decreased parasympathetic modulation in children with ASD using the pupillary light reflex.

The "*Restricted Interests and Repetitive Behavior*" score (one of the SRS-2 subscales) was significantly negatively associated with resting-state HF-HRV in the ASD group: ASD children with more severe restricted and stereotypic behaviors showed lower vagus nerve activity. This finding is not consistent with previous literature in which parent-reported autism spectrum traits were not associated with vagus nerve activity in the ASD group (Guy et al., 2014; Patriquin, Scarpa, Friedman, & Porges, 2013; Van Hecke et al., 2009). Restricted and stereotypic behaviors have shown a strong relationship with unusual sensory features (Joosten & Bundy, 2010; Lidstone et al., 2014; Wigham et al., 2015); thus, the association between visual/auditory sensitivity and HF-HRV, which was found in the present study, might affect the association between "*Restricted Interests and Repetitive Behavior"* and HF-HRV. The correlations between social behavioral deficits (evaluated with the SRS-2) and resting-state HF-HRV were not significant in the ASD group; this is consistent with the literature (Guy et al., 2014; Patriquin et al., 2013; Van Hecke et al., 2009). Our findings imply that resting-state vagus nerve activity in ASD is more involved in sensory reactivity to external environmental stimuli, than in highly advanced behaviors such as social interaction. It is not clear why a significant positive correlation was found between "social motivation" and HF-HRV in the typically developing children; typically developing children who showed less active social interaction had higher HF-HRV.

They were presumably less outgoing, shy, and passive in their community, and those behavioral characteristics may have a relation to vagus nerve activity.

The present study quantified resting-state HF-HRV during three times resting periods (baseline, intermediate, and recovery). The ASD group showed significantly lower resting-state HF-HRV, not only during the baseline period but also during the intermediate and recovery periods. Some other studies have reported no significant differences in HF-HRV at rest between ASD children and typically developing children (Levine et al., 2012; Schaaf et al., 2015). One of the reasons for this inconsistency might be the difference in the sampling of typically developing children. The samples of typically developing children in the present study did not include siblings of children with ASD, children who had been born prematurely, or who had exhibited developmental delays. Levine et al. (2012) included siblings of ASD among their samples of typically developing children. Schaaf et al. (2015) did not describe the detail of their typically developing participants; therefore, it is not clear whether siblings of ASD or premature survivors were included. Behavioral traits associated with ASD, although less pronounced, may be present in siblings of ASD children (for review, see Pisula & Ziegart-Sandowska, 2015). Therefore, vagus nerve activity of siblings of ASD can be similar to that of children with ASD, even though the siblings do not meet the criteria for ASD. Furthermore, premature infants showed a tendency for lower HF-HRV during quiet sleep than did full-term infants (Patural et al., 2008). Children who had been born prematurely may potentially have atypical vagus nerve activity even in their school age years. In addition to this difference in the typically developing samples, differences in the ages of the participants and in the baseline protocol may also be worthy of consideration.

Unusual sensory features influence the child's daily activities, including eating, dressing, and sleeping (Jasmin et al., 2009; Schaaf et al., 2011), and impact activity and social participation in ASD children (Little et al., 2015). Currently, there are no medications for unusual sensory features, although psychopharmacological studies have been conducted for valuable treatment models (for review, see Marco et al., 2011). Sensory processing interventions (e.g., sensory integration therapy; Ayres, 1979, sensory-based intervention) are commonly used for addressing behavioral problems associated with sensory features in children with ASD (for review, see Case-Smith, Weaver, & Fristad, 2015). Child-centered interventions, designed to enhance intrinsic motivation, interest in the environment, and playful intent, have been provided to promote self-regulation in their daily life. Certain types of sensory inputs (e.g., deep touch, brushing, and rocking) have also been thought to elicit adaptive behaviors for remaining calm, organizing their behaviors (for review, see Wan, Liu, Bissett, & Penkala, 2015). Case-Smith et al. (2015) suggested that these interventions may affect vagus nerve activity, although physiological evidence is limited. The findings of the present study have implications for new intervention focusing on parasympathetic nerve system to treat sensory processing problems in ASD children.

There are limitations to this study. Included subjects were only children who meet inclusion criteria on the PARS-TR; however, children with co-occurring conditions such as ADHD were included in the ASD group. Because such co-occurring conditions may have affected resting-state autonomic nervous system activity, it would be important in future studies to examine autonomic nervous system activity in ASD children without co-occurring conditions. The diagnoses of ASD were made without using a structured procedure, such as the ADI-R and Autism Diagnostic Observation

Schedule (Lord, Rutter, DiLavore, & Risi, 1999). Furthermore, analyzed ECG data were obtained only from children who could sit quietly during the resting period. This may have limited our results of the correlation between unusual sensory features and HF-HRV. The use of parent-reported measures such as the SSP and SRS-2 to reveal behavioral traits of children in daily life should also be considered as a potential limitation. For example, Patriquin et al. (2013) have suggested that experimenter-observed measures are more powerful than parent-reported measures. Finally, the possibility of false-positive results due to the number of statistical tests performed in this study should be considered.

5 Conclusions

Our findings revealed the relationship between unusual sensory features and resting-state vagus nerve activity in children with ASD. Future studies are warranted to clarify how vagus nerve activity affects sensory features in ASD. Elucidation of the physiological basis of unusual sensory features would enhance our understanding of behaviors in ASD children and improve clinical interventions for them.

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Table1 Participant characteristics

Characteristic	ASD (n = 37)	TD (n = 32)	
			t-test
Age (years) (mean ± SD)	8.9 ± 2.7	8.7 ± 1.5	t = 0.5, *p* = 0.60
Full scale IQ (mean ± SD)	95.1 ± 17.6	114.4 ± 12.8	t = 5.1, *p* < 0.001
			Fisher's exact test
Gender (male : female)	26 : 11	18 : 14	*p* = 0.32

Table2 SSP and SRS-2 scores in the ASD and TD groups

	Median score			
	ASD (n = 37)	TD (n = 32)	z score	*p* value
SSP (raw score)				
Total	144.0	181.0	6.17	< 0.001
Tactile Sensitivity	31.0	34.0	3.40	< 0.001
Taste/Smell Sensitivity	18.0	20.0	4.23	< 0.001
Movement Sensitivity	14.0	15.0	3.07	< 0.001
Underresponsive/Seeks Sensation	27.0	33.5	4.75	< 0.001
Auditory Filtering	19.0	27.0	5.52	< 0.001
Low Energy/Weak	20.0	30.0	5.49	< 0.001
Visual/Auditory Sensitivity	21.0	24.0	4.74	< 0.001
SRS-2 (raw score)				
Total	80.0	35.0	-7.03	< 0.001
Social Awareness	11.0	6.0	-5.94	< 0.001
Social Cognition	18.0	6.0	-6.60	< 0.001
Social Communication	27.0	10.0	-6.64	< 0.001
Social Motivation	13.0	7.0	-4.26	< 0.001
RRB	15.0	3.0	-6.82	< 0.001

Note. RRB = restricted interests and repetitive behavior.
Wilcoxon rank sum test.

Table3 Resting-state HF-HRV in the ASD and TD groups

	Mean ± SEM		
	Resting period 1 (baseline)	Resting period 2 (intermediate)	Resting period 3 (recovery)
ASD (n = 32)	6.19 ± 0.17	6.30 ± 0.16	6.32 ± 0.15
TD (n = 31)	7.68 ± 0.13	7.48 ± 0.14	7.52 ± 0.15

Note . HF-HRV measured in ln (ms^2)

Table 4 Correlation coefficients between SSP scores and resting-state HF-HRV

SSP	ASD (n = 37)	TD (n = 32)
Total	-0.00	-0.13
Tactile Sensitivity	0.15	-0.33
Taste/smell Sensitivity	-0.14	-0.02
Movement Sensitivity	0.07	-0.00
Underresponsive/Seeks Sensation	-0.06	-0.00
Auditory Filtering	-0.11	-0.26
Low Energy/Weak	0.05	0.17
Visual/Auditory Sensitivity	0.38 *	-0.17

Note. Spearman rank correlation: * $p < .05$

Table 5 Correlation coefficients between SRS-2 scores and resting-state HF-HRV

SRS-2	ASD (n = 37)	TD (n = 32)
Total	-0.12	0.18
Social Awareness	-0.08	0.03
Social Cognition	-0.11	0.07
Social Communication	-0.04	0.03
Social Motivation	-0.04	0.39 *
RRB	-0.33 *	0.08

Note.RRB = restricted interests and repetitive behavior.
Spearman rank correlation: * $p < .05$

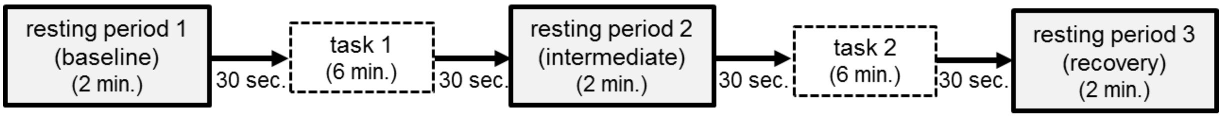

Fig.1 A schematic of the recording protocol. Three 2-min resting periods were recorded. Two sensory task periods were in between these resting periods.

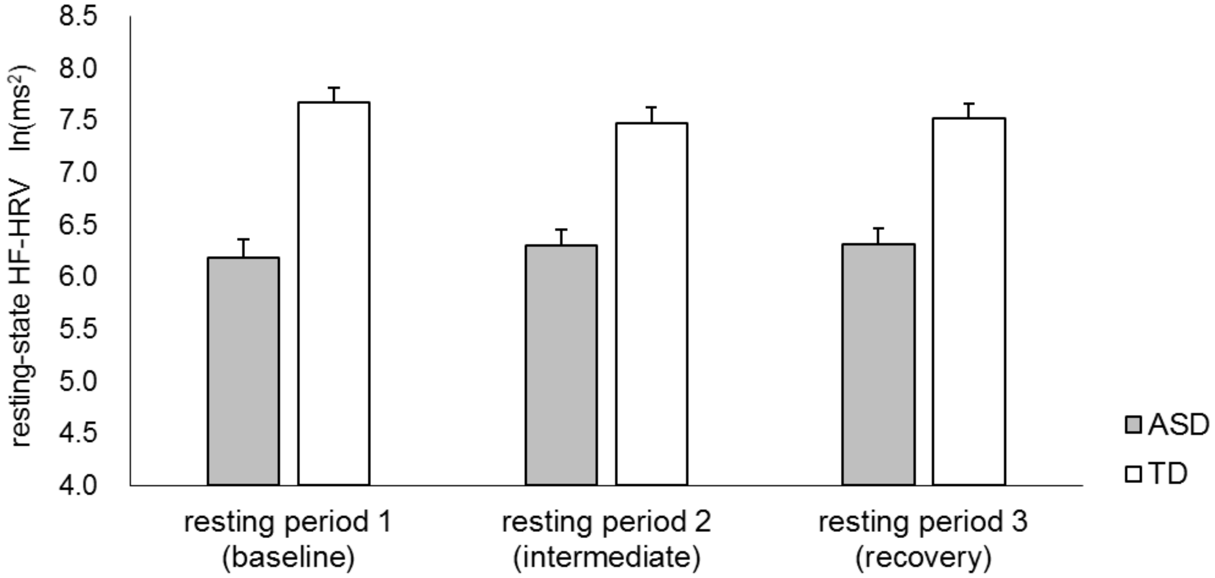

Fig.2. Resting-state HF-HRV across the three resting periods. Error bars represent standard errors of the mean. The ASD group, n = 32; The TD group, n = 31.

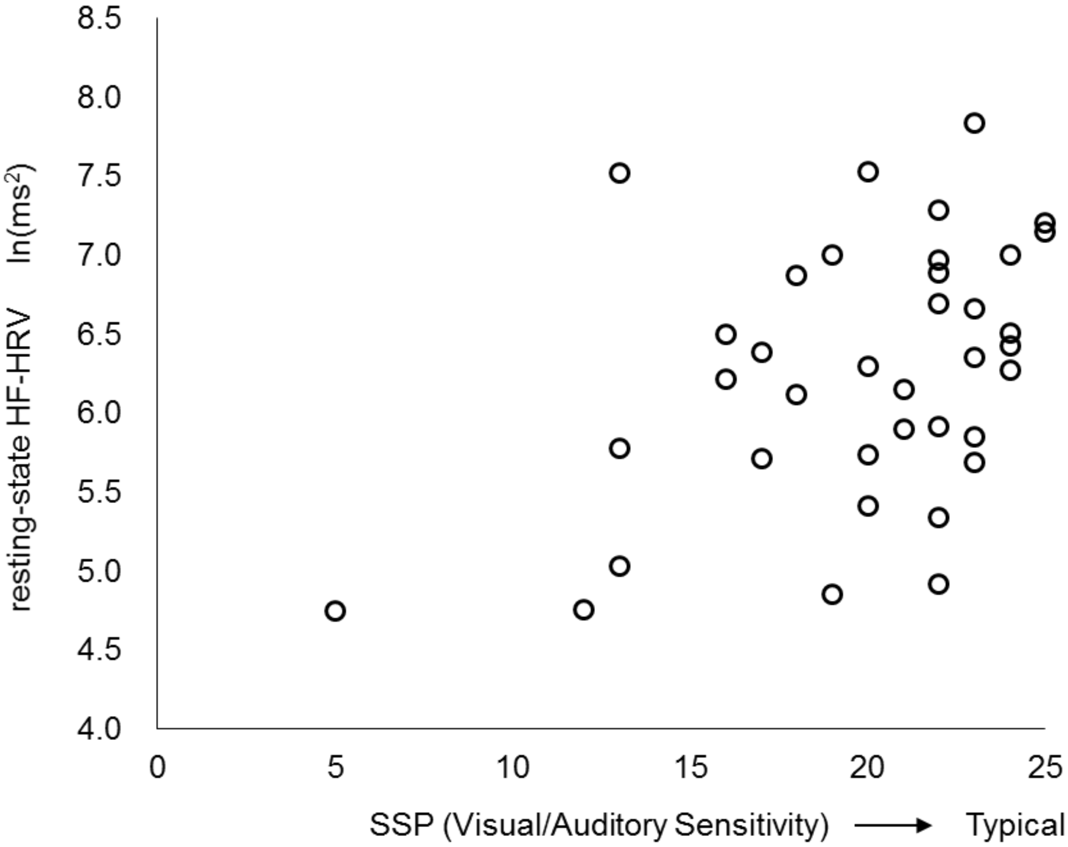

Fig.3 Relationship between SSP scores (Visual/Auditory Sensitivity) and resting-state HF-HRV within the ASD group. Lower scores of SSP indicate a greater severity of Visual/Auditory sensitivity. The ASD group, n = 37. ρ = 0.38, $p < 0.05$.

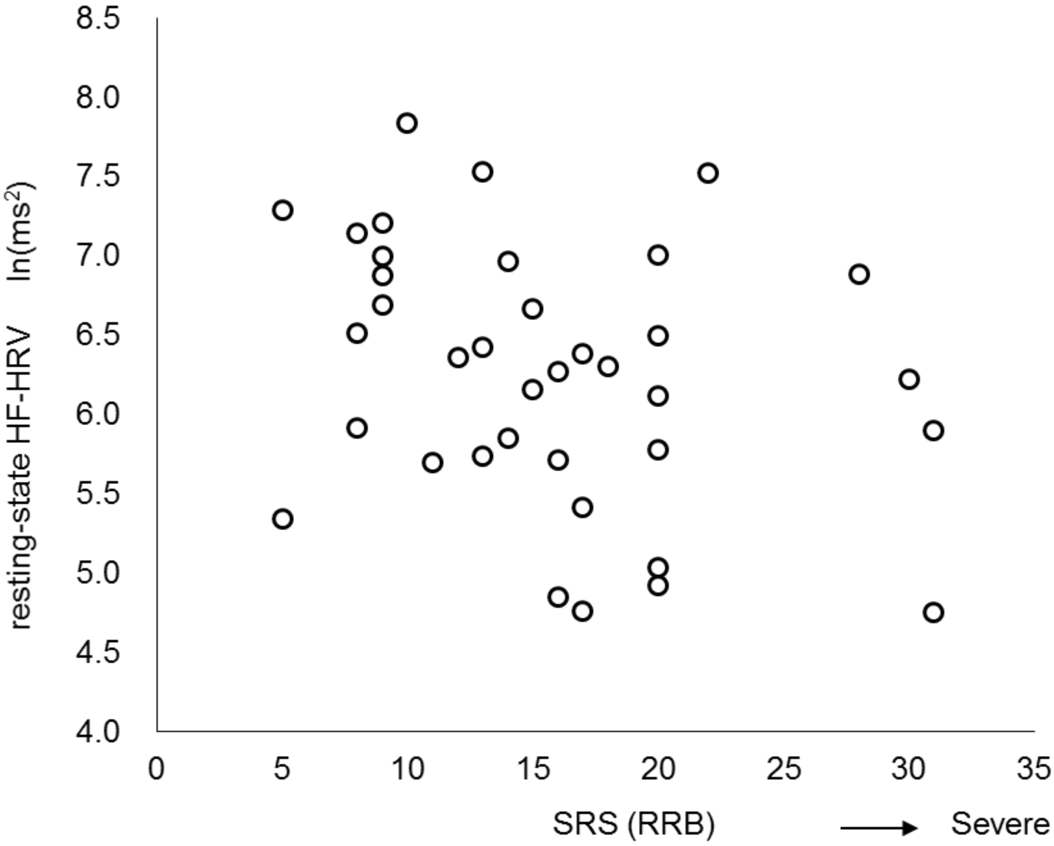

Fig.4 Relationship between SRS scores (restricted interests and repetitive behavior; RRB) and resting-state HF-HRV within the ASD group. Higher scores of SRS-2 indicate a greater severity of RRB symptoms. The ASD group, n = 37. ρ = 0.33, $p < 0.05$