



# Early life adversities and adolescent antisocial behavior: The role of cardiac autonomic nervous system reactivity in the TRAILS study

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## ABSTRACT

In the current study, the role of pre-ejection period (PEP) and respiratory sinus arrhythmia (RSA) was studied in the association between prior adversities and antisocial behavior in adolescence. PEP and RSA task reactivity and recovery to a public speaking task were assessed in adolescents from a longitudinal population-based study ( $N = 624$ ,  $M_{age} = 16.14$  years, 49.2% boys). Perinatal adversities were unrelated to antisocial behavior, but experiencing more stressful adversities between age 0 and 15 was associated with antisocial behavior at age 16 in boys with blunted PEP reactivity and smaller PEP differences from rest to recovery. Number of adversities between age 0 and 15 was associated with antisocial behavior in boys with blunted and girls with heightened RSA reactivity and larger PEP differences from rest to recovery. The association between prior adversities and antisocial behavior were small in effect size and depended upon sex and PEP and RSA reactivity and recovery.

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## 1. Introduction

Perinatal (i.e., before, during, and right after birth) and early life adversity – here defined as adversity during childhood and adolescence – have been associated with subsequent antisocial behavior in adolescence (Beck & Shaw, 2005; Hodgins, Kratzer, & McNeil, 2001; Raine, Brennan, & Mednick, 1994; Timmermans, van Lier, & Koot, 2010). One of the possible mechanisms underlying this association is the functioning of one of the major stress axes, the cardiac autonomic nervous system (ANS). It has been argued that perinatal adversities shape ANS functioning (Cohen, Vella, Jeffery, Lagercrantz, & Katz-Salamon, 2008; Jones et al., 2008; Kajantie & Raikkonen, 2010). In turn, these changes in ANS functioning may co- occur with changes in emotional and behavioral reactions to environmental stressors and may therefore be associated with the development of antisocial behavior (Ortiz & Raine, 2004; Lorber, 2004). Moreover, adversities during childhood and adolescence have been shown to interact with cardiac ANS functioning (El-Sheikh, Keller, & Erath, 2007; Erath, El-Sheikh, & Cummings, 2009; Gordis, Feres, Oleszki, Rabkin, & Trickett, 2010; Shenk, Noll,

Putnam, & Trickett, 2010). In particular, these studies showed that those who experienced adversities during childhood and adolescence and showed blunted or heightened ANS functioning were at increased risk of antisocial behavior. In the current study, we examined these two processes more closely; details and directions of these two mechanisms will be discussed below.

### 1.1. Autonomic nervous system

The cardiac ANS consists of two branches, namely the parasympathetic (PNS) and sympathetic (SNS), which can be assessed by Respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP), respectively (Alkon et al., 2003; Cacioppo, Tassinari, & Berntson, 2007; Camm et al., 1996). RSA is the heart rate variability due to respiratory gating of tonic vagal effects on the SA node of the heart (Berntson, Cacioppo, & Quigley, 1993), and is considered a measure of cardiac vagal control. PEP is derived as the time interval between the onset of ventricular depolarization and the opening of the semilunar valves (Sherwood et al., 1990) and commonly used as an index of myocardial contractility and sympathetic control of the heart (Berntson et al., 1994; Schachinger, Weinbacher, Kiss, Ritz, & Langewitz, 2001). These cardiac ANS measures are used as indicators of the complex processes that underlie autonomic responsiveness to a changing environment, e.g., from rest to

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a challenge or vice versa. ANS resting measures reflect a physiology state during a calm state. Challenging measures reflect physiological responses to a stressor, and stress reactivity measures indicate physiological responses to a stressor compared to a resting state, whereas recovery measures indicate physiological responses after a stressor compared to a subsequent resting state (Cacioppo et al., 2007).

### 1.2. Perinatal adversities and antisocial behavior

As suggested by evolutionary models of biobehavioral change, perinatal adversities may impact ANS reactivity and recovery because the plasticity of the ANS is strongest early in life (Boyce & Ellis, 2005; Del Giudice, Ellis, & Shirtcliff, 2011; Gunnar, Wewerka, Frenn, Long, & Griggs, 2009). Several studies support this idea by showing that perinatal adversity has an effect on cardiac ANS reactivity (Enlow et al., 2009; Jones et al., 2008; Kajantie & Raikonen, 2010). Based on these prior findings, alterations due to perinatal adversities may be expected to lead to heightened or blunted ANS reactivity in response to a stressor. In turn, empirical studies associating both PNS and SNS reactivity to antisocial behavior showed that reactivity of both branches of the ANS has been cross-sectionally associated with more antisocial behavior (i.e., aggression and externalizing behaviors) in children and adolescents (Beauchaine, Gatzke-Kopp, & Mead, 2007; Boyce et al., 2001; Calkins, Graziano, & Keane, 2007; Sijtsema, Shoulberg, & Murray-Close, 2011).

There is theoretical support for both directions, but previous research has shown more support for perinatal and early life adversities being associated with increased ANS reactivity (see Obradovic, 2013 for a discussion). However, both from a theoretical and empirical viewpoint there is reason to believe that the role ANS reactivity plays in the association between adversity and antisocial behavior is different in boys and girls. Evolutionary theorists have argued that in stressful environments it is more adaptive for females to be vigilant and attentive to environmental cues and thus show heightened ANS reactivity, with more internalizing problems as a result (Del Giudice, Hinnant, Ellis, & El-Sheikh, 2012; Glover & Hill, 2012). In contrast, in males it may be more important to respond less to environmental cues, as they are more programmed towards exploring and competing with other males, which may result in antisocial behaviors (Del Giudice et al., 2011). Previous studies investigating sex differences have indeed shown that the association between adverse environments and antisocial behavior was highest in boys with blunted ANS reactivity (Beauchaine, Hong, & Marsh, 2008; Sijtsema et al., 2013), whereas this was not the case in girls. Moreover, a recent study showed that boys high on externalizing problems showed blunted RSA withdrawal, whereas girls high on externalizing problems showed heightened RSA withdrawal (Hinnant, & El-Sheikh, 2013). In sum, perinatal adversities have been found to be associated with both ANS reactivity and antisocial behavior. However, whether ANS reactivity mediates the association between perinatal adversities and antisocial behavior is currently unknown. The first aim of the current study is to test this indirect effect. Because previous studies suggest important sex differences, we hypothesized that blunted ANS reactivity in boys and heightened ANS reactivity in girls mediates the association between perinatal adversities and antisocial behavior at age 16.

### 1.3. Adversities in childhood and adolescence and antisocial behavior

Adversities that take place later in life are less likely to impact alterations in ANS reactivity regulation mechanisms, due to decreased plasticity of the ANS (Boyce & Ellis, 2005; Del Giudice et al., 2011; Gunnar et al., 2009). However, ANS reactivity may

modify the association between adversities and antisocial behavior. Moderation by RSA reactivity of the relationship between adversities and antisocial behavior may rest on the premises that RSA withdrawal in response to stress (i.e., removing vagal control) is related to attention and emotional processing (Beauchaine, 2001; Porges, 1995). Arguably, RSA withdrawal in stressful situations reflects the ability to use attention and emotional strategies to form an appropriate reaction to stress (Bornstein, & Suess, 2000; Porges, 1995). Blunted physiological responses to stress could thus indicate inability to respond adequately to stressful situations. Moderation by PEP reactivity has been studied less frequently but may be related to the behavioral activation system (Brenner, Beauchaine, & Sylvers, 2005). As such, stressful situations or adversity may induce SNS reactivity and blunted reactivity may indicate inability to respond adequately to stressful situations (Beauchaine, 2001).

Research into the interaction between context and RSA and PEP reactivity has shown important links to antisocial behaviors (El-Sheikh, Erath, & Hinnant, 2011; El-Sheikh and Hinnant, 2007; Obradovic, Bush, & Boyce, 2011). Specifically, these studies showed that marital conflict in childhood had a stronger effect on externalizing problems (including antisocial behavior) in youth with blunted SNS and RSA reactivity. However, although marital conflict is an important stressor in childhood, these studies did not specifically examine adverse events (e.g., death/illness of a parent or divorce) and whether youth perceived these events as stressful. Moreover, previous studies largely focused on childhood behaviors and did not include adolescent behavior.

In addition, most of the studies discussed above have focused on physiological reactivity from rest to stress, but largely ignored recovery from a stressor. Recovery measures are meaningful as healthy individuals in general show elevated physiological activity to stress, but these levels typically decrease relatively quickly after the stressor has passed or after habituation to the stressor (cf. Koolhaas et al., 2011). When this natural recovery process is less effective, physiological activation may remain high, even after the stressor has passed. Based on models on allostatic load, chronic or severe stress may lead to a 'wear and tear' of the ANS and hence recovery from a stressor takes longer (McEwen, 2007). ANS recovery measures may thus prove an important index for how well individuals are able to regulate their emotions or adapt to their environment after a stressor has passed. However, there is little empirical evidence regarding cardiovascular recovery and some evidence seems to go against theories of prolonged ANS activity during a stressful situation in individuals who experienced more adversity. Research on chronic stress showed that adults with greater chronic stress showed greater systolic blood pressure recovery and higher cortisol levels, with no differences between males and females (Chatkoff, Maier, & Klein, 2010). Similarly, adults who were highest on anticipatory stress, showed the greatest recovery in blood pressure and cortisol (Juster et al., 2012), though another study in adolescents showed no associations between anticipatory stress and ANS recovery (Oldehinkel et al., 2011). We aim to extend previous research by examining whether ANS recovery moderates the association between early life adversities and adolescent antisocial behavior similar to ANS task reactivity. Specifically, based on the earlier presented evolutionary perspective on stress and sex, we hypothesized that in boys, blunted ANS reactivity exacerbates the association between early life adversities and antisocial behavior at age 16, whereas in girls, heightened ANS reactivity exacerbates this association. Similarly, we expected that smaller differences between ANS rest and recovery in boys and larger differences in girls exacerbate the association between early life adversities and antisocial behavior at age 16.

We tested these hypotheses separately for number of adversities and the stressfulness of adversities. In addition, we used an ecologically valid experimental condition to induce stress. Childhood

adversity and antisocial behavior often pertain to interpersonal stressors, and hence we used an experiment in which ANS reactivity and recovery could be measured in response to an interpersonal stress task (i.e., public speaking task; see Section 2).

## 2. Method

### 2.1. Participants

Data were collected in the general population study TRacking Adolescents' Individual Lives Survey (TRAILS), a large prospective population study of Dutch adolescents with bi- or triennial measurements from age 11 into adulthood (Huisman et al., 2008; Oldehinkel, Hartman, De Winter, Veenstra, & Ormel, 2004; Ormel et al., 2012). Detailed information about sample selection and analysis of non-response bias are reported elsewhere (de Winter et al., 2005; Nederhof et al., 2012). The current study used data from the first three measurement waves, which ran from September 2005 to December 2007. These assessment waves ran from March 2001 to July 2002 (wave 1), September 2003 to December 2004 (wave 2), and September 2005 to December 2007 (wave 3). At wave 1, 2230 children (mean age = 11.09 years,  $SD = 0.56$ ) enrolled in the study of whom 2149 (96.4%; mean age 13.56 years,  $SD = 0.53$ ) participated at wave 2, and 1816 (81.4%; mean age = 16.27 years,  $SD = 0.73$ ) at wave 3. During the third wave, a subsample of 744 adolescents was invited to perform a series of experimental tasks, in addition to the usual assessments, hereafter referred to as the experimental session. We slightly oversampled participants with high scores on frustration and fearfulness, low scores on effortful control, parental psychopathology (depression, anxiety, addiction, psychoses, or antisocial behavior), and living in a single-parent family. In total, these higher-risk adolescents represented 66% of participants in the experimental session, whereas they represented 58% of the total TRAILS population. Lower risk TRAILS participants represented 34% of participants in the laboratory session, while they represented 42% of the total TRAILS population. Of all invited adolescents, 715 (96.1%) agreed to participate. Data from adolescents with missing or distorted physiological data were discarded, leaving a sample of 624 adolescents (mean age 16.14 years,  $SD = 0.37$ , 49.2% boys) with available data on antisocial behavior as well. Independent sample *t*-tests and a chi-square test (with regard to sex) showed that the groups with complete and missing data did not differ on sex, age, number and stressfulness of adversities, and antisocial behavior at age 16. The experimental protocol was approved by the Central Committee on Research Involving Human subjects (CCMO). Parents and participants gave written consent prior to the experiment.

### 2.2. Procedure

During the experimental session, participants' psychophysiological responses at rest and to a variety of challenging conditions were recorded. The challenge conditions included orthostatic stress (from supine to standing), a spatial orienting task, a gambling task, a startle reflex task, and a social stress test. The test assistants, 16 in total, received extensive training in order to optimize standardization of the experimental session. The experimental sessions took place on weekdays, in sound-proof rooms with blinded windows at selected locations in the towns where participants resided. The sessions lasted about 3 h and 15 min, and started between 08:00 and 09:30 a.m. (morning sessions, 49%), or between 01:00 and 02:30 p.m. (afternoon sessions, 51%). Participants were asked to refrain from smoking and from using coffee, milk, chocolate, and other sugar containing foods in the 2 h before the session. At the start of the session, the test assistant explained the procedure and

administered a short checklist on current medication use, quality of sleep, and physical activity in the last 24 h.

Participants were attached to the equipment for cardiovascular registrations. The participants filled out a number of questionnaires at the start and end of the session. Participants were asked to relax until 35 min after the start of the session. After this period of rest, cardiovascular measures were recorded at rest in sitting position for 5 min. Subsequently, the challenges were administered in the aforementioned order. Every challenge was followed by a short break, during which participants reported subjectively experienced arousal, unpleasantness, and dominance. The social stress test was the last challenge of the experimental session. Cardiovascular measures during this part were used for the stress measure for the current study. Thereafter, participants were debriefed about the experiment and could relax for about 35 min, after which cardiovascular measures were recorded once more for 5 min. The latter assessment was used as the rest measurement because it is free from potential anticipation stress.

GSST. Cardiovascular measures were assessed in response to the Groningen Social Stress Task (GSST) (Bouma, Riese, Ormel, Verhulst, & Oldehinkel, 2009; Oldehinkel et al., 2011), a standardized protocol inspired by the Trier Social Stress Task (Kirschbaum, Pirke, & Hellhammer, 1993) for the induction of moderate performance-related social stress. Cardiovascular measures were recorded during and after the GSST in four blocks: a 6 min speech task, a 3 min rest period (c.q. recovery), a 6 min arithmetic task, and a 3 min rest period. Before the task participants had 7 min for preparation and afterwards followed a 5 min emotion regulation task. We only used cardiac ANS data from the first 3 min of the speech task and the immediate subsequent recovery period, and the final rest period at the end of the whole experimental session (see Fig. 1). Only the first 3 min of the speech task were used because stress responses were likely to be highest in the beginning. Moreover, this way the speech and recovery period both spanned a period of 3 min. In short, participants were instructed, on the spot, to prepare a 6-min. speech about themselves and their lives and deliver this speech in front of a video camera. They were told that their videotaped performance would be judged on content of speech as well as on use of voice and posture and rank-ordered by a panel of peers after the experiment. The risk of being judged negatively by peers was included to induce threat of social rejection. The test assistant watched the performance critically, without showing empathy or encouragement. After 6 min of continuous speech, the participants were told that there was a problem with the computer and they had to sit still and be quiet for a 3-min period of rest (recovery) which was followed by another stress task (mental arithmetic) and another 3-min period of rest.

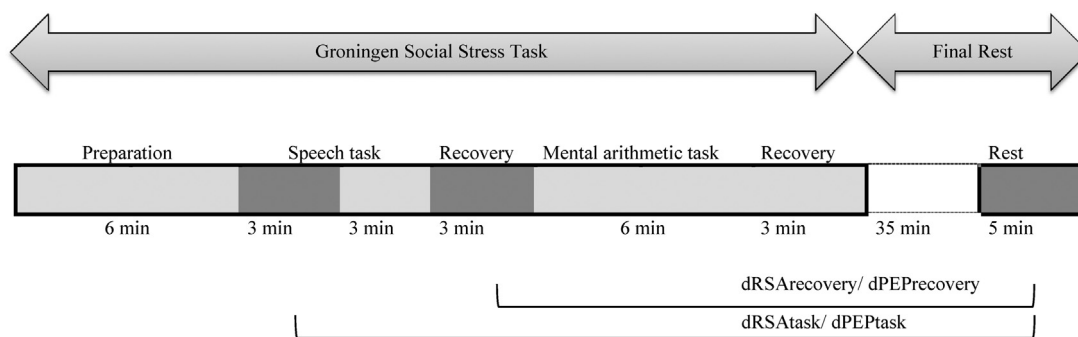
## 3. Measures

### 3.1. Antisocial behavior

Self-reported antisocial behavior was assessed via the Antisocial Behavior Questionnaire (ASBQ) (Moffitt & Silva, 1988). Participants indicated whether they had committed antisocial behavior (e.g., 'hit someone at school/on the street/at home', 'used a weapon in a fight', and 'purposely broken or vandalized things at school/on the street/in and around the home') in the past twelve months (25 items;  $\alpha = .85$ ). Answers were rated on a five-point scale ranging from 'no, never' (0) to '7 times or more' (4). Scores were averaged over the 25 items.

### 3.2. Perinatal adversities

At T1, well-trained interviewers visited the parents at their homes to administer an interview covering perinatal adversities.



**Fig. 1.** Schematic overview of the Groningen social stress task and final rest measurement of the experimental session.

Note: Dark-shaded sections of the task were used for the construction of the reactivity and recovery measures used in the current study (see Section 2).

Perinatal adversities were operationalized as the sum of maternal psychological problems during pregnancy or the three months after delivery, preterm delivery ( $\leq 33$  weeks), low birth weight ( $\leq 2500$  g), hospitalization of mother or child within one month after delivery, and maternal alcohol use or smoking during pregnancy. For birth weight and gestational age we used records of the Preventive Child Healthcare (PCH) services (Reijneveld, Brugman, Verhulst, & Verloove-Vanhorick, 2004). In the current study, 35.0% of the participants were not exposed to any, 40.8% to one, 15.7% to two, 5.5% to three, 2.1% to four, 0.6% to five, and 0.2% to six perinatal adversities.

### 3.3. Number of adversities between ages 0 and 15 years

Adversities experienced between ages 0 and 15 years were assessed for the age categories of 0–5, 6–11, 12–13 and 14–15 years, as described by Bosch et al. (2012). Information on adversities in early childhood (0–5 years) and middle childhood (6–11 years) was collected during a detailed interview with the parents at T1, and included the number of times the child had experienced parental divorce, hospitalization, the death of a family member or friend, out-of-home placement, parental addiction or parental mental health problems. The total number of adversities experienced in early adolescence (12–13 years) was assessed with a self-report questionnaire at T2. The 25 adversities included illness or injury of the participant, a family member or a friend; parental divorce; death of family member or friend; changes in family composition; parental unemployment; conflicts with family or friends; and being bullied. Adversities in middle adolescence (14–15 years) were assessed at T3 during an Event History Calendar Interview with the adolescent (Caspi et al., 1996). The list of possible events consisted of conflicts, physical or sexual intimidation, victim of bullying/gossiping, loss or lack of friends, psychological/addiction problems of family or friends, out-of-home placement, running away from home, death/illness of family member, hospitalization of participant, and parental divorce.

Based on the above-mentioned event measures, we calculated a measure of total adversities experienced between ages 0 and 15 years by standardizing the sum score of the number of adversities for each age category, and summing the standardized scores into a sum score which was used in the statistical analyses (see also Van der Knaap et al., 2014).

### 3.4. Stressfulness of adversities experienced between ages 0 and 15 years

At T2, both parents and adolescents were asked to rate the overall stressfulness of the adolescents' lives between ages 0 and 11 years, and of the last two years (12–13 years), on a scale ranging

from 1 (not at all stressful) to 10 (extremely stressful). The mean of the standardized parent and adolescent scores was used as an overall index of experienced stress. At T3, chronic stress reflected the summed duration (in months) of the following adversities: physical or sexual abuse/assault, bullying/gossiping, lack of friends, conflicts, severe problems of family members or friends, out-of-home placement, and running away from home. These scores were standardized and subsequently averaged to compute one measurement of stressfulness of adversities between ages 0 and 15 years.

### 3.5. Cardiac ANS measures

During the experimental session, a three-lead electrocardiogram (ECG) and a four-lead impedance cardiogram (ICG) was registered using 3 M/RedDot–Ag/AgCl electrodes (type 2255, 3M Health Care, D-41453 Neuss, Germany), while the participant breathed spontaneously. With a BIOPAC Amplifier-System (MP100), the signals were amplified and filtered before digitization at 250 samples/second. Dedicated software (PreCARSPAN, previously used in, e.g., Dietrich et al., 2007), was used to check signal stationarity, to correct for artifacts, to detect R-peaks, and to calculate the interbeat-interval (IBI) between two heart beats. ECG blocks were considered invalid if they contained artifacts with duration of more than five seconds, if the total artifact duration was more than 10% of the registration period, or if the block length was less than 100 seconds. This resulted in RSA data of 687 participants for the rest measurement after the GSST, 661 during the first 3 min of the GSST and 654 during recovery after the GSST. Calculations of the RSA was performed by power spectral analyses in the CARSPAN software program using estimation techniques based on Fourier transformations of IBI series (Mulder, Dellen, van Muelen, & van der Opheikens, 1988). RSA was obtained from the power in the high-frequency (0.15–0.40 Hz) band and expressed in  $\text{ms}^2$ .

Thoracic impedance was assessed with a BIOPAC NICO100C Noninvasive Cardiac Output Module. The PEP reflects the time interval (in ms) between the onset of the electromechanical systole (Q-wave onset) in the ECG and the opening of the aortic valves co-occurring with the B-point in the ICG. B-points were manually scored by an extensively trained rater using the VU-AMS interactive software ([www.vu-ams.nl/](http://www.vu-ams.nl/)), which graphically displays the large-scale ensemble averages ICG (Riese et al., 2003) during each minute. When there was doubt about the B-point, the scoring was discussed with a second rater. Outliers were checked and quality of the PEP rates was scored on a 0–10 scale, using the ICG scoring principles provided in the VU-AMS manual (2013). PEP data were considered invalid if the quality of the PEP was low (i.e., score  $< 6$ ) or the signal contained too many artifacts. This resulted in PEP data of 577 participants for the rest measurement after the GSST, 560 during the first 3 min of the GSST and 556 during recovery after the GSST.

**Table 1**  
Means, standard deviations, and correlations between all study variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	N	Mean	SD
1. Sex (1 = boy)	–														–	–	–
2. Antisocial behavior at age 16	<b>.23</b>														613	0.22	0.29
3. Number perinatal adversities	–.06	.04													617	1.01	1.03
4. SA ages 0–15 (Z)	.01	<b>.15</b>	<b>.16</b>												595	0.72	2.63
5. NA ages 0–15 (Z)	–.07	<b>.12</b>	<b>.23</b>	<b>.44</b>											621	0.01	2.70
6. PEP during rest (ms)	–.05	.04	–.05	–.04	.04										622	122.82	19.15
7. PEP during speaking task (ms)	.00	<b>.08</b>	–.10	.02	.07	<b>.54</b>									619	106.97	19.50
8. PEP during recovery (ms)	–.04	.03	–.09	–.02	.06	<b>.64</b>	<b>.88</b>								615	116.08	19.15
9. dPEPtask	.05	.04	–.06	.06	.03	–.47	<b>.49</b>	<b>.26</b>							617	–15.71	18.60
10. dPEPrecovery	.00	–.01	–.05	.04	.02	–.43	<b>.40</b>	<b>.42</b>	<b>.86</b>						613	–6.65	16.26
11. RSA during rest (lnms <sup>2</sup> )	–.02	<b>.08</b>	.02	.08	–.00	–.18	–.12	–.16	.07	.04					612	7.00	1.11
12. RSA during speaking task (lnms <sup>2</sup> )	<b>.18</b>	<b>.17</b>	–.03	<b>.11</b>	.00	–.07	.05	–.01	<b>.13</b>	.07	<b>.60</b>				608	6.97	1.04
13. RSA during recovery (lnms <sup>2</sup> )	–.04	<b>.09</b>	.06	.06	–.03	–.17	–.14	–.19	.03	–.01	<b>.82</b>	<b>.59</b>			597	7.14	1.14
14. dRSAtask	<b>.17</b>	.06	–.06	–.00	–.03	<b>.12</b>	<b>.16</b>	<b>.15</b>	.05	.03	–.52	<b>.31</b>	–.27		602	0.15	0.89
15. dRSArecovery	–.05	–.01	.05	–.03	–.06	.01	–.04	–.05	–.05	–.07	–.27	.01	<b>.34</b>	<b>.40</b>	591	0.14	0.69

Note: Correlations in bold are significant at  $p < .05$ ; SD = standard deviation; Z = Z-transformed scores; RSA = respiratory sinus arrhythmia; PEP = pre-ejection period; NA = number of adversities; SA = stressfulness adversities between age 0 and 15; dPEPtask = pre-ejection period difference score between rest and task; dPEPrecovery = pre-ejection period difference score between rest and recovery; dRSAtask = respiratory sinus arrhythmia difference score between rest and task; dRSArecovery = respiratory sinus arrhythmia difference score between rest and recovery; more details are given in the Section 2.

Two difference scores were calculated for the RSA and PEP measures obtained during the final rest measurement, the GSST and the recovery measurement immediately after the GSST; for the reactivity measures values obtained during the final rest period were subtracted from the first 3 min of the speech task (dRSAtask, dPEPtask) and for the recovery measures values obtained during the final rest period were subtracted from the rest measurement immediately after the speech task (dRSArecovery, dPEPrecovery) (see also Fig. 1). For the speaking task, we used the average RSA and PEP activity during the first 3 min of the task, which is common procedure. For the final rest assessments we averaged RSA and PEP activity of the 5 min recording. To calculate the task – rest reactivity scores (dRSAtask, dPEPtask), we subtracted the averaged resting values from the averaged values measured during the speaking task. For the recovery – rest scores (dRSArecovery, dPEPrecovery), we subtracted the values obtained during the recovery block after the speaking task from the resting values during final resting block. Please note that for the RSA scores we used logtransformed scores to calculate reactivity (e.g.,  $dRSAtask = \ln[\text{high frequency inter beat interval task}] - \ln[\text{high frequency inter beat interval rest}]$ ).

#### 4. Results

First, distributions of the variables were checked for approaching normality. The distributions of antisocial behavior were skewed and therefore logarithmically transformed prior statistical analyses. Antisocial behavior was still slightly skewed after transformation (skewness = 1.88). All analyses were performed in IBM SPSS 19.0 and hypotheses were tested two-sidedly using a  $p$ -value of  $< .05$  to indicate significance. We also reported marginally significant effects ( $p < .10$ ), but interpreted these with caution.

In Table 1 means, standard deviations, and ranges are reported of all study variables as well as the Spearman correlations between these variables. Boys were significantly higher on antisocial behavior, RSA levels during the speaking task, and dRSAtask compared to girls. No further sex differences were found. Participants who experienced more and more stressful adversities between ages 0 and 15 years were more likely to report antisocial behaviors at age 16. Although perinatal adversities were unrelated to antisocial behavior, participants who experienced more perinatal adversities also experienced more and more stressful adversities between ages 0 and 15 years. Moreover, longer PEP during the speaking task and higher RSA levels during rest, speaking task, and recovery were associated with more antisocial behavior. RSA during speak-

ing task was furthermore associated with having experienced more stressful adversities between age 0 and 15. In contrast, perinatal adversities were negatively associated with PEP duration during speaking task and recovery.

##### 4.1. Law of initial values

The correlations between rest and difference scores of RSA and PEP allowed us to test whether the Law of Initial Values (LIV) was applicable to our data. Based on Geenen and Van de Vijver (1993), we assumed the LIV would be applicable when  $-r_{xd} > r_{yd}$ . In other words, the LIV is applicable when the correlation between the rest assessment and the difference between the rest and task assessment is larger than the correlation between the task assessment and the difference between the rest and task assessment. As can be observed from the correlation matrix in Table 1, this only applied to the RSA task reactivity measures (i.e.,  $-(.52) > .31$ ). To test whether the presence of the LIV is significant, we conducted a Student's  $t$ -test which showed that RSA rest and task scores were significantly different ( $t(600) = 2.14$ ,  $p < .05$ ). Hence, we have adjusted our analyses accordingly and included the rest assessment of RSA as a control in the analyses in which we tested the associations between RSA task reactivity and antisocial behavior.

##### 4.2. Mediation by ANS difference scores

To assess the indirect (mediation) effect of perinatal adversities on antisocial behavior via ANS reactivity, we tested three paths: (a) the effect of perinatal adversities on antisocial behavior, (b) the effect of ANS reactivity on antisocial behavior, and (c) the direct effect of perinatal adversities on antisocial behavior (e.g., Preacher, Rucker, & Hayes, 2007). Correlations in Table 1 indicate that perinatal adversities were not associated with antisocial behavior, yet indirect effects may still be present (MacKinnon, Fairchild, & Fritz, 2007). We tested this via moderated mediation analysis using a bootstrap procedure that produces 5000 random samples and hence accounts for the skewness in antisocial behavior at age 16. We tested whether indirect effects were different for boys and girls as either the result of sex differences in the associations between perinatal adversities and ANS reactivity or between ANS reactivity and antisocial behavior, or both. Models were tested separately for dPEPtask, dPEPrecovery, dRSAtask, and dRSArecovery. Bootstrap analyses yielded no significant indirect effects.

4.3. Moderation analyses

To test for moderation effects, regression analyses were performed for each cardiac ANS measure (dPEPtask, dPEPrecovery, dRSAtask, dRSArecovery) separately. The dependent variable was antisocial behavior at age 16. Independent variables were a cardiac ANS measure (dPEPtask, dPEPrecovery, dRSAtask, or dRSArecovery), sex, and an adversity measure (number of adversities or stressfulness of adversity). We started the regression analyses with the full model, which included all main effects and all higher order interactions. Subsequently, non-significant interactions were removed from the model specification, and the regression analysis procedure was performed again. This step-down procedure ended when an exclusive significant interaction or main effect was found (McCullagh & Nelder, 1989).

Significant interactions were plotted using simple slope analysis (Aiken & West, 1991) and we calculated which slopes significantly differed from zero. To reduce problems with multicollinearity and to ensure that the values plotted in the figures are accurate representations of the data, independent variables were standardized to a mean of 0 and a standard deviation of 1 (Frazier, Tix, & Barron, 2004).

4.4. Moderation by PEP difference scores

First, we tested our hypothesis that PEP reactivity and recovery moderates the effect of early life adversities on antisocial behavior. In Table 2 significant two-way interactions are reported between sex and dPEPtask and dPEPrecovery respectively ( $sr^2 = .01$  for both interactions) in the models including the number of adversities (NA; model 1 and model 3), suggesting that blunted dPEPtask and dPEPrecovery scores were associated with more antisocial behavior in boys. Model 2 also showed a marginally significant three-way interaction between sex, stressfulness of adversities, and dPEPtask ( $sr^2 = .01$ ). This effect is depicted in Fig. 2. Simple slope analyses indicated that only in boys with more blunted dPEPtask,

Antisocial behavior at age 16

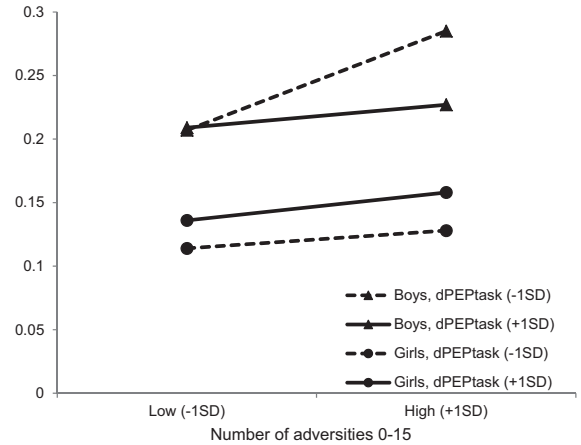


Fig. 2. Simple slopes of number of adversities between ages 0 and 15 on antisocial behavior at age 16 plotted at -1 and +1 standard deviation of dPEPtask (model 2/4 in Table 2) for boys and girls.

higher stressfulness of adversities were associated with antisocial behavior ( $\beta = .17, p < .05$ ). In girls, the association between the stressfulness of adversities and antisocial behavior was unrelated to dPEPtask. These results (model 2) were similar for dPEPrecovery (model 4).

4.5. Moderation by RSA difference scores

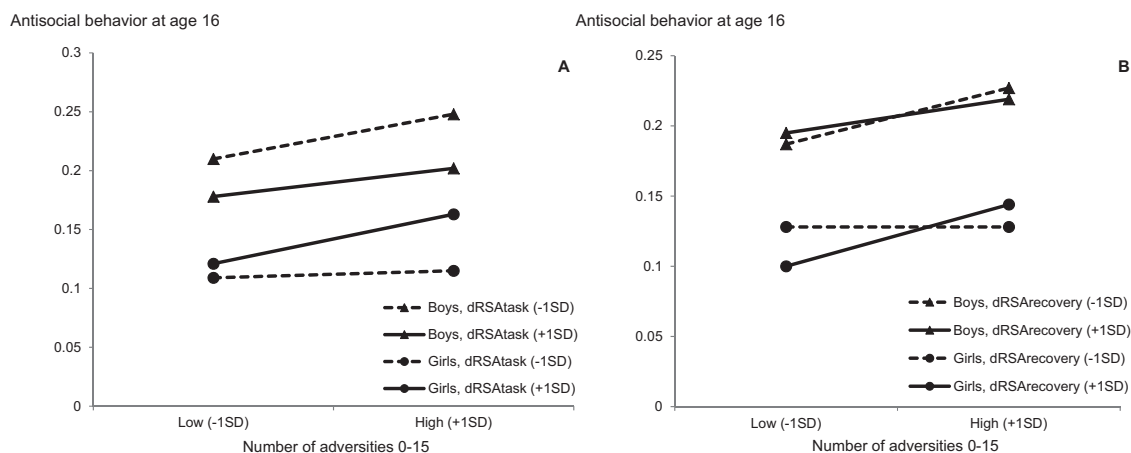
Next, we tested our hypothesis that RSA reactivity moderates the effect of early life adversities on antisocial behavior. There was a marginally significant interaction between sex, dRSAtask, and number of adversities between ages 0 and 15 years ( $sr^2 < .01$ ; model 5). However, simple slope analysis (Fig. 3A) indicated that the separate slopes for boys were significantly different from zero.

Table 2  
Beta-coefficients of the effects of sex, adversities, and pep and rsa difference scores on antisocial behavior.

Model	Pred1	$\beta$	Pred2	$\beta$	Pred3	$\beta$	Pred4	$\beta$	Pred5	$\beta$	Pred6	$\beta$
dPEPtask												
1 ( $R^2 = 10.5\%$ )	Sex	0.27 ***	NA	0.17 ***	Sex <sup>†</sup> dPEP	-0.11 †						
2 ( $R^2 = 11.9\%$ )	Sex	0.27 ***	SA	0.13 *	Sex <sup>†</sup> dPEP	-0.12 *			Sex <sup>†</sup> SA <sup>†</sup> dPEP	-0.10 †		
dPEPrecovery												
3 ( $R^2 = 10.7\%$ )	Sex	0.27 ***	NA	0.17 ***	Sex <sup>†</sup> dPEP	-0.17 **						
4 ( $R^2 = 12.5\%$ )	Sex	0.27 ***	SA	0.13 *	Sex <sup>†</sup> dPEP	-0.16 **			Sex <sup>†</sup> SA <sup>†</sup> dPEP	-0.10 †		
dRSAtask												
5 ( $R^2 = 10.4\%$ )	Sex	0.21 ***	NA	0.19 ***	RSAr	0.13 *	Sex <sup>†</sup> dRSA	-0.10 *	dRSA <sup>†</sup> NA	0.12 *	Sex <sup>†</sup> dRSA <sup>†</sup> NA	-0.08 †
6 ( $R^2 = 9.1\%$ )	Sex	0.20 ***	SA	0.15 †	RSAr	0.11 *	Sex <sup>†</sup> dRSA	-0.12 *				
dRSArecovery												
7 ( $R^2 = 9.3\%$ )	Sex	0.22 ***	NA	0.16 **	dRSA <sup>†</sup> NA	0.15 **	Sex <sup>†</sup> dRSA <sup>†</sup> NA	-0.12 *				
8 ( $R^2 = 7.7\%$ )	Sex	0.22 ***	SA	0.12 **								

Pred = predictor; NA = number of adversities between age 0 and 15; SA = stressfulness adversities between age 0 and 15; dPEPtask = pre-ejection period difference score between rest and task; dPEPrecovery = pre-ejection period difference score between rest and recovery; RSAr = respiratory sinus arrhythmia rest score; dRSAtask = respiratory sinus arrhythmia difference score between rest and task; dRSArecovery = respiratory sinus arrhythmia difference score between rest and recovery; more details are given in Section 2; see Supplementary online appendices for the full tables, including B(SE), 95% confidence intervals, and squared semipartial correlations for all parameters.

†  $p < 0.10$ .  
\*  $p < .05$ .  
\*\*  $p < .01$ .  
\*\*\*  $p < .001$ .



**Fig. 3.** A and B: Simple slopes of number of adversities between ages 0 and 15 on antisocial behavior at age 16 plotted at  $-1$  and  $+1$  standard deviation of dRSAtask (A, model 5 in Table 2) and dRSArecovery (B, model 7 in Table 2) for boys and girls.

That is, boys with more blunted dRSAtask and a higher number of adversities were more likely to report antisocial behavior than boys with heightened dRSAtask ( $\beta = .27, p < .01$  and  $\beta = .18, p < .05$ , respectively). In girls, the association between number of adversities between ages 0 and 15 years was stronger for those with heightened dRSAtask (1SD above average;  $\beta = .29, p < .001$ ) compared to those with blunted dRSAtask (1SD below average;  $\beta = .07, n.s.$ ). These marginally significant three-way interactions were in line with the significant two-way interactions in model 5. There were no significant interactions between dRSAtask and stressfulness of adversities (see model 6).

In Model 7 a significant three-way interaction was found with regard to dRSArecovery ( $sr^2 = .01$ ; see Fig. 3B), which can be interpreted in a similar way. The number of adversities was more strongly associated with antisocial behavior in girls with heightened dRSArecovery ( $\beta = .31, p < .01$ ) compared to girls with blunted dRSArecovery. In boys, experiencing more adversities between age 0 and 15 was associated with reporting more antisocial behavior, irrespective of dRSArecovery ( $\beta = .28, p < .01$  for low dRSArecovery and  $\beta = .16, p = .10$  for high [1SD above average] dRSArecovery). There were no significant interactions between dRSArecovery and stressfulness of adversities (see model 8).

## 5. Discussion

In the current study, two distinct hypotheses were tested regarding the associations between perinatal adversities and adversities between ages 0 and 15 years with antisocial behavior at age 16. First, our findings suggest that perinatal adversities do not put youth at a greater risk for antisocial behavior. This finding goes against our hypothesis and findings from previous studies (Beck & Shaw, 2005; Tremblay, 2010; Wakschlag et al., 1997).

Second, when examining associations between adversities during childhood and adolescence, we showed that blunted PEP recovery difference scores were associated with more antisocial behavior in boys. Partly in line with our hypothesis, reported stressfulness of adversities between ages 0 and 15 years modified this association, albeit marginally. We found only one study that specifically examined the main association between PEP reactivity and antisocial behavior and these findings are in line with ours, reporting reduced PEP reactivity in aggressive boys (Beauchaine et al., 2008). Relatedly, Brenner and Beauchaine (2011) showed in a sample at risk for conduct problems ( $n = 206$ , ages 8–12 years, 65% boys) that blunted PEP reactivity to reward was associated with more alcohol use at a 1–2 year follow-up. Our findings correspond with these studies and with theories suggesting that blunted SNS

reactivity in boys may be associated with a lack of fear and an increased need for sensation which can ultimately result in antisocial behavior (Raine, 2002; Ortiz & Raine, 2004). Our findings suggest that experiencing highly stressful adversities may exacerbate these associations in boys.

Third, our findings supported the hypothesis that RSA reactivity moderated the association between adversities and antisocial behavior with different associations for boys and girls. In boys, having experienced more adversities was associated with more antisocial behavior. This effect was strongest in those who showed blunted PNS reactivity. In contrast, we found that in girls more adversities were only associated with antisocial behavior in those who showed heightened RSA reactivity. With regard to recovery from the speaking task, we found similar effects. That is, more adversities were associated with antisocial behavior in girls with more heightened PNS recovery and in boys with blunted PNS recovery.

Together, our findings suggest (1) different effects of timing of adversities in relation to antisocial behavior, and (2) that adolescents who have experienced early life adversities and either have blunted (i.e., in boys) or heightened (i.e., in girls) ANS reactivity to stress are at increased risk for future antisocial behavior. The distinction between the number of adversities and stressfulness of adversities seems to be less clear as both indices of adversities interacted with ANS reactivity, albeit with different branches of the ANS. The different effects for girls and boys may be accounted for by the Adaptive Calibration Model, which suggests that ANS responses to stress are shaped by environmental stress and in turn interact with concurrent stressors (Del Giudice et al., 2011). Based on this model, differences between boys and girls would be larger at moderate to high levels of environmental stress because strategies for sex competition become more diverse (i.e., boys may engage more in risk taking and high-mating strategies, whereas girls may display more low-mating strategies). Strategies for boys involve more unemotional responsivity patterns, as this is helpful for engaging in risky activity, whereas strategies for girls are likely to involve more vigilant responsivity patterns to cope effectively with threats in the environment. A recent study indeed showed that girls experiencing high levels of environmental stress were more likely to be in the vigilant (i.e., heightened stress responses) class (Del Giudice et al., 2012). Boys who experienced high levels of environmental stress were often in the unemotional (i.e., blunted stress response) class. Consolidated with our findings, this suggests that girls' and boys' behavior are driven by different ANS reactivity profiles in response to stressful environments.

Moreover, we showed that the interaction between experiencing early life adversities and ANS recovery follows a similar pattern as ANS reactivity to the speaking task. In fact, effects for RSA recovery from stress were more pronounced in our study compared to the marginally significant RSA task reactivity effects. These findings suggest that adolescents at risk for antisocial behavior not only show heightened responses during a stressful task, but are also more likely to remain physiologically aroused after the stressor has passed.

In examining the stressfulness of adversities, we found no support for the hypothesis that RSA reactivity and recovery moderate the association between adversities and antisocial behavior. There are several explanations for not finding this moderation effect. For one, it is possible that ANS functioning is in part continuously shaped by adversities during the life course. Research on allostatic load has indeed indicated the wear and tear of the ANS due to exposure to stress, also during late childhood and adolescence (El-Sheikh, & Hinnant, 2011; McEwen, 2007). Therefore, it may be that continuously experiencing (severe) stress also continuously shapes individuals' physiological responses to stress. Alternatively, our findings suggest that when adolescents experience many adversities or highly stressful adversities, they are at risk for antisocial behavior, irrespective of their physiological responses to stress. Although physiological responses to stress may be indicative of emotional and behavioral regulation (Brenner, Beauchaine, Sylvers, & PD, 2005), it seems that in light of highly stressful adversities even adolescents with 'healthy' physiological stress reactivity are not impervious to the negative effects of these adversities in terms of antisocial behavior.

### 5.1. Limitations

Our findings should be interpreted in light of several limitations. Our sample consisted of participants who were slightly more at risk in comparison to the general population, but the variation was still within a normal range. However, this oversampling may have provided us with a more representative general population sample, as individuals with more antisocial behavior were more likely to drop-out from the TRAILS study (Huisman et al., 2008; Nederhof et al., 2012). Moreover, childhood adversities were assessed retrospectively. Memories can be less accurate due to forgetting or re-shaping events, especially those related to traumatic and stressful events (Deffenbacher, Bornstein, Penrod, & McGorty, 2004; Herlihy, Jobson, & Turner, 2012). Our study may have suffered from recall biases given the long period of time that could have passed between the actual adverse event and administering the questionnaire at age 11. However, most adversities were rather objective (e.g., death of a parent, long-term illness) and this recall bias may have been less of a problem. Relatedly, childhood adversities were treated as a total measure of adversity across childhood and early to middle adolescence. This limits the study of adversities at specific ages (i.e., ages 0–5, 6–11, 12–13, and 14–15) and future research may thus want to conduct more fine-grained analyses as the timing of adversities can matter in predicting stress responses (e.g., Bosch et al., 2012).

In addition, in the current study we were not able to study the simultaneous development of ANS reactivity and antisocial behavior, because ANS reactivity was not assessed at the earlier measurement waves. For future research it may be informative to predict changes over time in antisocial behavior as a function of changes in ANS reactivity and vice versa, to assess both the stability and (bi) directionality of these associations.

The findings related to the PEP and RSA measures during the speaking task should be treated with caution as well. Speaking is likely to have increased respiration and may have distorted both ANS measures (Sherwood et al., 1990). However, all reactivity

analyses were repeated with the recovery measures during which participants were not allowed to speak which produced similar findings and support the same conclusions. For future research, it may still be helpful to account for respiratory influences. Unfortunately, these deviations are difficult to assess, as words may for example differ in length, expression, and the intensity with which they are spoken. Moreover, there is the possibility that order effects during the experiment have introduced systematic error. To eliminate this error, it would be helpful for future research to counterbalance task order during the stress experiment. Finally, we relied solely on self-reported antisocial behavior. Although adolescents were informed that all information would be treated confidentially and anonymously, they may still have under- or over-reported antisocial behaviors as a result of fear for repercussions by parents, teachers, or law enforcement, or because of boasting. Despite this limitation, self-reported measures on antisocial behavior were associated with our physiological measures (i.e., RSA and PEP reactivity during the public speaking task) and parent-reported data on adversities, and hence speak to the validity of these reports.

In conclusion, we showed that the number and stressfulness of adversities between ages 0 and 15 years are associated with antisocial behavior at age 16. The association between the number of adversities during childhood and early adolescence with antisocial behavior was strongest in boys with blunted PNS and SNS reactivity and recovery and girls with heightened PNS reactivity and recovery. Although these effects were small, these differences point to the importance of taking into account ANS reactivity in studying the association between early life adversities and antisocial behaviors.

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### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.biopsycho.2015.06.012>



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