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Altered pre-ejection period response to social evaluative threat in adolescents with autism spectrum disorder

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ABSTRACT

Introduction: The autonomic nervous system (ANS) is involved in regulating social behavior; Autism Spectrum Disorder (ASD) is characterized by alterations in social behavior and reduced physiological response to threat. We hypothesized that adolescents with ASD would show reduced ANS response to social threat.
Methods: Eighteen males with ASD and thirteen males with typical development (TD), ages 12 to 17, completed a social threat paradigm while wearing an impedance cardiography apparatus. We calculated pre-ejection period (PEP) and tested for between-group differences in PEP response to social threat. We also conducted correlation analyses between PEP change scores and clinical symptom scales.
Results: There was an effect of diagnosis on change in PEP from baseline to the onset of social threat ($F = 7.60$, $p = 0.01$), with greater changes in PEP in TD compared to ASD. PEP change score and the Social Communication Questionnaire ($r = 0.634$, $p = 0.005$) and the ADHD Problems Subscale of the Child Behavior Checklist ($r = 0.568$, $p = 0.014$) were correlated.
Conclusions: These findings suggest reduced arousal in response to social threat in ASD, with preliminary evidence that reduced sympathetic activation is associated with increased social behavior symptoms.

1. Background

The autonomic nervous system (ANS) facilitates adaptive social behavior by regulating the avoidance of and engagement with potential threat through the sympathetic branch (SNS, Sapolsky, Romero, & Munck, 2000) and facilitating flexible engagement with social stimuli through the parasympathetic branch (PNS, Porges, 2001, 2007). Increased activity of the SNS facilitates arousal (Sapolsky et al., 2000) including through the regulation of heart rate via sympathetic trunk projections, primarily to the ventricles, resulting in the release of norepinephrine, which binds to beta-1 adrenergic receptors at the neuromuscular junction. SNS influence on cardiac rhythm can be indexed by pre-ejection period (PEP), which is defined as the interval from stimulation of the left heart ventricle to the opening of the aortic valve. A decrease in the time between heart contractions results in a decrease in PEP, which reflects an increase in sympathetic activation (Berntson et al., 1994).

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A large body of literature has investigated individual differences in SNS reactivity through measurement of PEP in the context of social evaluation (Mills & Dimsdale, 2013). A commonly used experimental paradigm in this field is the Trier Social Stress Test (TSST), which requires individuals to give a speech in front of an audience and reliably activates physiological stress systems (Kirschbaum, Pirke, & Hellhammer, 1993). A recent study used both high-threat and low-threat versions of the TSST in typically developing (TD) children and found that the low-threat version of the TSST was associated with longer PEP than the standard high-threat protocol, indicating reduced SNS engagement during low SET (Yim, Quas, Rush, Granger, & Skoluda, 2015). In this context, SNS activation is likely adaptive (Quas, Yim, Rush, & Sumaroka, 2012) and has been associated with improved emotional regulation (Schuengel, Sterkenburg, Jeczynski, Janssen, & Jongbloed, 2009; Stifter, Dollar, & Cipriano, 2011). Thus, ANS measures of arousal in social contexts could serve as an important biomarker for psychiatric disorders associated with social impairments.

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by a primary deficit in social behavior and cognition (APA, 2013). Differences in regulatory systems that underlie social approach and avoidance behavior, including alterations in the ANS, could be related to observable differences in social behavior in ASD (Benevides & Lane, 2013). Impedance cardiography may be particularly beneficial in assessing ANS reactivity in ASD; it is non-invasive and can act as an objective measure of reactivity to a variety of stimuli (Schaaf, Benevides, Leiby, & Sendecki, 2015). Despite the benefits of impedance cardiography both methodologically and empirically, there have been few ASD studies that utilize PEP. One study found that children with ASD did not have significantly different changes in PEP compared to controls following a sensory challenge (Schaaf et al., 2015). In another study, which asked participants to interact with a novel adult and with a parent, children with ASD demonstrated disorganized ANS responses. Specifically, typically developing boys showed the expected decrease in SNS influence over heart rate when interacting with a familiar adult, while those with ASD showed similar SNS responses to both novel and familiar partners (Neuhaus, Bernier, & Beauchaine, 2016).

Studies of TD populations suggest pubertal effects on PEP (Allen & Matthews, 1997; Benevides & Lane, 2013). Studies employing the TSST in pre-pubertal children with ASD have found decreased physiological reactivity to SET (Lanni, Schupp, Simon, & Corbett, 2012; Levine et al., 2012). Specifically Levine et al. (2012) found differences in the salivary cortisol response to the TSST in children with ASD compared to TD, by subtracting baseline cortisol from cortisol during the TSST to get a measure of cortisol response to the TSST; children with ASD showed a reduction in salivary cortisol during the TSST relative to baseline, and TD children showed an increase. However, this study also examined electrodermal activity (EDA), an indirect measure of SNS activity, and found no differences at baseline or during the TSST between groups. Lanni et al. (2012) similarly found reduced salivary cortisol response to the TSST in ASD; in this study, change scores calculated by subtracting baseline cortisol from cortisol response during the TSST found no difference from zero in ASD, but a significant response in the TD group. Interestingly, both studies did not find between-group differences in baseline physiology or in the maintenance of the stress response, but instead, differences between groups seem to be limited to the initial response to the onset of the TSST. This suggests that potential SNS functional differences in ASD may be characterized by a reduced response to the onset of SET. In contrast, one study of adults with ASD did not find differences in HPA axis reactivity in ASD versus TD groups when comparing cortisol response before, during, and after the TSST (Jansen et al., 2006). Because the finding of reduced SNS reactivity was not present in adults with ASD, this could suggest a possible developmental mechanism that occurs during the transition to adulthood. However, no PEP studies have been conducted in adolescents.

In the present study, adolescent participants with and without ASD completed the TSST. We used ambulatory impedance cardiography measures to collect PEP data throughout the TSST. We hypothesized that individuals with ASD would show reduced SNS reactivity to the TSST compared to TD adolescents (i.e., longer PEP) associated with the onset of TSST. We also hypothesized that PEP change in response to the TSST would be correlated with social behavior.

2. Methods

2.1. Participants

The Vanderbilt University Institutional Review Board approved this study. Study participants were recruited from IRB-approved flyers posted at area schools, resource centers, and university clinics, as well as university-wide and local autism email listservs. Informed consent was obtained from the parents of participants prior to the study, and assent was obtained from participants. Research participants included 13 adolescent males with TD and 18 males with ASD between the ages of 12 and 17 (Table 1). Participants were matched for age and IQ as measured by the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999). For inclusion in the present study, all participants had a full-scale IQ >70. All ASD participants had diagnosis confirmed by administration of the Autism Diagnostic Observation Schedule Version II module three (ADOS-2, Lord et al., 2012) by a research-reliable clinician. All ASD participants had ADOS total scores greater than seven. Completion of the Social Communication Questionnaire (SCQ, Rutter, 2003) and Social Responsiveness Scale (SRS-2, Constantino & Gruber, 2012) to parents further supported diagnosis and confirmed that none of the TD participants demonstrated social-communication difficulties commensurate with a diagnosis. No TD participants had an SCQ >10. For the SRS, no TD participant had a total T-score greater than 50. Mean T-scores for the sub scales in the ASD group were as follows: Social Awareness: 69.95; Social Cognition: 68.75; Social Communication: 73.2; Social Motivation: 69.15; Restricted Repetitive Interests or Behaviors: 74.95.