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# Interaction between prenatal risk and infant parasympathetic and sympathetic stress reactivity predicts early aggression

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ABSTRACT

Nonreciprocal action of the parasympathetic (PNS) and sympathetic (SNS) nervous systems, increases susceptibility to emotional and behavioral problems in children exposed to adversity. Little is known about the PNS and SNS in interaction with early adversity during infancy. Yet this is when the physiological systems involved in emotion regulation are emerging and presumably most responsive to environmental influences. We examined whether parasympathetic respiratory sinus arrhythmia (RSA) and sympathetic pre-ejection period (PEP) response and recovery at six months, moderate the association between cumulative prenatal risk and physical aggression at 20 months ($N$ = 113). Prenatal risk predicted physical aggression, but only in infants exhibiting coactivation of PNS and SNS (i.e., increase in RSA and decrease in PEP) in response to stress. These findings indicate that coactivation of the PNS and SNS in combination with prenatal risk is a biological marker for the development of aggression.

Exposure to adversity during the prenatal period, such as maternal psychiatric problems, substance (ab)use, single parenthood and poverty, has been shown to predict aggression in childhood that persists into adolescence and adulthood (Côté, Vaillancourt, LeBlanc, Nagin, & Tremblay, 2006; Hay et al., 2011; NICHD Early Child Care Research Network, 2004). Yet, not all children seem to be equally affected by adversity. Guided by theories of differential susceptibility (Belsky & Pluess, 2009) and biological sensitivity to context (Boyce & Ellis, 2005), a number of studies have demonstrated that individual differences in stress reactivity, as measured by indices of the cardiac autonomic nervous system (ANS), can predispose or protect against the effects of adversity on children's behavioral maladjustment (e.g. El-Sheikh & Erath, 2011). Although these studies provide important insights into physiological measures of susceptibility, they have focused mostly on older children. Little is known about the role of the cardiac ANS in interaction with early adversity during infancy when the physiological systems involved in emotion regulation are emerging and presumably most responsive to environmental influences (Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008; Laurent, Harold, Leve, Shelton, & Van Goozen, 2016).

Altered ANS functioning has been consistently linked to aggression in children, adolescents and adults (Van Goozen, Fairchild, Snoek & Harold, 2008). The ANS is comprised of a sympathetic (SNS) and parasympathetic (PNS) branch. PNS activity is often assessed by respiratory sinus arrhythmia (RSA). RSA is the heart rate variability at the frequency of respiration (Cacioppo, Uchino, & Berntson, 1994), and is considered to index the neural control of the heart via the vagus nerve (Porges, 2007). During restful periods, the vagus exerts an inhibitory influence on the heart acting as a 'brake' by increasing vagal output to the sino-atrial (SA) node of the heart and limiting sympathetic influences which contribute to a slow and steady heart rate. In response to stress, the vagal 'brake' is disengaged resulting in a decrease in vagal output to the SA node of the heart and thus contributing to an increase in heart rate (Porges, 2007). If withdrawal of the vagal 'brake' is not sufficient to manage a stressor, the sympathetic activity is expected to increase in order to prepare the body for a more active stress response.

The majority of research examining stress reactivity in young children has focused on RSA or global measures of cardiac autonomic functioning like HR without specific assessments of activity within the sympathetic branch. Pre-ejection period (PEP) reflects the time interval between the onset of the heartbeat and ejection of blood into the aorta (Cacioppo et al., 1994) and is commonly used as an index of myocardial contractility and sympathetic control of the heart (Berntson et al., 1994). Both RSA and PEP are used as indicators of the complex processes that underlie responsiveness of the ANS to a changing environment, e.g., from rest (baseline) to challenge or vice versa.

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Low baseline PNS activity, as indicated by RSA, has been identified as a vulnerability factor that exacerbates the relation between adversity (e.g. marital conflict, parental drinking problems) and children's externalizing behavior (El-Sheikh, 2005a; El-Sheikh et al., 2001). Other studies have measured RSA reactivity to stress, with decreases in RSA in response to stress considered to be indicative of better adaptation (El-Sheikh & Erath, 2011). RSA withdrawal in response to stress has been associated with lower levels of externalizing behavior in the context of adversity (El-Sheikh, 2001; Katz, 2007), although findings have been inconsistent (Obradovic, Bush, Stamperdahl, Adler, & Boyce, 2010). Studies investigating interactions between adversity and SNS activity (measured as skin conductance level [SCL] in most studies) indicate that either very low or very high baseline levels of SCL and high SCL reactivity may increase the risk of aggression and externalizing behavior in the context of adversity (El-Sheikh, 2005b; El-Sheikh et al., 2007).

It is clear that ANS functioning has important implications for the association between adversity and the development of aggression. However, such associations may be less straightforward in infancy. For example, recent studies indicated a stronger positive relation between higher (rather than lower) baseline RSA and (externalizing) problem behavior in infants and toddlers exposed to a more negative caregiving environment (Conradt, Measelle, & Ablow, 2013; Eisenberg et al., 2012). Measures of RSA reactivity and SNS functioning in infants have not been studied as moderators of relations between early adversity and aggression before, although there is one study in toddlers reporting no effects of RSA reactivity (Eisenberg et al., 2012).

Adaptation to stressful contexts requires a delicate balance in the operation of both the PNS and SNS (Porges, 2007), and the synergistic action of both systems determines the effectiveness of regulation (Berntson, Cacioppo, & Quigley, 1991). Although the effects of both branches of the ANS on the heart is generally believed to be reciprocal, with increased activity in one branch and decreased activity in the other, reactivity in both branches can also be nonreciprocal (i.e., increased or decreased activity of both branches at the same time; Berntson et al., 1991). Reciprocal cardiac PNS activation, with increased PNS stimulation and decreased SNS stimulation on the heart, is expected during calm states, while reciprocal SNS activation (i.e., increased SNS activity and decreased PNS activity) is more adaptive when confronted with challenging stressful situations. Previous studies have suggested that reciprocal cardiac SNS activation in response to stress is normative in children, adolescents and adults (Alkon, Boyce, Davis, & Eskenazi, 2011; Berntson et al., 1991; Salomon et al., 2000), and linked to better emotion regulation in young children (Stifter, Dollar, & Cipriano, 2011). Conversely, nonreciprocal activation of PNS and SNS, as indicated by coactivation (i.e., increased activity in both the PNS and SNS) and coinhibition (i.e., decreased activity in both the PNS and SNS), has been linked to more externalizing problems in school-aged children in the context of marital conflict, compared to patterns of reciprocal SNS activation or reciprocal PNS activation (El-Sheikh et al., 2009). Similar findings have been reported in the context of maltreatment predicting aggression in girls (Gordis, Feres, Olezeski, Rabkin, & Trickett, 2010).

So far, there have been no studies that we know of that have examined measures of both PNS and SNS functioning in infancy as potential moderators of the effects of early adversity on outcome in toddlerhood. Elucidating how early physiological systems increase or decrease susceptibility to aggression, may enhance our ability to identify children at risk of aggression at an early age, before developmental trajectories begin to be set.

In the present study, we investigated the interaction between ANS response to and recovery from stress measured in 6-month-old infants, taking into consideration both the PNS and SNS, and prenatal risk in predicting physical aggression at 20 months of age. We were specifically interested in cumulative risk as previous work has shown a dose-dependent relation between the presence of multiple risk factors and child adjustment, with increases in the number of risk factors being associated with increased levels of problems (Appleyard, Egeland, van Dulmen, & Sroufe, 2005). We measured parasympathetic RSA and sympathetic PEP response and recovery from stress. Although previous studies involving PNS and SNS interactions have focused on SCL (El-Sheikh et al., 2009; Gordis et al., 2010), PEP is considered to be a more direct measure of cardiac SNS activity (Cacioppo et al., 1994), that can be reliably measured in infants (Alkon et al., 2006; Quigley & Stifter, 2006). We hypothesized that higher levels of *coactivation* and *coinhibition* would exacerbate the relation between cumulative prenatal risk and physical aggression, whereas, *reciprocal PNS activation* and *reciprocal SNS activation* would attenuate the association between cumulative risk and physical aggression.

## 1. Methods and materials

### 1.1. Participants

The participants in this study were part of an ongoing longitudinal study into neurobiological and neurocognitive predictors of early behavior problems (Mother- Infant NeuroDevelopment Study in Leiden, The Netherlands [MINDS − Leiden]). We oversampled women based on the presence of one or more risk factors (see criteria under Cumulative risk). The sample was composed of 113 mothers and their infants (55.8% males) who had completed the prenatal home-visit during the third trimester of pregnancy (T1), and the postpartum home-visits at six (T2) and 20 months (T3). The mean age of the children was 6.03 months ($SD = 0.41$, range 5–7 months) at T2 and 19.94 months ($SD = 0.81$, range 18–24 months) at T3. The mothers were on average 22.96 years ($SD = 2.12$, range 17–27 years) at T1. Approximately 96% of the mothers had a partner (87.6% was married or living with a partner) and 32.7% of the mothers had a high educational level (Bachelor's or Master's degree). Families were predominantly Caucasian (88.5%).

Of the 136 mothers originally enrolled in the study at T1, 10 did not participate at T2, and another 13 dropped out between T2 and T3. Main reasons for families dropping out were inability to contact, moving away or too busy. Sample attrition was unrelated to demographic variables (i.e., maternal age, ethnicity, marital status, educational level; $ps > 0.05$). However, mothers who dropped out were more often single ($\chi^2(1) = 8.41$, $p = 0.013$).

The study was approved by the ethics committee of the Department of Education and Child Studies at the Faculty of Social and Behavioral Sciences, Leiden University, and by the Medical Research Ethics Committee at Leiden University Medical Centre. Informed consent was obtained from all parents of infants included in the study. Mothers were compensated for each completed home or laboratory visit and children were given a small present for their participation.

### 1.2. Procedures

The protocol during the six-month home-visit (2 h), included attachment of cardiac monitoring equipment to the infant's chest and back after which they watched a 2-min relaxing movie while lying on a blanket, followed by two procedures designed to elicit physiological responses to social stress (Still Face Paradigm) and frustration (Car seat). The social stress and frustration tasks were administered with a break in between to limit carry over effects. Infants were only assessed in the next procedure when they were calm and displayed no distress. The home-visits were scheduled at a time of the day when mothers deemed their infant to be most alert.

The Still Face Paradigm (SFP; Mesman, Van IJzendoorn, & Bakermans-Kranenburg, 2009) is a well-established social stress paradigm comprising a sequence of three 2-min episodes during which the mother is asked to interact normally with the infant (SFP baseline), then withhold interaction (SFP social stress), and then