Psychosocial adversity and adolescents' mental health problems
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Sensitivity to psychosocial chronic stressors and adolescents’ externalizing problems: Combined moderator effects of resting heart rate and parental psychiatric history


Under revision
Abstract

From the literature it is not clear whether low resting heart rate (HR) reflects low or high sensitivity to the detrimental effects of adverse environments on externalizing problems. We studied parental psychiatric history (PH), reflecting general vulnerability, as possible moderator explaining these inconsistencies. Using Linear Mixed Models, we analyzed data from 1914 subjects, obtained in three measurement waves (mean age 11, 13.5, and 16 years) from the TRacking Adolescents’ Individual Lives Survey population-based cohort and the parallel clinic-referred cohort. As hypothesized, more chronic stressors predicted more externalizing problems in vulnerable individuals with high resting HR but not in those with low resting HR, suggesting high vs. low sensitivity, respectively, to adverse environmental influences. In adolescents with low vulnerability, in contrast, the association between chronic stressors and externalizing problems did not substantially differ by resting HR level. Future research may demonstrate whether our findings extend to other adverse, or beneficial, influences.

Keywords: Chronic stressors; Psychosocial adversity; Sensitivity to the environment; Externalizing problems; General vulnerability; Parental psychiatric history; Resting heart rate; Adolescence.
Introduction

Adolescents’ exposure to psychosocial stressors is a well-established risk factor of psychopathology, including disruptive (externalizing) behavior such as aggression and rule-breaking (for an overview, see Grant, Compas, Thurm, McMahon, & Gipson, 2004). However, the strength of this relationship differs greatly across individuals (Jenkins, 2008; Rutter, 2005), suggesting that some individuals are more sensitive to the environment than others. Determining which factors over time influence (i.e., moderate) the association between chronic stressors and externalizing problems may ultimately aid in timely identification of those most in need of intervention. This study investigated two potential moderators simultaneously: resting heart rate (HR), reflecting autonomic arousal; and parental psychiatric history (PH), reflecting general vulnerability. We hypothesized that the moderator effect of resting HR would be more pronounced in more vulnerable individuals.

Biological Sensitivity to Context theory and the Differential Susceptibility hypothesis (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Boyce & Ellis, 2005; Ellis & Boyce, 2008; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011) have proposed individual differences in sensitivity to the environment, for better and for worse. Specifically, whereas sensitive individuals are positively affected by beneficial environmental influences (e.g., parental emotional warmth) and negatively by adverse influences (e.g., parental hostility), less sensitive individuals are less affected by both. Individual characteristics that have been implicated in sensitivity to beneficial and/or adverse environmental influences are thus of interest as potential moderators of the association between chronic stressors and externalizing problems.

Recent findings suggest that resting HR captures individual differences in sensitivity to beneficial environmental influences on disruptive behavior in youth. There appears to be a positive association between autonomic arousal level, including resting HR, and efficacy of cognitive behavioral therapy (CBT) in reducing antisocial behavior in youth (Cornet, De Kogel, Nijman, Raine, & Van der Laan, 2014). For example, in a sample of 7-12-year olds who had been referred for disruptive behavior and treated with cognitive behavioral therapy, those who showed significant improvement (i.e., decrease in disruptive symptoms) were characterized by relatively high resting HR, whereas those who did not improve were characterized by low resting HR (Stadler et al., 2008). In addition, and with regard to adverse influences, our research group has recently demonstrated that higher chronic stressor levels predicted greater severity of (externalizing and internalizing) mental health problems in preadolescents with high resting HR, but not in those with low resting HR (Oldehinkel, Verhulst, & Ormel, 2008). Together, these findings suggest that resting HR may be reflective of sensitivity to environmental influences, both
beneficial (such as cognitive behavioral therapy) and adverse (such as chronic stressors), in line with the Differential Susceptibility hypothesis. That is, youth with high resting HR may experience greater positive effects as a result of beneficial environmental influences and greater negative effects as a result of adverse influences. Conversely, preadolescents with low resting HR may not only be less sensitive to the positive effects of beneficial environments but also to the detrimental effects of adverse environments.

However, in contrast to the latter, there have also been findings that the combination of low resting HR and environmental risk factors such as violence exposure, poor parent-child relationship, or low socio-economic status, resulted in increased risk of externalizing problems (Raine, 2002; Scarpa, Tanaka, & Haden, 2008). This is consistent with the well-established negative association between resting HR and externalizing problems, that is, low resting HR increases risk (Lorber, 2004; Ortiz & Raine, 2004; Portnoy & Farrington, 2015) whereas high resting HR is protective against externalizing problems (Portnoy, Chen, & Raine, 2013; Raine, 2002).

These opposite effects of low resting HR suggest the influence of an additional moderator. A likely candidate is parental psychiatric history as index of individual differences in general vulnerability, given that genetic risk factors, including those linking low resting HR to externalizing problems (Baker et al., 2009), are more likely present in more vulnerable individuals. In the present paper, we examine the hypothesis that the effect of resting HR on the stressors-externalizing association is conditional upon individual differences in general vulnerability. We hypothesize that the moderator effect of resting HR, in terms of sensitivity to chronic stressors, manifests especially in more vulnerable individuals. We expect that, especially in this group, higher levels of chronic stressors are associated with higher subsequent externalizing problem levels in individuals with high resting HR, but that chronic stressors are not associated with externalizing problems in individuals with low resting HR.

**Methods and Materials**

**Sample**

We derived the data used in this study from the two cohort studies of the longitudinal “TRacking Adolescents’ Individual Lives Survey.” TRAILS aims to contribute to the understanding of the determinants of mental health problems by following 10-12 year-old Dutch children into adulthood. TRAILS was approved by the National Dutch Medical Ethics Committee, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.
To obtain a large sample with wide ranges of parental psychiatric history severity, problem severity and chronic stress, we pooled data from the population-based birth cohort \( n = 2230 \) and a parallel clinic-referred cohort \( n = 543 \). We included three measurement waves: T1, T2, and T3, with mean ages about 11, 13.5, and 16 years, respectively. The sampling procedures, descriptive statistics and response rates of both cohorts are well-documented (e.g., De Winter et al., 2005; Huisman et al., 2008; Ormel et al., 2012). In brief, TRAILS approached 135 primary schools in five municipalities in the Northern Netherlands to build the population cohort. 90.4% of the schools agreed to participate. TRAILS contacted eligible students and their parents, enrolling 76% \( n = 2230 \) of those contacted in the study. The three data waves we included in this study were collected from March 2001 to July 2002 (T1), September 2003 to December 2004 (T2), and September 2005 to August 2007 (T3), with response rates consistently above 80%.

The smaller, clinic-referred sample \( n = 543 \) consisted of preadolescents who had been referred to the Groningen University Child and Adolescent Psychiatric Outpatient Clinic at any point in their life (20.8% ≤5 years, 66.1% 6-9 years, 13.1% 10-12 years) for consultation or treatment. The first three data waves in the clinic-referred cohort ran two years behind those of the population cohort: from September 2004 to December 2005 (T1), September 2006 to November 2007 (T2), and September 2009 to February 2011 (T3). The measurement instruments and design for the clinic-referred cohort were the same as those of the population cohort. Of the 1264 eligible preadolescents, 543 (65.9% boys, mean age 11.11, SD 0.50, range 10.13-12.40) enrolled in the study and finished baseline measurements (T1). Of these 543 baseline participants, 85.1% \( n = 462 \) participated in the second wave (T2). Of the T2 participants, 71.1% \( n = 386 \) also participated in the third wave (T3). Another 30 T2 dropouts agreed to participate in the third wave, resulting in a total T3 response rate of 76.6% \( n = 416 \) of the original sample.

**Measures**

**Externalizing Problems**

TRAILS administered the Achenbach System of Empirically Based Assessment (ASEBA) family at each measurement wave to assess mental health problems over time (Achenbach & Rescorla, 2001; Verhulst & Van der Ende, 2013). The Child Behavior Checklist is a parent-report questionnaire that contains 120 items assessing behavioral and emotional problems in children over the past 6 months. These items can be rated as 0 = not true, 1 = somewhat or sometimes true, or 2 = very or often true. We used DSM-oriented subscales to define externalizing problems as the sum of the average scores of oppositional defiant problems \( k = 5 \), Cronbach’s \( \alpha = .81 \) and conduct problems \( k = 17 \), \( \alpha = .81 \). We chose to use average scale scores and sum these in order to balance the influence of subscales with
different numbers of items. We followed the same procedure for the Youth Self-Report, with externalizing problems defined as the summed weighted average of oppositional defiant \( (k = 5, \alpha = .65) \) and conduct problems \( (k = 15, \alpha = .74) \).

Based on the significant correlations between externalizing and internalizing problems at both T2 \( (r = .51 \) parent-report, and \( r = .39 \) self-report) and T3 \( (r = .53 \) parent-report, and \( r = .33 \) self-report), our main focus is on externalizing problems adjusted for co-occurring internalizing problems \( (\text{EXTadj}) \). To that end, we computed the summed weighted average of anxiety \( (k = 6, \alpha = .72 \) and .62 for parent-report and self-report, respectively) and affective problems \( (k = 13, \alpha = .72 \) and .71 for parent-report and self-report, respectively), after which we computed residual externalizing scores \( (M = 0, SD = 1) \). Although these standardized residuals are informative in terms of pure externalizing behavior, adjusting for the variance shared with internalizing problems inevitably includes, to some extent, adjustments for individual differences in problem severity as well. Therefore, externalizing problems unadjusted for co-occurring internalizing problems \( (\text{EXT}) \) are also addressed.

**Chronic stressors preceding T2 and T3**

We operationalized chronic stressors as the number of long-term difficulties since the previous measurement. One of the parents, typically the mother, filled out a TRAILS questionnaire (e.g., Oldehinkel et al., 2008; Zandstra et al., 2015) that listed long-term difficulties to which the adolescent might have been exposed since the previous interview. The stressors included: (1) chronic illnesses or physical handicaps of the child (2) or a family member; (3) high work pressure at school; (4) housing problems; (5) neighborhood problems, such as violence or discrimination; (6) financial problems; (7) lack of friends; (8) being bullied; (9) long-lasting conflicts with family members (10) or others; and (11) long-lasting conflicts between family members. On an open item, parents could disclose additional long-term difficulties. We coded these additional problems either as a long-term difficulty or dismissed them according to well-defined rules; in particular whether the described situation is typically considered stressful and enduring. For example, we coded a turbulent home environment, such as moving frequently from house to house or parents having an on/off relationship, as long-term difficulty. Situations that we rejected as long-term difficulty included normative or non-enduring situations such as the transition to middle school, puberty, and quarrels with siblings. The number of reported difficulties ranged from 0 to 10. To reduce the possible influence of extreme and rare scores, we grouped subjects into 4 categories; 0, 1, 2, or 3 or more long-term difficulties.
Resting heart rate (HR)

Preadolescents participated in HR measurements at T1; either at school for the population cohort; or at the University Child and Adolescent Outpatient Clinic in Groningen, the Netherlands for the clinic-referred cohort. Both cohorts used the same measurement protocol to assess resting supine HR at T1. Individual measurements took place in the morning (generally between 8.30 AM and noon in the population cohort and between 10.20 and 11.00 AM in the clinic-referred cohort), either in a quiet room either at school (population cohort, Dietrich et al., 2006) or at the Groningen University Child and Adolescent Outpatient Clinic (clinic-referred cohort, Dietrich et al., 2012). Subjects assumed the supine position and were equipped with a three-lead electrocardiogram. They were asked to relax and neither move nor talk during the assessment. When signals had reached a stabilized steady-state, generally within 5 minutes, continuous HR was recorded for 4 minutes during spontaneous breathing using a sample frequency of 100Hz (Dietrich et al., 2009). Specialized software was used for R-peak detection (CARSPAN, Mulder, Van Dellen, Van der Meulen, & Opheikens, 1988) with missing R-peaks inserted by visual screening. Poor quality interbeat intervals of up to 5 seconds were interpolated using this software. Measurements that contained too many artifacts, such as signal gaps of more than five seconds or with a total signal length less than 100 seconds were discarded (Dietrich et al., 2006). HR, expressed in beats per minute was calculated as $60,000 = 60 \text{ seconds} = 60,000 \text{ milliseconds}$ divided by the mean inter-beat interval in milliseconds. More detailed information on cardiovascular measurement procedures in both cohorts is given elsewhere (Dietrich et al., 2006; Dietrich et al., 2009; Dietrich et al., 2012). These procedures have shown satisfactory short-term test-retest reliability of the supine resting HR measurements (Dietrich et al., 2010).

Parental psychiatric history (PH)

The TRAILS Family History Interview (Ormel et al., 2005) was administered at two time points to assess PH. Prevalence rates using this instrument were comparable to reported rates from the Dutch NEMESIS study, which were obtained using the Composite International Diagnostic Interview (Bijl, Ravelli, & Van Zessen, 1998; Ormel et al., 2005).

At T1, trained assistants conducted the interview. The second time (at T2 for the clinic-referred cohort, at T3 for the population cohort), parents completed the questions themselves. After reading vignettes describing DSM-IV key symptoms for depression, anxiety, substance dependence, and persistent antisocial behavior, one parent was asked to indicate whether the behavior described in each vignette had ever applied to her/him and the other biological parent. We identified parents who had indicated a definite episode (in contrast to a possible episode), reported in at least one of the two assess-
ments, who in addition indicated having received treatment or medication during that episode, or, in case of antisocial behavior, had been in contact with the police.

We counted the number of diagnosis dimensions in each parent (0 = no PH; 1 = either internalizing or externalizing PH; 2 = both internalizing and externalizing PH). Then, we indexed PH severity for each adolescent by summing the scores of the two parents, resulting in the following possibilities: 0) no PH in either parent; 1) one parent with single-domain PH; 2) one parent with PH in both domains or two parents with single-domain PH; 3) one parent with single-domain PH plus other parent with PH in both domains, or two parents with PH in both domains. We labeled the groups as 0 = no PH; 1 = mild PH; 2 = severe PH; and 3 = very severe PH.

We focused on severity rather than on presence versus absence or on the domain (internalizing vs. externalizing) of PH, for the following reasons. PH is a strong predictor of increased genetic and environmentally-driven vulnerability for psychopathology in offspring (Burke, Loeber, & Birmaher, 2002; Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005). This vulnerability is not limited to problem domain, given that internalizing and externalizing PH are each associated with both problem types in offspring (e.g., Kim-Cohen et al., 2005; Marmorstein, Malone, & Iacono, 2004). If indeed familial transmission (partially) results in a non-specific vulnerability for psychopathology, the severity (i.e., complexity) of PH may be an important indicator of the degree of vulnerability. In line with this, prior research findings demonstrate increased risk of psychopathology in offspring when a parent is affected by both internalizing and externalizing psychopathology compared to only one type (Kim-Cohen et al., 2005), whereas offspring of two affected parents may be at even higher risk (Dierker, Merikangas, & Szatmari, 1999; Marmorstein et al., 2004).

Data analysis

Data preparation and preliminary analyses

For this study, our statistical analysis method required at least one value for each predictor on T1-T3 and at least T2 or T3 externalizing problems. Thus, we needed T2 and/or T3 parent-reported and/or self-reported externalizing problems, T2 and/or T3 chronic stressors, T1 resting HR, and complete psychiatric history of both parents, reported in at least one of the two assessments. We performed independent samples t-tests to check whether included and excluded subjects differed with respect to our study variables.

Main analyses

We computed Pearson’s correlation coefficients between the predictors and T2 and T3 EXT and EXTadj problems. We used Linear Mixed Modeling (LMM) to investigate the
effects of resting HR, chronic stressors, and PH severity; and their hypothesized interactions in predicting subsequent EXTadj problems. LMM allows for missing data at different measurement waves, which is an important advantage for a longitudinal design (Kwok et al., 2008). Using PASW Statistics for Windows 18.0 (SPSS Inc., Chicago IL), we conducted multivariate LMM analyses (T2 and T3 in a single analysis). Analyses were performed separately for parent-report and self-report. We included the independent variables of age (time-variant covariate), sex (0_female, 1_male), initial EXTadj level at T1, chronic stressors (time-variant), resting HR, PH severity, as well as all possible interactions between chronic stressors, resting HR, and PH severity. Since resting HR may exert its effect on externalizing problem levels particularly at extremes in its distribution, rather than linearly, we allowed for a curvilinear (quadratic) effect of resting HR. All non-dichotomous variables were mean-centered before analysis. We used the Maximum Likelihood estimation procedure and considered a p-value <.05 to be statistically significant.

For interpretation of interaction effects, we plotted the outcome variable based on the estimated regression coefficients, for different levels of each predictor. For significant three-way interaction effects of resting HR, chronic stressors, and PH severity; we tested whether resting HR and chronic stressors significantly interacted within the very severe PH group, within the no PH group, or both. Estimates, standard errors, and p-values were computed using SAS 9.3. To investigate the influence of pre-existing externalizing problems on our findings, we repeated the analysis of EXTadj without controlling for initial EXTadj at T1. To check the influence of adjusting externalizing problems for co-occurring internalizing problems, we repeated the analysis replacing the outcome variable EXTadj with EXT; that is, externalizing problems unadjusted for co-occurring internalizing problems.

Results

Results of preliminary analyses

HR was not measured for 398 subjects (n = 380 population cohort, n = 18 clinic-referred cohort), primarily because autonomic measurements in the population cohort started a few months after the TRAILS data collection had already begun. Other causes for missing HR data included moving to another area or lack of time. One hundred and eighteen subjects had invalid HR data, consisting of 88 participants in the population cohort and 24 in the clinic-referred cohort. Criteria for invalidation were lost or unusable data due to measurement errors, such as flat signals, and rejection of data based on quality restric-
tions (e.g., too many artefacts, signal length < 100s, Dietrich et al., 2006). Three hundred and nine participants had missing data for both measurements of chronic stress, 218 for PH, and 137 for parent-reported as well as self-reported externalizing problems. Altogether, we excluded a total of 859 participants (n = 727 population cohort, n = 132 clinic-referred cohort) from this study, resulting in a final sample size of 1914 subjects (n = 1503 population cohort, n = 411 clinic-referred cohort).

We compared the final study sample (mean age 11.05; SD 0.50; range 10.01-12.58; 52.5 % boys; 78.5 % population cohort) with those who were not included. We found that included participants were younger (t (1393.225) = -8.530, p < .001), had higher resting HR (t = (2261) = 2.007, p = .045), and had somewhat fewer parent-reported externalizing problems (t (2585) = -1.900, p = .058). There were no significant differences between the groups with respect to sex (p = .94), T2 chronic stressors level (p = .84), self-reported externalizing problems (p = .31), or PH severity (p = .98).

**Results of main analyses**

Table 1 shows descriptive statistics of the final sample and Table 2 shows correlations. As shown in Table 3, a three-way interaction effect of PH severity, HR-square, and chronic stressors was statistically significant in predicting parent-reported EXTadj (p = .035).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wave</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>1912</td>
<td>11.05 (0.50)</td>
<td>10.01-12.58</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>1886</td>
<td>13.37 (0.60)</td>
<td>11.58-15.03</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>1671</td>
<td>16.14 (0.67)</td>
<td>14.42-18.48</td>
<td></td>
</tr>
<tr>
<td>Stressors*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>1846</td>
<td>1.23 (1.50)</td>
<td>0-10</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>1513</td>
<td>1.30 (1.54)</td>
<td>0-10</td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>1914</td>
<td>76.40 (11.05)</td>
<td>47.57-115.92</td>
<td></td>
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<tr>
<td>CBCL EXT*</td>
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<td></td>
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<tr>
<td>T1</td>
<td>1838</td>
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<td>0-31</td>
<td></td>
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<tr>
<td>T2</td>
<td>1844</td>
<td>4.50 (4.70)</td>
<td>0-31</td>
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<tr>
<td>T3</td>
<td>1508</td>
<td>4.43 (4.94)</td>
<td>0-28</td>
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<tr>
<td>YSR EXT*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>T1</td>
<td>1895</td>
<td>5.88 (4.36)</td>
<td>0-28</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>1834</td>
<td>5.79 (4.12)</td>
<td>0-29</td>
<td></td>
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<tr>
<td>T3</td>
<td>1563</td>
<td>6.09 (4.48)</td>
<td>0-26</td>
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<td>PH severity</td>
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<tr>
<td>0</td>
<td>T1/T3</td>
<td>1055</td>
<td></td>
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<td>1</td>
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<tr>
<td>3</td>
<td></td>
<td>46</td>
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<td></td>
</tr>
</tbody>
</table>

CBCL = Child Behavior Checklist; YSR = Youth Self Report; EXT = Externalizing problems; PH = Parental psychiatric history

*Number of long-term difficulties experienced since previous measurement of scores on 22 items for parent-report (CBCL) and 20 items for self-report (YSR), largest possible scale score 44 and 40, respectively.
Table 2  Correlation matrix of predictors and outcome variables, with parent-reported externalizing problems below and self-reported externalizing problems above diagonal

<table>
<thead>
<tr>
<th>Variables</th>
<th>T2 Stressors</th>
<th>T3 Stressors</th>
<th>T1 HR</th>
<th>PH</th>
<th>T2 EXT</th>
<th>T2 EXTadj</th>
<th>T3 EXT</th>
<th>T3 EXTadj</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2Stressors</td>
<td>1</td>
<td>.56***</td>
<td>-.01</td>
<td>.20***</td>
<td>.17***</td>
<td>.08***</td>
<td>.11***</td>
<td>.04</td>
</tr>
<tr>
<td>T3Stressors</td>
<td>.56***</td>
<td>1</td>
<td>-.02</td>
<td>.24***</td>
<td>.15***</td>
<td>.06*</td>
<td>.15***</td>
<td>.08**</td>
</tr>
<tr>
<td>T1HR</td>
<td>-.01</td>
<td>-.02</td>
<td>1</td>
<td>.02</td>
<td>-.04</td>
<td>-.04</td>
<td>-.04</td>
<td>-.06*</td>
</tr>
<tr>
<td>PH</td>
<td>.20***</td>
<td>.24***</td>
<td>.02</td>
<td>1</td>
<td>.06**</td>
<td>.03</td>
<td>.04</td>
<td>.02</td>
</tr>
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</table>

Parent-report

<table>
<thead>
<tr>
<th>Variable</th>
<th>T2EXT</th>
<th>T2EXTadj</th>
<th>T3EXT</th>
<th>T3EXTadj</th>
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</thead>
<tbody>
<tr>
<td>T2EXT</td>
<td>.39***</td>
<td>.30***</td>
<td>-.09***</td>
<td>.19***</td>
</tr>
<tr>
<td>T2EXTadj</td>
<td>.15***</td>
<td>.12***</td>
<td>-.09***</td>
<td>.09***</td>
</tr>
<tr>
<td>T3EXT</td>
<td>.31***</td>
<td>.37***</td>
<td>-.05*</td>
<td>.15***</td>
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<tr>
<td>T3EXTadj</td>
<td>.11***</td>
<td>.13***</td>
<td>-.05</td>
<td>.04</td>
</tr>
</tbody>
</table>

HR = Resting heart rate; PH = Parental history severity; EXT = Externalizing problems; EXTadj = Externalizing problems adjusted for internalizing problems.

***p < .001, **p < .01, *p < .05

Table 3  Parental psychiatric history severity, resting heart rate, and chronic stressors significantly predicted parent-reported but not self-reported externalizing problems

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parent-reported EXTadj</th>
<th>Self-reported EXTadj</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Estimate*</td>
<td>SE*</td>
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<tr>
<td>Intercept</td>
<td>7.99</td>
<td>24.27</td>
</tr>
<tr>
<td>Age</td>
<td>6.68</td>
<td>7.73</td>
</tr>
<tr>
<td>Sex*</td>
<td>18.79</td>
<td>33.60</td>
</tr>
<tr>
<td>T1 EXTadj</td>
<td>594.85</td>
<td>16.93</td>
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<tr>
<td>Stress</td>
<td>53.15</td>
<td>13.24</td>
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<tr>
<td>HR</td>
<td>-2.40</td>
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<tr>
<td>HR-square</td>
<td>0.07</td>
<td>0.10</td>
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<tr>
<td>PH</td>
<td>20.25</td>
<td>22.14</td>
</tr>
<tr>
<td>HR*Stressors</td>
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<td>1.18</td>
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</tr>
<tr>
<td>PH*HR</td>
<td>-2.64</td>
<td>1.90</td>
</tr>
<tr>
<td>PH*HR-square</td>
<td>-0.08</td>
<td>0.12</td>
</tr>
<tr>
<td>PH*Stressors</td>
<td>-3.85</td>
<td>16.64</td>
</tr>
<tr>
<td>PH<em>HR</em>Stressors</td>
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<td>1.38</td>
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<tr>
<td>PH<em>HR-square</em>Stressors</td>
<td>-0.18</td>
<td>0.09</td>
</tr>
</tbody>
</table>

EXTadj = Externalizing problems adjusted for internalizing problems; HR = Heart rate; PH = Parental psychiatric history severity

*Values multiplied by 1000 for increased readability

Participants varied significantly (p < .01) in intercept for parent-reported EXTadj, var(\(u_{0j}\)) = 260.63*, chi-square(1) = 252.08, and self-reported EXTadj, var(\(u_{0j}\)) = 312.09*, chi-square(1) = 199.36

Sex was coded as 0 = female, 1 = male.
We plotted the levels of parent-reported EXTadj for low, average, high, and very high levels of chronic stressors (corresponding to 0, 1, 2, and 3 or more long-term difficulties, respectively) and low, average, and high resting HR (-1SD, average, and +1SD, corresponding to 65.35, 76.40 and 87.45 beats per minute, respectively); separately for very severe PH and no PH. Visual inspection (Figure 1) shows that, in the presence of severe PH (left panel), higher levels of chronic stressors were associated with higher subsequent EXTadj in individuals with high or average resting HR, whereas chronic stressor levels were not associated with EXTadj in individuals with low resting HR. Rather, it appeared as if these adolescents had lower levels of EXTadj under high compared to low levels of chronic stressors. Post-hoc estimate and standard error calculation (using SAS 9.3) for the slope of EXTadj across levels of chronic stressors showed that it did not significantly differ from zero ($p = .53$) and should thus be interpreted as stable across levels of chronic stressors. Thus, individuals with low resting HR and severe PH, although typically showing high EXTadj, did not show an increase in EXTadj following chronic stressors. This lack of increase cannot be explained by a ceiling effect since the highest observed EXT level in our sample was still far from the scale maximum (see Table 1). In the absence of parental psychiatric history (right panel), externalizing levels did not seem to differ by resting HR level, regardless of the level of chronic stressors.

In contrast to parent-reported EXTadj, self-reported EXTadj was not significantly predicted by a three-way interaction effect of HR-square, chronic stress, and PH severity ($p = .20$). For purposes of checking if the pattern of findings was the same as in the parent-reported findings, we plotted self-reported EXTadj (available upon request) following Figure 1.

**Figure 1** Externalizing problems as reported by parents, plotted for different levels of chronic stressors and resting heart rate, and separately depicted for very severe (a) versus no parental psychiatric history (b)

EXTadj = Parent-reported externalizing problems adjusted for internalizing problems. Levels of chronic stressors refer to the number of long-term difficulties, corresponding to centered values of -1.09, -0.09, 0.91, and 1.91, respectively. Low, average, and high resting heart rate (-1SD, M, and +1SD) correspond to 65.35, 76.40, and 87.45 beats per minute, respectively.
the procedure described above. Visual inspection showed that the association between stressors and self-reported EXTadj was relatively weak in individuals with low resting HR and severe PH, which is consistent with our findings on parent-reported EXTadj.

**Post-hoc analyses**

We tested whether the three-way interaction of HR-square, chronic stressors and PH in predicting parent-reported EXTadj applied to the extremes of the PH distribution. That is, we tested for a two-way interaction effect of resting HR and chronic stressors within the very severe PH group, within the no PH group, or both. We found \( p \)-values that were very close together; \( p = .06 \) and \( p = .049 \) for very severe PH and no PH, respectively. Note that the sample size and associated power to detect effects should be taken into account in interpreting these \( p \)-values. Specifically, given the small sample size (\( n = 46 \)) associated with very severe PH, an effect would have to be rather large (as illustrated by Figure 1, left panel) in order to find a slope significantly different from zero. Conversely, the large sample size (\( n = 1055 \)) given no PH is associated with high power to detect even small effects (as illustrated by Figure 1, right panel).

Without controlling for initial EXTadj levels at T1, a three-way interaction effect of PH severity, HR-square and chronic stressors was somewhat weaker (\( p = .06 \)) in predicting parent-reported EXTadj levels. This is according to expectation, given that the exposure to chronic stressors was measured between T1 and T2 and between T2 and T3 but not at baseline. Plots were highly comparable to our main results (see Figure 1). Thus, whether or not corrected for initial EXTadj level at baseline, an attenuating effect of low resting HR on the association between chronic stressors and EXTadj was more pronounced in individuals with more severe PH.

Without adjusting our outcome measure for the variance shared by externalizing and internalizing problems, a three-way interaction effect of PH severity, HR-square and chronic stressors significantly predicted parent-reported EXT (\( p = .010 \)). Plots were highly comparable to those of EXTadj. These showed that due to co-occurring internalizing problems, the association between chronic stressors level and EXT was generally stronger than for EXTadj. However, just as in Figure 1, the association between chronic stressors and EXT was attenuated in adolescents with low resting HR and severe PH.

These post-hoc analyses show the robustness of our main results on parent-reported EXTadj. Tables and figures from these analyses are available upon request.
Discussion

This study investigated the combined effects of general vulnerability, as indexed by parental psychiatric history, and resting HR on the association between chronic stressors and externalizing problems from preadolescence well into adolescence.

In general, higher stressor levels were associated with higher parent-reported externalizing levels. As hypothesized, this association was moderated by resting HR, especially in more vulnerable individuals. Specifically, in individuals with high general vulnerability and low resting HR, unlike those with relatively high resting HR, externalizing levels were not influenced by the level of chronic stressors, in accordance with our hypothesis. In adolescents with low general vulnerability, in contrast, the association between chronic stressors and externalizing problems did not substantially differ by resting HR level. Although these findings were not statistically significant for self-reported externalizing problems, results from post-hoc analyses demonstrated that our findings on parent-reported externalizing problems were robust, in that they did not depend on prior externalizing levels or on the adjustment of externalizing problems for co-occurring internalizing problems.

We have extended findings from a prior TRAILS study (Oldehinkel et al., 2008) that demonstrated a stressor-buffering effect of low resting HR, by showing that this effect continued into adolescence and was more pronounced in more vulnerable individuals. Our results contrast with prior findings that the combination of low resting HR and environmental risk factors resulted in increased risk of externalizing problems, which suggested that effects of risk factors on externalizing problems accumulate (Raine, 2002b; Scarpa et al., 2008). Possibly, these prior findings pertain predominantly to samples with low general vulnerability. Given our finding that in vulnerable individuals with low resting HR, externalizing levels were typically high and not influenced by chronic stressors, it could be argued that these results suggest an alternative, competing risk factors explanation (Raine, 2002). That is, whereas psychosocial influence of externalizing problems may be masked in the presence of strong biological influence on externalizing problems, it may be exposed in the absence of biological influence, and vice versa. However, from this perspective, we would have expected low general vulnerability and low levels of chronic stressors (i.e., weak psychosocial influence) to expose the biological influence of low resting HR on (higher) externalizing levels. In contrast, our findings suggest no influence of resting HR level under these circumstances. Rather, they suggest that resting HR may reflect individual differences in sensitivity to the environment, especially in more vulnerable individuals, making the competing risk factor explanation less likely.

Whether or not individuals that are relatively prone to the detrimental effects of adverse influences may also benefit relatively more from beneficial influences was not
addressed in the current study. That is, rather than performing a formal test of the Differential Susceptibility hypothesis, which includes both beneficial and adverse aspects of the environment, we have only addressed the latter, reflecting a Diathesis-Stress model (Zuckerman, 1999). Future research may demonstrate whether our findings extend to a broader range of adverse environmental influences or are rather specific to chronic psychosocial stressors, and if our findings extend to beneficial influences.

It is important to note two limitations of our study, as well as several strengths. First, results based on self-reported externalizing problems did not reach statistical significance. Adolescents may have underreported externalizing problems (Salbach-Andrae, Lenz, & Lehmkuhl, 2009) due to socially desirable responding, indifference, or lack of insight. Additionally, since our measure of chronic stressors was only assessed by parents, stronger associations for parent-reported externalizing problems may be in part due to shared method variance, although this tends to inflate main effects in particular (rather than moderator effects). In TRAILS, we collected parent-reports of long-term difficulties because we assumed that parents are better and more stable judges of the difficulties that put chronic strain on family life. Nevertheless, it is possible that what is perceived as stressful differs between parents and adolescents. The stressors we examined included issues as housing problems and neighborhood problems. Possibly, such factors are not noted as stressful by adolescents. Self-reports on chronic stressors, more oriented towards adolescents’ point of view, could perhaps have led to stronger associations with self-reported externalizing problems.

A second limitation is that the PH data do not reflect clinical diagnoses. Conducting comprehensive diagnostic interviews with both parents, the gold standard, was not possible due to financial and practical constraints, such as limited time and risk of increased drop-out due to the high demands placed on research participants. We focused on lifetime disorders that had involved a professional, such as a psychiatrist, a general practitioner, or law enforcement. Although this method enabled a more reliable identification of individuals with severe PH, it may have led to underestimating individuals with mild PH. Furthermore, relying on one parent to describe the other parent’s psychiatric history may also have resulted in underestimations of participants’ PH. Taken together, potential bias in either long term difficulties or family history assessment may have led to underestimation of effects.

Strengths of the study include the large sample of longitudinal data from preadolescence well into adolescence; large inter-individual differences in problem severity and chronic stressor exposure; our use of linear mixed modeling, allowing for optimal use of all available data from multiple measurements; and sensitivity analyses on prior externalizing levels and on externalizing levels unadjusted for co-occurring internalizing problems.
In sum, this study has demonstrated that the moderating effect of resting HR on the association between chronic stressors and adolescents’ externalizing problems was more pronounced in the presence of general vulnerability, as indexed by parental psychiatric history. Our findings suggest that vulnerable adolescents with low resting HR, in contrast to those with relatively high resting HR, were less sensitive to the detrimental effects of chronic stressors on externalizing problems. This contrasts with previous findings that the combination of low resting HR and psychosocial risk factors resulted in increased risk of externalizing problems. Our findings thus suggest that low resting HR may be reflective of low sensitivity to environmental influences, but only in the presence of general vulnerability.
Resting heart rate and chronic stressors

References


