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Childhood adversity predicts reduced physiological flexibility during the processing of negative affect among adolescents with major depression histories

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Abstract

Background—Adversity during early development has been shown to have enduring negative physiological consequences. In turn, atypical physiological functioning has been associated with maladaptive processing of negative affect, including its regulation. The present study therefore explored whether exposure to adverse life events in childhood predicted maladaptive (less flexible) parasympathetic nervous system functioning during the processing of negative affect among adolescents with depression histories.

Methods—An initially clinic-referred, pediatric sample (N = 189) was assessed at two time points. At Time 1, when subjects were 10.17 years old (SD = 1.42), on average, and were depressed, parents reported on adverse life events the offspring experienced up to that point. At Time 2, when subjects were 17.18 years old (SD = 1.28), and were remitted from depression, parents again reported on adverse life events in their offspring's lives for the interim period. At time 2, subjects' parasympathetic nervous system functioning (quantified as respiratory sinus arrhythmia) also was assessed at rest, during sad mood induction, and during instructed mood repair.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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The authors declare that there is no potential or actual conflict of interest.

Results—Extent of adverse life events experienced by T1 (but not events occurring between T1 and T2) predicted less flexible RSA functioning 7 years later during the processing of negative affect. Adolescents with more extensive early life adversities exhibited less vagal withdrawal following negative mood induction and tended to show less physiological recovery following mood repair.

Conclusions—Early adversities appear to be associated with less flexible physiological regulatory control during negative affect experience, when measured later in development. Stress-related autonomic dysfunction in vulnerable youths may contribute to the unfavorable clinical prognosis associated with juvenile-onset depression.

Keywords

early adversity; physiological flexibility; respiratory sinus arrhythmia; negative affect processing; adolescents; depression

1. Introduction

An extensive body of research has documented that stressful events, particularly developmentally early adversities, can have lasting negative effects on neurobiological systems involved in the regulation of affect and response to stress (for reviews, see Kaffman and Meaney, 2007; Lupien et al., 2009; Heim and Binder, 2012). This work has included both non-human and human subjects and has mostly targeted neuroendocrine functioning via the hypothalamic-pituitary-adrenal (HPA) axis and its neural substrates (Chen et al., 2010; Pesonen et al., 2010; Rao et al., 2010; Bush et al., 2011; Hanson et al., 2015).

Autonomic regulation, often indexed as respiratory sinus arrhythmia (RSA; Porges, 2007), is another neurobiological system potentially vulnerable to the negative effects of early adversities. Associations between early-life adversity and RSA impairment have been documented despite considerable heterogeneity in the types of early-life adversities examined and in how impaired RSA was defined (for a review, see Propper and Holochwost, 2013). Namely, negative events as diverse as parental depression (Field et al., 1995; Pickens and Field, 1995), domestic violence (Rigterink et al., 2010), marital conflict (Porter et al., 2003; Moore, 2010; El-Sheikh and Hinnant, 2011), neglect and disordered attachment (Oosterman et al., 2010), and institutional care (McLaughlin et al., 2015) have been associated with altered RSA, either in the form of lower baseline RSA (Field et al., 1995; Pickens and Field, 1995; Porter et al., 2003; Moore, 2010; Rigterink et al., 2010; El-Sheikh and Hinnant, 2011), more blunted RSA in response to an experimental stressor (Oosterman et al., 2010; McLaughlin et al., 2015), or both (Conradt et al., 2014; but see Gottman and Katz, 1989; Katz, 2007; Skowron et al., 2014 for contradictory findings).

In turn, in separate literatures, exposure to adverse life events and altered RSA each has been linked to depression risk (Hammen, 2005; Williamson et al., 2005; Stroud et al., 2008; Kemp et al., 2010; Heim and Binder, 2012; Hamilton and Alloy, 2016; Infurna et al., 2016). The association between stressful, adverse life events and depressive disorders and symptoms has been shown across the life span (e.g., Chapman et al., 2004; Hankin, 2015), both in prospective and retrospective studies (Tram and Cole, 2000; Ge et al., 2001; Pine et

al., 2002; Southall and Roberts, 2002; Franko et al., 2004). Notably, the reported associations are robust regardless of how stressful events are defined (e.g., specific traumatic events, total negative event counts, weighted stressful event counts). For example, isolated adverse childhood experiences such as separation from or loss of a parent, as well as cumulative stressful adverse events, predict elevated depression symptoms and increased risk of a depressive disorder (e.g., Agid et al., 1999; Pine et al., 2002). Using total event counts, we found that clinically referred children with depressive disorders experienced about twice as many lifetime stressful events than did a school-based control group, and had accumulated those events by a younger age than did the controls (Mayer et al., 2009).

The relations of altered RSA and depression have been examined in samples that varied in age and type of depression-proneness (Rottenberg, 2007; Kemp et al., 2010; Hamilton and Alloy, 2016). For example, among adults, atypical RSA reactivity (compared to controls) is most consistently found when subjects are currently depressed (Hamilton and Alloy, 2016). Among children, atypical development of resting RSA has been reported for those at high familial risk for depression (Gentzler et al., 2012). Additionally, combinations of high resting RSA and robust RSA reactivity to negative mood induction were found to predict reduced depressive symptoms among depression-prone adults and their children (Yaroslavsky et al., 2013, 2014; Yaroslavsky et al., 2016), and indirectly contributed to lower risk of recurrent depression among adolescents (Kovacs et al., 2016).

While the contribution of early adversities to physiological dysfunction, and the role of stressful or adverse events in depression risk, have been documented in mostly separate literatures (for a review see Anacker et al., 2014), an emerging body of work has sought to link these areas. For example, specific trauma, namely sexual or physical abuse among depressed adults and youths has been associated with greater HPA activation in response to experimental stress (Kaufman et al., 1997; Heim et al., 2000). Further, among depressed women, those with severe trauma history evidenced blunted RSA reactivity to a stress-inducing task, relative to depressed women without severe trauma history (Cyranowski et al., 2011). Since these studies focused on extreme trauma, it is unclear if cumulative exposure to a variety of adverse life events has similar consequences on physiological response systems.

The present study seeks to extend the literature by integrating information on early adversities and physiological dysfunction measured years later, in the context of high depression risk. Specifically, we explored for the first time if reduced RSA flexibility among adolescents, who had histories of childhood-onset major depressive disorder, is related to developmentally early adversities. We focused on reduced physiological flexibility because context-appropriate RSA modulation is thought to reflect a functionally adaptive response to environmental demands (Porges, 1995; Porges et al., 1996). Early adversities were quantified as event counts, based on parental reports at initial (time 1 or T1) assessment. Several years later (time 2 or T2), we assessed RSA flexibility during the processing of sad affect and focused on individual differences in the context of a repeated-measures design. We hypothesized a dose-response relationship between greater exposure to childhood adversities and less flexible RSA functioning while adolescents were processing dysphoric affect.

Although the literature on the detrimental effects of adversities on later physiological functioning is most compelling for exposure during the *early phases of development,* we also examined the potential contribution of temporally closer T2 (more recent) adversities. In order to eliminate the confounding effects of current depression on physiological functioning (Salomon et al., 2013), we tested our hypotheses with adolescents who were remitted from their last episode of major depression.

2. Methods and Materials

2.1 Participants

We report on adolescent probands with histories of childhood onset major depressive episodes (MDE) who were assessed at two time points, approximately 7.01 years (*SD* = 1.15) apart, and whose depressions were in remission at the time of the physiological assessment. The Time 1 (T1) assessments were part of a genetic investigation in a national sample of clinically referred children in Hungary, recruited through 23 child mental health clinical sites. At T1, probands were 7- to 14-years old and met DSM-IV (American Psychiatric Association [APA] 1994) criteria for a depressive disorder, as determined via a stringent series of research diagnostic interviews (for details, see Tamás et al., 2007; Kovacs et al., 2015).

The subsequent study of emotion regulation (Time 2 [T2] assessments) enrolled only a portion of the prior, original sample due to funding constraints. Because the T2 study included a laboratory-based physiological protocol, living within commuting distance of the research laboratories was the primary enrollment criterion. Subjects were aged 14–18 years at enrollment in the T2 study of emotion regulation.

The present sample includes 189 probands (96.3% Caucasian). Average age at T1 was 10.17 years (*SD* =1.42); there were 122 (64.6%) boys. Age at onset of first MDD episode was 8.97 years (*SD* = 1.71); the average number of major depressive episodes was 1.5 (*SD* = 0.73). At T1, average socioeconomic status (SES), using the Hollingshead (2011) index was *M* = 32.93, *SD* = 13.18, which corresponds to middle class. At T2, subjects' average age was 17.18 years (*SD* = 1.28). By T2, 59.8% of the youths still had only one MDD episode, while 30.2% had 2 episodes, and 10.1% had 3 or more episodes. At T2, only 3 probands were taking psychotropic medication, consistent with the sample's remitted status. The temporal windows for the data collection in this article included January 2001 to February 2006 for T1, and April 2010 to May 2013 for T2.

2.2 Procedures

At T1, all participants received a psychosocial assessment that included the following: a) 2 separate standardized semi-structured clinical diagnostic interviews, at least one month apart, by different trained interviewers with parents about the subjects and with the subjects about themselves, which used DSM-IV diagnostic criteria (APA, 1994), b) review of the diagnoses by two trained senior child psychiatrists who then had to achieve "best estimate" diagnoses (Maziade et al., 1992), c) ascertainment of psychosocial information from parents, including offspring's' history of stressful life events, medication use, and cigarette smoking

history, d) completion of self-rated questionnaires, including the Paffenbarger Physical Activity Questionnaire (PPAQ; Paffenbarger et al., 1978), and e) determination of participants' weight and height. The procedures have been described in detail elsewhere (e.g., Kiss et al., 2007; Tamás et al., 2007). At T2, participants completed again a full psychosocial evaluation and an experimental protocol with psychophysiological recording (also noted in Kovacs et al., 2015, and below).

2.3 Quantification of Adverse, Stressful Life Events

Exposure to major adverse life events was determined twice during fully structured interviews with the parent as to whether or not the offspring had been exposed to the specified events. At T1, the parent reported on *life-time* events to which the offspring was exposed up to T1. At T2, the parent report on events experienced by the offspring only during the period between T1 and T2. Time elapsed between T1 and T2 was 6.29 years (*SD* = 1.14), on average. The interview queried about 31 adverse life events, which represent five developmentally meaningful event clusters: a) Parental health: hospitalization, physical illness, or psychiatric illness of biological or stepparents; b) Death of close relatives: parental, or other death in the family; c) Sociodemographic events: financial problem, moving, parental unemployment, natural disaster, loss of home; d) Intrafamilial events: birth, hospitalization, psychiatric illness of sibling, foster care, family arguments, and divorce of biological parents; and e) Physical or sexual abuse. The final score was the arithmetic sum of the events that were endorsed.

We have previously reported that our event list discriminated normal school-based controls and youths with major depressive disorder (Mayer et al., 2009). Furthermore, the rate of negative life events reported for our Hungarian school-based controls (Mayer et al., 2009) was comparable to that reported for normative USA samples in studies with similar lists of life events (Ge et al., 1994; Franko et al., 2004).

2.4 Measurement of RSA

At T2, RSA was measured as part of a multicomponent physiological protocol via an electrocardiogram (ECG), using Mindware BioLab software. Participants were asked to sit as still as possible during the experimental protocol. A research assistant tracked compliance and no collection errors were noted.

The ECG signals were acquired according to published guidelines (Berntson et al., 1997); the electrodes were placed on the participant's left and right rib cage at heart level. Heart values were sampled online at 1000Hz using the Mindware Bionex system (MindWare Technologies, Ltd., Gahanna, OH). Subject's respiration was measured only during paced breathing and reactivity periods. Respiration was collected by placing a band around the abdomen, calibrated against a fixed volume bag. Respiration rate was calculated breath by breath by the Mindware HRV software (MindWare Technologies, Ltd., Gahanna, OH).

RSA was calculated using MindWare HRV 3.0.21 software (MindWare Technologies, Ltd., Gahanna, OH). R-wave markers in the ECG signal were processed with the MAD/MED artifact detection algorithm; signals were visually inspected and suspected artifacts were manually corrected (Berntson et al., 1997). The interbeat interval (IBI) series was resampled

in equal 250 ms intervals, linearly detrended, and tapered using a Hanning window. Heart rate variability (HRV) was calculated using Fast Fourier transformation analysis of the IBI series and RSA was defined as the log transformed high frequency (HF) power band of HRV (0.15–0.40 Hz range; see Berntson et al., 1997). Hereafter we refer to HF-HRV as RSA.

The protocol included a paced breathing period, which provided the baseline-resting RSA value. For a 180- second period, subjects listened to a soft tone and were instructed to breathe in when the tone was rising, breathe out when the tone was falling, and pause between breaths when there was no tone. The tone pattern was set to induce a respiratory frequency of 12 cycles per minute with a normal fractional inspiratory ratio of 40%.

RSA reactivity was assessed during negative mood induction (watching a sad film clip or trying to solve an unsolvable puzzle). RSA recovery was assessed during an attention refocusing task designed to help subjects recover from negative mood (described in Kovacs et al., 2015). RSA was calculated for each epoch separately. Mean heart rate during the paced breathing baseline was 72.61 (SD = 10.54), it was 68.31 (SD = 9.08) during the sad film, 73.69 (SD = 9.71) during the unsolvable puzzle, and 72.61 (SD = 9.14) during mood repair task.

2.5 Negative mood induction

Subjects were randomized to either a *Sad film* or an *Unsolvable task* mood induction condition. The former was a 164 second clip from the *Champ* (dubbed in Hungarian), in which a child witnesses the death of his boxer champion father after a match (Rottenberg et al., 2005, 2007). This clip has been extensively used with both pediatric and adult samples (e.g., Gross and Levenson, 1995; Rottenberg et al., 2002), and was also pilot tested with Hungarian youths (see Kovacs et al., 2015). The *Unsolvable puzzle* was a computerized task wherein subjects had to re-recreate a pattern by moving pieces on a computer screen (horizontally or vertically) containing letters of the alphabet. A solvable practice puzzle was first given (15s), which was followed by two puzzles that were programmed to be unsolvable (mirroring Nolen-Hoeksema et al., 1995; Cole et al., 2007). Subjects had 180s to work on each unsolvable puzzle. Subjects also rated the intensity of feeling ‘sad’ and ‘blue’ on a 0- to 7-point Likert-type scale at baseline and after negative mood induction.

For manipulation checks, we computed mean “sadness” ratings based on the above noted two items and entered them in a repeated measures ANOVA of induction type and time (baseline, mood induction). The results showed a main effect of time, such that sad mood increased from baseline to post- mood induction (M_{Baseline} = 0.42, SD_{Baseline} = 0.92, $M_{Moodinduction}$ = 0.85, $SD_{Moodinduction}$ = 1.18; $F(1,187) = 22.44$, $p < .01$, partial $\eta^2 = .11$). Although both types of mood inductions significantly increased sad mood, the increase in sadness was stronger following the unsolvable puzzle than following the sad film ($F(1,187) = 8.62$, $p < .01$, partial $\eta^2 = .04$). Therefore, type of mood induction was entered as a covariate in all relevant analyses.

2.6 Mood repair task

Focusing attention away from one’s dysphoria is regarded as a key emotion regulatory strategy that can attenuate distress (Erber and Tesser, 1992). The effectiveness of attention

refocusing for mood repair, which can be implemented through various means, has been documented across the age span in observational and experimental studies (e.g., Rippere, 1977; Thayer et al., 1994; Eisenberg et al., 2000; Posner and Rothbart, 2000; Joormann et al., 2007; Kovacs et al., 2015). In the present study, attention refocusing was implemented via an "illusion kaleidoscope" task, which was adopted from a study of pediatric pain (Carlson et al., 2000). Subjects were handed a standard kaleidoscope (15 cm in length; 4 cm in diameter) and were asked to keep looking through it for 120s. During the task, the experimenter posed standardized questions such as "What shapes do you see? What are the different colors?" to reinforce task engagement.

2.7 Statistical Analyses

RSA scores, sum of early negative life events, interim negative life events, and all related variables were transformed to z-scores. To test our primary hypothesis, we conducted a repeated measures ANCOVA (rANCOVA) on RSA using epoch (resting, reactive, recovery phases) as a within-subject factor and early adverse life event (T1) score as the predictor (independent) variable, with a relevant set of additional variables treated as covariates to control for their effects. In order to examine whether the chronologically later T1 to T2 interim life events contributed to the prediction of RSA, the rANCOVA was repeated with the addition of interim adverse event counts as a further predictor variable. Significant interactions were probed by a set of linear regression models, adjusting for relevant confounding variables.

3. Results

3.1 Characteristics of the Sample and Measures

Table 1 presents the correlations among key variables. Although extent of early adversities ($M = 5.90$, $SD = 2.99$) correlated with extent of T1-T2 adversities ($M = 3.85$, $SD = 2.53$), the scores in early childhood were higher ($t = 9.04$, $p < .001$). The higher adverse event scores at T1 (compared to T1-T2 scores) may partly reflect that the T1 assessment covered a longer period of children's lives (M = 10.17 years; $SD = 1.42$) than did the T1-T2 interim assessment (M = 7.01 years, $SD = 1.15$). As also shown in Table 1, early childhood adversity positively correlated with age, while interim adversity was higher for males than for females ($M_{males} = 4.38$, $SD_{males} = 2.59$, $M_{females} = 2.91$, $SD_{females} = 2.09$, $t = 4.01$, $p < .001$).

Body mass index (BMI), computed from height and weight (age and sex adjusted), along with cigarette smoking, physical activity index, and respiration rate at mood induction are reported in Table 1 because they are potential confounds of RSA. However, as BMI, physical activity level, and smoking were not significantly correlated with baseline RSA, they were not considered in subsequent statistical models. Although only three probands were on psychotropic medication, which can affect RSA, we nevertheless included this variable in all models (excluding these participants from analysis did not change the significance of the results). While age at onset of first MDD episode did not correlate with RSA (Table 1), it may account for a possible link between adversities and RSA flexibility, thus this variable was also taken into account in our analyses. The influence of respiration

rate (M = .26, SD = .03) was entered in the analyses as well, but it did not alter the pattern of results.

3.2 Early Adversities and RSA Flexibility

To test our hypothesis regarding a dose-response relationship between adversity in childhood and less flexible RSA functioning in adolescence, we conducted a rANCOVA of childhood adversity scores on RSA (with sex, T2 age, time elapsed between T1 and T2, medication use, onset age of MDD and type of mood induction as covariates). There were no main effects of early adversities (F(1,181) = .23, p = .63, partial η^2 < .01), or experimental epoch (F(2,180) = 0.84, p = .44, partial η^2 < .01; $M_{resting}$ = 7.24, $SD_{resting}$ = 1.15, $M_{reactivity}$ = 6.60, $SD_{reactivity}$ = 1.03, $M_{recovery}$ = 6.81, $SD_{recovery}$ = .97). Importantly, there was an interaction between early adversity and experimental epoch (F(2,180) = 3.66, p = .03, partial η^2 = .04).

To unpack this interaction, we computed two RSA change scores: a) the difference between resting RSA and RSA reactivity values and b) the difference between RSA reactivity and RSA recovery values. The change scores were computed by subtracting the RSA value of the subsequent epoch (reactivity or recovery) from the RSA value of the prior epoch (baseline or reactivity): thus, positive RSA change scores represent RSA Augmentation (higher RSA) and negative values represent RSA Withdrawal (lower RSA). A linear regression predicting RSA change score for resting vs. reactivity (controlling for sex, age at T2, time elapsed between T1 and T2, medication use and type of mood induction) indicated a negative association with early adversities (B = −.05, t = −2.55, p = .01; ΔR^2 = .034). In other words, early adversities predicted blunted RSA withdrawal during mood induction.

A second linear regression predicting RSA change score for reactivity vs. recovery (controlling for the above noted covariates) indicated a marginal positive association with early adversities (B = .03, t = 1.83, p = .07; ΔR^2 = .017). In other words, early adversities predicted a trend toward less RSA augmentation during mood repair. As illustrated in Figure 1, youths who had been exposed to higher rates of early adversities displayed less RSA flexibility during different phases of sadness processing than youths exposed to lower levels of early life adversities.

3.3 Later Adversities and RSA Flexibility

Do negative life events occurring later in development also have adverse effects on autonomic functioning? To examine this question, we repeated the above noted rANCOVA with the addition of the T1 to T2 interim life event scores. There was no main effect for recent/interim life events (F(1,180) = 0.04, p = .85, partial η^2 < .01), nor was there a significant epoch by recent stressful life events interaction (F(2, 179) = .45, p = .64, partial η^2 < .01). However, the T1 early adversities score by epoch interaction remained significant (F(2,179) = 3.98, p = .02, partial η^2 = .04). Thus, the relationship between adverse life events and RSA functioning during the processing of dysphoric affect was explained by earlier adversities experienced during childhood rather than by adversities the youths experienced during their adolescence.

3. Discussion

Using a prospective design, we examined whether childhood adversities have harmful effects on autonomic nervous system functioning later in life during the processing of sad affect among adolescents who had histories of childhood-onset major depressive disorder. We focused on physiological functioning during the processing of dysphoric affect because of its importance in the context of depression risk.

Our subjects constitute a sample at high-risk for future depression because all of them had past episodes of major depression, from which they were in remission. However, because we did not have a never-depressed control group, we cannot tease out the extent to which depression may have moderated the effects of early adversities on later physiological functioning. Our central finding is that depression-prone adolescents with more extensive exposure to childhood adversities exhibited less flexible RSA functioning during the experience and regulation of dysphoric affect than did their peers with lower levels of early stress exposure. Reduced RSA flexibility was manifest as less extensive vagal withdrawal in response to negative mood induction and as a trend toward less extensive vagal augmentation following mood repair. Withdrawal of vagal influences on the heart during stress or external provocation and a rapid return of vagal influences post-stress are considered to be important substrates of flexible and adaptive physiological and behavioral functioning (Porges, 1995, 1997).

The present results add to a large body of literature on the association between early adversities or negative life events and enduring dysfunctional physiological changes in humans (e.g., Pesonen et al., 2010; Rao et al., 2010). Specifically, we found that an additive accumulation of adverse negative life events was associated with physiological impairment. While similar associations have been documented when early-life adversities were defined by exposure to a discrete stressor (Field et al., 1995; Pickens and Field, 1995; Porter et al., 2003; Moore, 2010; Oosterman et al., 2010; Rigterink et al., 2010; El-Sheikh and Hinnant, 2011; Conradt et al., 2014; McLaughlin et al., 2015), our findings suggest that such associations are not event specific but represent a generalized pattern. In other words, early adversities appear to contribute to impaired physiological self-regulation in a dose-response fashion.

Results of our study also extend the literature on RSA and stress. Although we cannot argue for a causal association between early adversity and atypical RSA in response to affective challenge, our study is the first to examine adverse life events that temporally predated RSA assessment. Further, while previous studies have focused on RSA at rest and in response to sad mood induction (e.g., Katz and Gottman, 1997; El-Sheikh et al., 2001; El-Sheikh and Whitson, 2006; McLaughlin et al., 2015), we examined RSA while youths were in the process of repairing their negative mood. Exploring RSA under differing conditions (rest, mood induction, mood repair) provides a more ecologically valid picture of RSA functioning over time (Yaroslavsky et al., 2013). Further, while adversity early in life has been associated with blunted RSA reactivity to experimental stress (Oosterman et al., 2010; Cyranowski, et al., 2011; McLaughlin et al., 2015), the present results suggest that early stress may play a role in the lack of context-appropriate RSA flexibility.

Exposure to adversities during the first decade of life (but not during adolescence) was associated with atypical RSA functioning, underscoring that the consequences of stress appear to vary as a function of the developmental *timing* of the exposure. There are windows of vulnerability when brain regions and more downstream response systems might be maximally sensitive to environmental influences, the effects of which persist over time (Andersen and Teicher, 2008). Our finding that exposure to more recent negative life events did not contribute to dysfunctional RSA (beyond the prediction provided by early adversities) is in line with reports on the effects of stressors on various other physiological systems, such as cortisol secretion (Pesonen et al., 2010; Bosch et al., 2012) and regional brain volume (Andersen and Teicher, 2008).

Finally, the finding of less flexible RSA functioning during the laboratory experience and regulation of dysphoric affect, as a function of early adversity, also adds to the literature on mood repair. Maladaptive mood repair responding (by self-report) has been associated with atypical, less flexible RSA (Williams et al., 2015; Kovacs et al., 2016). Overall, it appears that physiological regulatory flexibility in the context of affective challenge may be one contributor to individual differences in competent mood repair performance, which, in turn, may be compromised by exposure to adversities during early development.

In spite of its strengths, the present study also had several limitations. Most critically, as already noted, because we lack a control group with parallel T1 and T2 data, we cannot address whether the findings are specific to youths with depression histories. The absence of an experimental manipulation of stress makes it difficult to argue for a *causal* association between childhood adversities and laboratory-based physiological functioning. Further, our index of life events did not take into account the length of exposure to a given stressor, or multiple exposures to the same stressor across time. Despite these limitations, the association between developmentally early adversities and later physiological dysfunction in the present sample may help to better understand the mood repair difficulties and unfavorable long-term clinical prognosis of youths with pediatric-onset depression (Kovacs et al., 2016).

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Highlights

- We explored the link between adversities and PNS functioning in depression prone youths.
- Youths with more adversities exhibited less RSA flexibility 7 years later.
- Less RSA flexibility was exhibited during experience of negative affect and recovery.
- Recent adversities did not contribute to the prediction of RSA flexibility.

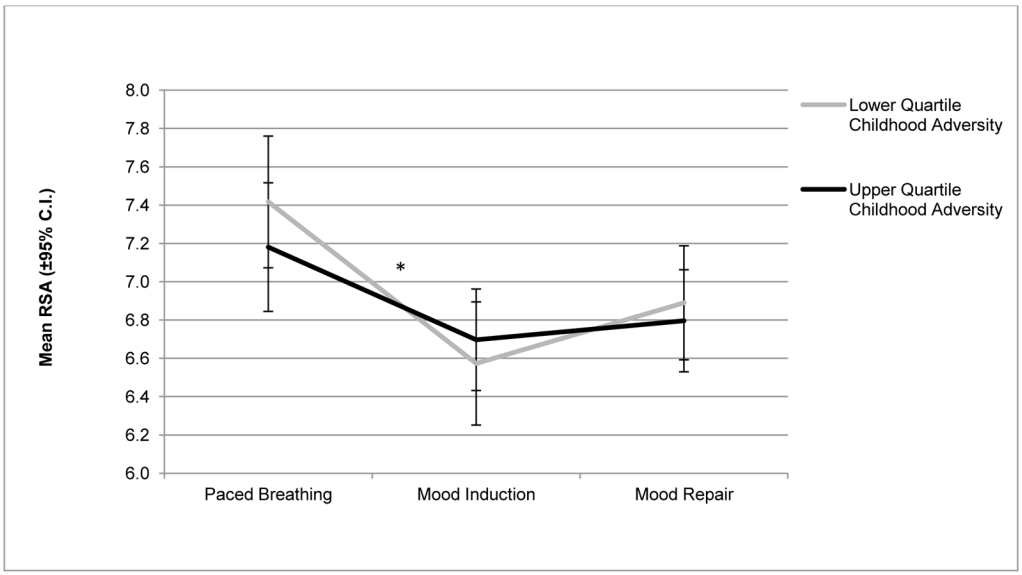

Figure 1.

RSA values (with 95% confidence intervals) across three assessment points in the experimental protocol (paced breathing baseline; sad mood induction; instructed mood repair) among adolescent probands in the upper and lower quartiles of exposure to childhood adversity.

*p < 0.05, for RSA change score from mood induction to mood repair ($B = -0.05$, $t = -2.55$, $p = .01$; $\Delta R^2 = 0.034$).

Table 1

Correlations among demographic characteristics and key study variables ($N = 189$).

	Sex	Age	Early events	Interim events	Smoking	BMI	Physical activity	RSA PB	RSA MI	RSA MR	Onset age of MDD	MDD episodes
Sex		−.03	−.09	−.28**	−.12	−.03	−.24**	.17*	.13	.12	.03	.08
Age			.16*	.08	.36**	.05	−.19**	−.01	−.03	−.02	.49**	.10
Early events				.37**	.17*	−.10	−.11	−.09	.03	−.03	.06	.11
Interim events					.08	.07	.07	−.04	−.02	−.03	−.01	−.03
Smoking						−.12	.08	.07	.15*	.10	.32**	−.17*
BMI							−.03	.14	.10	.05	−.13	−.02
Physical activity								−.03	.01	.03	−.15*	−.03
RSA PB									.70**	.70**	.01	−.05
RSA MI										.80**	−.01	.02
RSA MR											−.01	−.01
Onset age of MDD												−.30**
MDD episodes												

Sex = high value represents females, Age = age at T2, Early events = number of childhood adversities, interim events = number of adversities over the T1 to T2 follow up period, smoking = high value represent smokers, BMI = Body Mass Index, Physical activity = Paffenbarger Physical Activity score, RSA = Respiratory Sinus Arrhythmia, PB = paced breathing, MI = mood induction, MR = mood repair, Onset age of MDD = age at onset of first MDD episode, MDD episodes = number of episodes.

* $p < .05$,

** $p < .01$