Cumulative lifetime acute stressor exposure interacts with reward responsiveness to predict longitudinal increases in depression severity in adolescence

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Abstract

Background. Life stress and blunted reward processing each have been associated with the onset and maintenance of major depressive disorder. However, much of this work has been cross-sectional, conducted in separate lines of inquiry, and focused on recent life stressor exposure, despite the fact that theories of depression posit that stressors can have cumulative effects over the lifespan. To address these limitations, we investigated whether acute and chronic stressors occurring over the lifespan interacted with blunted reward processing to predict increases in depression over time in healthy youth.
Method. Participants were 245 adolescent girls aged 8–14 years old (M_{age} = 12.4, s.d. = 1.8) who were evaluated at baseline and two years later. The reward positivity (RewP), an event-related potential measure of reward responsiveness, was assessed at baseline using the doors task. Cumulative lifetime exposure to acute and chronic stressors was assessed two years later using the Stress and Adversity Inventory for Adolescents (Adolescent STRAIN). Finally, depressive symptoms were assessed at both baseline and follow-up using the Children's Depression Inventory.
Results. As hypothesized, greater lifetime acute stressor exposure predicted increases in depressive symptoms over two years, but only for youth exhibiting a blunted RewP. This interaction, however, was not found for chronic stressors.
Conclusions. Lifetime acute stressor exposure may be particularly depressogenic for youth exhibiting a blunted RewP. Conversely, a robust RewP may be protective in the presence of greater acute lifetime stressor exposure.

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Major depressive disorder (MDD) is a pervasive and recurrent psychiatric condition that causes a substantial disease burden in adolescents and adults (Slavich & Irwin, 2014). In the United States, the lifetime prevalence is approximately 19%, with similar estimates documented in other countries (Bromet et al., 2011). Individuals with MDD often report considerable social and occupational impairment (Kessler et al., 2008; Kupferberg, Bicks, & Hasler, 2016). The economic burden of depression is also high. For example, in 2010, adults with MDD incurred approximately $100 billion in direct costs related to medical and pharmaceutical services sought for MDD, and another $100 billion in work-related costs attributable to days missed at work and lack of productivity (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015). Among those who have experienced one lifetime major depressive episode (MDE), 60% are likely to develop a second MDE, with recurrence rates increasing as an individual experiences more MDEs (Monroe & Harkness, 2011; Solomon et al., 2000). MDD is thus a relatively common and highly burdensome disorder.

Major life stressors are one of the strongest known precipitants of MDD (Hammen, 2005; Kessler, 1997; Slavich, 2016), with their occurrence substantially increasing the risk for developing depressive symptoms and MDD in both adolescents and adults (Bouma, Ormel, Verhulst, & Oldehinkel, 2008; Fried, Nesse, Guille, & Sen, 2015; Ge, Lorenz, Conger, Elder, & Simons, 1994; Kendler, Karkowski, & Prescott, 1999; Mazure, 1998; van Praag, 2004). Stressor duration also has been found to be an important dimension associated with risk for depressive symptoms and MDD (Carter & Garber, 2011; Slavich, Stewart, Esposito, Shields, & Auerbach, 2019). Both acute and chronic stressors have been related to the onset of a depressive episode (Hammen, Kim, Eberhart, & Brennan, 2009); however, research suggests that acute stressors may be particularly depressogenic (Monroe, Slavich, & Georgiades, 2009; Slavich, O'Donovan, Epel, & Kemeny, 2010).

Despite the abundance of research examining the association between life stressor exposure and depression, much of this work has focused on recent life stressors. In addition, the neurobiological mechanisms linking stress with depression remain unclear. One possible pathophysiological mechanism involves stress-induced reductions in reward-related brain activity that may lead to increases in depression (Pizzagalli, 2014). For example, experimental research using functional magnetic resonance imaging (fMRI) provides support indicating that laboratory stressors blunt activity in the mesolimbic and mesocortical reward pathways (Kumar et al., 2014; Lincoln et al., 2019; Porcelli, Lewis, & Delgado, 2012). Moreover, electroencephalogram (EEG) research has identified the reward positivity (RewP) as an index of reward processing evident approximately 250 ms to 350 ms following feedback indicating rewards compared to losses (Proudfit, 2015). Prior research has shown that the RewP has good internal consistency in both adolescents and adults (Levinson, Speed, Infantolino, & Hajcak, 2017; Luking, Nelson, Infantolino, Sauder, & Hajcak, 2017) and that it relates to other measures of reward processing. Specifically, a larger RewP has been associated with greater self-reported reward responsiveness, ventral striatum activation, and reward response bias (Becker, Nitsch, Miltner, & Straube, 2014; Bress & Hajcak, 2013; Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011). Overall, the RewP has good psychometric properties and construct validity.

A reduced RewP has been shown to be evident among children and adults with increased depressive symptoms and MDD (Belden et al., 2016; Bowyer et al., 2019; Bress, Smith, Foti, Klein, & Hajcak, 2012; Brush, Ehmann, Hajcak, Selby, & Alderman, 2018; Foti & Hajcak, 2009; Klawohn, Burani, Bruchnak, Santopetro, & Hajcak, 2020; Liu et al., 2014). Moreover, a reduced RewP has been observed prior to the onset of depression, suggesting that it may be a pre-clinical marker of subsequent risk for MDD (Bress, Foti, Kotov, Klein, & Hajcak, 2013; Nelson, Perlman, Klein, Kotov, & Hajcak, 2016). Collectively, the evidence indicates that the RewP is a reliable neural indicator of reward processing that is frequently blunted in individuals with elevated depressive symptoms and MDD and reduced among those at increased risk for depression (Proudfit, 2015).

In addition, prior research has indicated that reward processing, as measured by the RewP, interacts with life stressor exposure to predict increases in depressive symptoms in adolescents and adults. In a cross-sectional study of young adults, Pegg et al. (2019) examined whether social *v.* non-social lifetime stressor severity as measured by the Stress and Adversity Inventory for Adults (STRAIN) interacted with the RewP, measured during a social reward task, to predict depressive symptoms. The authors found that greater lifetime social stressor severity interacted with a blunted RewP to social rewards to predict greater increases in depressive symptoms; however, this was not found for non-social stress severity. In a separate longitudinal study using the Adolescent Life Events Questionnaire, Burani et al. (2021) found that experiencing more recent stressful life events interacted with a blunted RewP to predict greater increases in depressive symptoms one year later in adolescent girls. Similarly, Goldstein et al. (2020) found that experiencing more stressful life events, as measured using the UCLA Life Stress Interview, interacted with a blunted RewP to predict greater increases in depressive symptoms three years later. Collectively, these cross-sectional and longitudinal studies are consistent with a diathesis-stress model of depression (Monroe & Simons, 1991), wherein life stressors are most likely to precipitate depression for persons

exhibiting a blunted RewP. To our knowledge, however, no studies have examined how stressors occurring over the entire life course interact with this neural marker indicator of reward-related brain activity to predict changes in depressive symptoms in adolescents over time.

The absence of lifetime stressor studies on this topic is notable because cumulative lifetime stressor exposure has been hypothesized to have adverse effects on neurobiological systems such as the hypothalamic–pituitary–adrenal (HPA) axis (Lupien, McEwen, Gunnar, & Heim, 2009), the reward system (Casement, Shaw, Sitnick, Musselman, & Forbes, 2015), and the immune system (Slavich, 2020; Slavich & Irwin, 2014), each of which have been associated with depression. Stressor exposure activates the HPA axis, which leads to the production of cortisol that helps to mobilize the body's response to stressors; however, repeated exposure to stressors can cause prolonged hyperactivation of the HPA axis that has health-damaging effects (Lupien et al., 2009). Similarly, repeated exposure to stressors during adolescence predicts blunted activation of the ventral striatum – a brain region linked to the RewP – during adulthood (Hanson et al., 2016). Likewise, chronic and repeated stressor exposure has been found to contribute to increased inflammatory activity (Furman et al., 2019), which has been implicated in depression (Slavich & Irwin, 2014). Therefore, multiple findings underscore the importance of investigating how cumulative lifetime stressor exposure interacts with the RewP to shape the risk for stress-related disorders such as depression.

The present study addresses this issue by examining whether acute and chronic stressors occurring over the life course prospectively predict increases in depressive symptoms in the context of a blunted RewP in a large community sample of 8- to 14-year-old girls who were assessed longitudinally over two years. Acute stressors were defined as those lasting a few days (e.g. hearing bad news, getting into an accident), whereas chronic stressors were defined as those lasting at least one month (e.g. persistent housing, financial, or relationship problems; Slavich et al., 2019). Recent evidence suggests that acute stressors are stronger proximal predictors of MDD as compared to chronic stressors (Monroe et al., 2009; Slavich et al., 2010). Therefore, we were particularly interested in whether acute stressor exposure interacts with the RewP to predict subsequent increases in depressive symptoms.

To investigate this possibility, at baseline, our sample of adolescent females completed a reward task while EEG data were collected; they also completed the Children's Depression Inventory (CDI) to assess their depressive symptoms. Two years later, these participants again completed the CDI as well as the Adolescent STRAIN to assess their lifetime stressor exposure. Based on the literature summarized above, we hypothesized that the RewP assessed at baseline would interact with participants' lifetime stressor exposure to predict subsequent increases in depression. Given prior research on the topic (e.g. Monroe et al., 2009; Slavich et al., 2010), we expected that acute lifetime stress exposure, in particular, would be most strongly related to increases in depression for youth exhibiting a blunted RewP.

Method

Sample

Participants were recruited from Long Island, New York, as part of a longitudinal study examining processes associated with

developmental changes in reward processing. The complete sample included 317 adolescent girls between 8 and 14 years old (M_{age} = 12.4, s.d. = 1.8). Of these 317 participants, three did not complete the reward task and nine were excluded due to poor EEG data quality. Therefore, the final sample at baseline included 305 participants (M_{age} = 12.4, s.d. = 1.8). At baseline, participants completed the reward task and the CDI (see below).

Two years later, participants returned for a follow-up visit, during which time STRAIN and CDI data were collected (n = 245; M_{age} = 14.4, s.d. = 1.8). Participants who completed both the baseline visit and follow-up visit were younger than those who only completed the baseline visit (M_{diff} = 0.52, t(303) = 2.06, p = 0.040). Importantly, these two groups did not differ on baseline CDI or RewP scores (ps = 0.667).

At the follow-up visit, participants were predominantly White (87%) with the remaining participants self-identifying as African American (6.5%), American Indian/Alaskan Native (0.8%), or Other (5%). Nine percent of the sample at the follow-up visit reported being Hispanic. All participants also completed the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) at baseline. Of the 245 participants included in the final sample, 6 individuals (~2.4% of the sample) met the diagnostic criteria for MDD according to the Diagnostic Statistical Manual of Mental Disorders-IV. The average household income of the final sample was $127 190 (s.d. = $75 159). All participants and their parents provided informed assent and consent, respectively, as approved by the Institutional Review Board at Stony Brook University.

Stress and Adversity Inventory for Adolescent STRAIN

Lifetime stressor exposure was assessed at the follow-up session (n = 245) using the Adolescent STRAIN (Slavich et al., 2019; see https://www.strainsetup.com). Participants reported on 33 acute life events and 42 chronic difficulties for a total of 75 stressors that spanned 12 primary life domains (i.e. Housing, Education, Work, Treatment/Health, Marital/Partner, Reproduction, Financial, Legal/Crime, Other Relationships, Guardian/Parent Relationships, Death, Life-Threatening Situations) and five core social-psychological characteristics (i.e. Interpersonal Loss, Physical Danger, Humiliation, Entrapment, Role Change/Disruption). For each stressor endorsed, the STRAIN generates additional questions assessing the stressor's severity, frequency, timing of exposure, and duration.

Acute life events (i.e. acute stressors) in the STRAIN system are defined as stressors typically lasting a few days, such as learning of a death, getting fired, or being physically attacked (Slavich et al., 2019). Chronic difficulties (i.e. chronic stressors), in turn, typically last a minimum of one month though many last longer, such as persistent educational, housing, or financial problems (Slavich et al., 2019). Based on participants' responses, the STRAIN produces cumulative lifetime stressor indices summarizing each individual's total lifetime stressor exposure (i.e. number of stressors experienced) and severity, the latter of which is based on a five-point Likert stressor severity scale. These scores can then be calculated separately for acute and chronic stressors. The STRAIN assesses a variety of stressors across 12 life domains. Higher scores always represent greater lifetime stressor exposure. The Adolescent STRAIN has been validated against clinical, cognitive, and behavioral outcomes (Slavich et al., 2019) as has its sister instrument, the Adult STRAIN (Banica, Sandre, Shields, Slavich, & Weinberg, 2020, 2021; Cazassa, da Oliveira, Spahr, Shields, & Slavich, 2020;

Slavich & Shields, 2018; Sturmbauer, Shields, Hetzel, Rohleder, & Slavich, 2019).

Reward task

The doors task is a simple monetary reward paradigm in which participants are presented with two doors displayed side-by-side and are instructed to select the door they believe will yield a prize (i.e. money) using the left or right mouse button. Once participants make a decision, a fixation cross is presented for 1500 ms followed by feedback indicating whether they won (i.e. green arrow pointing upwards signifies +$0.50) or lost (i.e. red arrow pointing downwards signifies −$0.25); this feedback was presented for 2000 ms. Following each trial, text on the screen instructed participants to 'Click for next round,' followed by a fixation cross presented for 1000 ms. There was a total of 30 gain and 30 loss trials, presented pseudorandomly using Presentation version 17.0 (Neurobehavioral Systems, Albany, CA). Participants were told they had a chance to earn up to $15; all participants were given $8 at the end of the task.

Children's Depression Inventory (CDI)

The CDI assesses depressive symptoms over the last two weeks and has been well-validated in children between 7 and 17 years old (Kovacs, 1992). It consists of 27 items rated on a 3-point Likert scale ranging from 0 to 2, with 0 indicating an absence of a symptom and 2 indicating the definite presence of the symptom. Total scores range from 0 to 54, with higher scores indicating greater depressive symptom severity. Participants completed the CDI at baseline (n = 305; α = 0.89) and two years later (n = 255; α = 0.90).

EEG processing

Continuous EEG data were recorded while participants completed the doors task using the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands) using an elastic cap containing 34 electrode sites placed according to the 10/20 system (i.e. 32 channels plus Iz and FCz). Facial electrodes were placed above and below the left eye, and near the outer canthi of the left and right eyes to monitor horizontal and vertical electrooculographic activity. Two additional electrodes were placed on the left and right mastoids. The EEG signal was pre-amplified at the electrode to improve signal-to-noise ratio, and data were digitized at a 24-bit resolution with a sampling rate of 1024 Hz using a low-pass fifth-order sinc filter with a half-power cutoff of 204 Hz. Active electrodes were measured online with reference to a common mode sense active electrode constructing a monopolar channel.

EEG data were processed offline using BrainVision Analyzer 2.1 (Brain Products, Gilching, Germany). Raw EEG data were re-referenced to the average of the left and right mastoids. The re-referenced data were filtered from 0.1 Hz to 30 Hz using a 2nd order filter. The EEG data were then segmented from −200 ms prior to the onset of feedback and up to 1000 ms following feedback. Eyeblinks and ocular movement correction was performed using the Gratton, Coles, and Donchin (1983) regression-based method. Prior to averaging the data as a function of feedback type, segments containing a voltage greater than 50 μV between consecutive sample points, a voltage difference of 300 μV within a segment, or a maximum voltage difference of less than 0.5
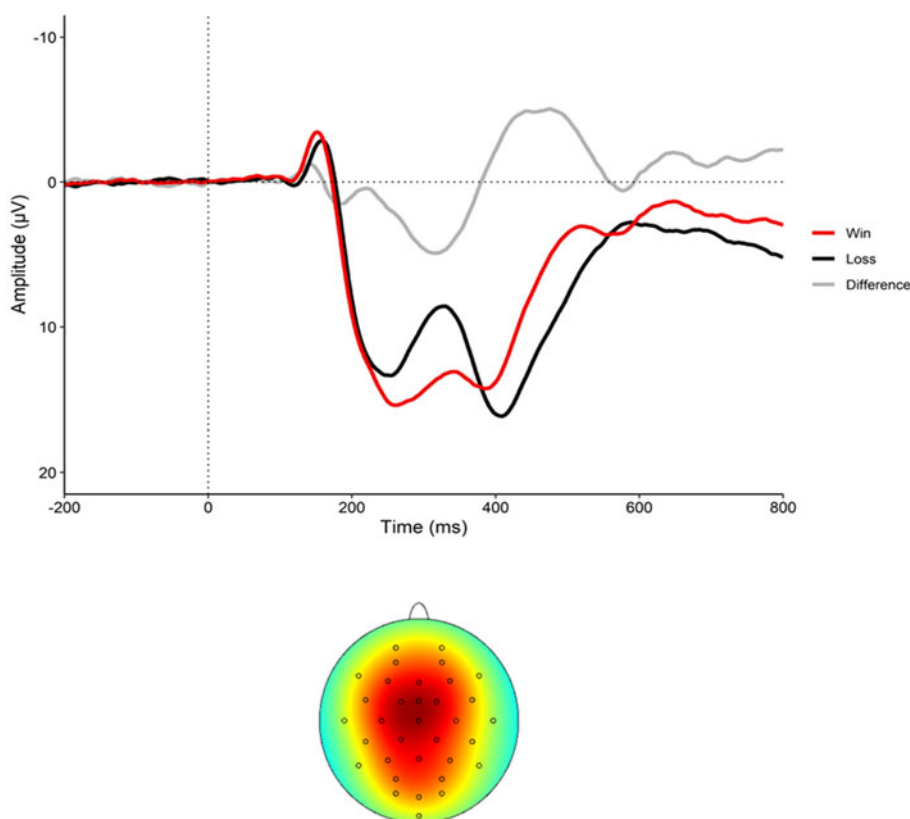
Fig. 1. The event-related potential (ERP) to wins (red) and losses (black) as well as the difference waveform (RewP) at electrode FCz (top graph) and the scalp topography (bottom graph) (*N* = 245).

µV within 100-ms intervals were identified as artifacts and automatically rejected. The 200-ms pre-feedback interval was used for baseline correction.

RewP quantification

The RewP was calculated as the mean activity within a 100-ms time window around the most positive peak of the gain (M_{trials} = 29.3; S.D. = 1.8) minus loss (M_{trials} = 29.2; S.D. = 1.9) difference waveform extracted from a 200 ms to 400 ms time window at FCz for each participant (Burani et al., 2021). No participants were excluded for having a low number of trials.

Data analysis

All analyses were conducted in R version 4.0.2 (R Core Team, 2020). First, bivariate Pearson correlations were conducted to determine associations between the Adolescent STRAIN variables, Baseline RewP, Baseline Age, and CDI scores at baseline and follow up using the *psych* R package (Revelle, 2020). Internal consistency was calculated using the *Psychometric* package (Fletcher, 2010). To test our primary hypothesis, a multiple linear regression was conducted. CDI scores at follow up were predicted from Baseline RewP, Baseline Age, Baseline CDI scores, Lifetime Acute Stressor Exposure, Lifetime Chronic Stressor Exposure, the Lifetime Acute Stressor Exposure × Baseline RewP interaction, and the Lifetime Chronic Stressor Exposure × Baseline RewP interaction. All variables were mean-centered in the regression analyses. For the multiple linear regression, we used the *stats* R package (R Core Team, 2020), and follow-up simple slopes analyses were performed and plotted using the *interactions* package (Long,

2019). The Johnson-Neyman technique was used to identify the region of significance wherein the simple slope analyses showed a significant interaction (Johnson & Neyman, 1936). The Johnson-Neyman plot thus provides values of the moderator for which the relation between the predictor and outcome are both non-significant and significant. The final sample size for the regression analyses was 245.

To test for the robustness of any significant effect observed, we also performed sensitivity analyses that included household income and ethnicity as additional covariates. The household income variable was recoded into a categorical variable prior to being entered into the regression such that an increase of $ 30 000 placed participants into a higher category (e.g. 0 = less than $29900, 1 = between 29 900 and 59 000, etc., up to 299 900). All participants who reported an income of more than $ 299 900 were all placed in one category. Given that the sample consisted largely of White participants, ethnicity was dichotomized into White (0) and non-White (1). The *car* R package was used to generate the variance inflation factor (Fox, 2020) which indicates the degree of multicollinearity.

Results

Descriptive statistics

Figure 1 displays the event-related potential to wins and losses as well as the RewP (i.e. difference waveform) and the scalp topography of the sample. Demographics for the sample, and descriptives of all study variables, are presented in Table 1. Correlations between the variables are presented in Table 2. Participants experienced an average of 13.9 lifetime stressors (S.D. = 10.63; range 0–56), with 8.1 acute stressors (S.D. = 6.52; range 0–34) and 5.8 chronic stressors (S.D. = 4.90; range 0–28). Average RewP amplitude at baseline was

Table 1. Descriptives for the study variables, and demographics of the sample (*N* = 245).

Variable	*M* (s.d.)	Min–Max	Skewness
Lifetime total stressor exposure (STRAIN)	13.9 (10.6)	0–56	1.21
Lifetime chronic stressor exposure (STRAIN)	5.8 (4.9)	0–28	1.06
Lifetime acute stressor exposure (STRAIN)	8.1 (6.5)	0–34	1.38
Baseline RewP (μV)	5.5 (6.2)	−16.70 to 21.37	−0.06
Baseline age	12.3 (1.8)	8.01–14.99	−0.52
Baseline depressive symptoms (CDI)	6.6 (6.4)	0–31	1.28
Follow-up depressive symptoms (CDI)	6.6 (6.5)	0–36	1.54
Ethnicity	N		
White	203		
African American	13		
Hispanic	11		
Other	11		
Income	*M* = $127 190 (s.d. = $75 159)		

STRAIN, Stress and Adversity Inventory; RewP, Reward Positivity; CDI, Children's Depression Inventory.
Note: Of the 245 participants in the final sample, data on ethnicity were available for 238 participants.

5.53 μV (s.d. = 6.2). Of note, the RewP did not correlate with any lifetime stressor exposure variables (see Table 2).

Lifetime chronic and acute stressor exposure

We examined whether lifetime acute stressor exposure and lifetime chronic stressor exposure interacted with baseline RewP to predict depressive symptoms at follow up, controlling for baseline depressive symptoms and baseline age (Table 3). Higher baseline depressive symptoms and greater lifetime chronic stressor exposure predicted higher depressive symptoms at follow up. Baseline RewP, baseline age and lifetime acute stressor exposure, however, did not predict elevations in depressive symptoms at follow up. Finally, lifetime acute, but not chronic, stressor exposure interacted with baseline RewP to predict greater depressive symptoms at follow up. Simple slopes analyses indicated that lifetime acute stressor exposure predicted higher depressive symptoms at follow up for youth with a low (−1 s.d.) but not average or high (+1 s.d.) RewP (see Table 4 and Fig. 2).

Online Supplementary Table S1 contains a multiple regression model predicting depressive symptoms at follow up with the same predictors as the main regression model but, in addition, includes household income and ethnicity as covariates. With household income and ethnicity included, lifetime acute stressor exposure and the RewP interacted to predict depressive symptoms at follow up at a trend level. These results suggest that income and ethnicity may partially explain this interactive effect on depression.

Lifetime chronic and acute stressor severity

Online Supplementary Table S2 contains the results of a multiple regression model predicting CDI scores at follow up from the lifetime acute stressor severity and lifetime chronic stressor severity variable while controlling for baseline RewP, baseline CDI and baseline age. This analysis was conducted to examine the specificity of effects for stressor exposure *v.* stressor severity. Baseline age, baseline RewP, and lifetime acute stressor severity were not significant predictors of depression at follow up; however, greater baseline depressive symptoms and lifetime chronic stressor severity predicted higher follow-up depressive symptoms. Finally, lifetime acute, but not chronic, stressor severity interacted with the RewP to predict increases in depressive symptoms at follow up such that lifetime acute stressor severity predicted depressive symptoms but only for those with a blunted RewP (see online Supplementary Table S2a). Therefore, the results for lifetime acute stressor exposure and severity were similar.

Residualized wins and residualized losses

To examine whether these results were driven by wins or losses, we used residualized difference scores for both wins and losses (Meyer, Lerner, De Los Reyes, Laird, & Hajcak, 2017) in separate regression models. Overall, the results indicated that only residualized wins interacted with lifetime acute stressor exposure to predict depressive symptoms at follow up. In sum, therefore, these data suggest that the results may be driven by neural responses to rewards instead of losses (see online Supplementary Tables S3, S3a and S4).

Discussion

The present study examined whether stressors occurring across the life course moderated the association between the RewP and longitudinal increases in depressive symptoms in a large sample of 8-to-14-year-old girls. We found that exposure to chronic (but not acute) stressors over the lifespan predicted increases in depressive symptoms over time. As hypothesized, however, only acute lifetime stressor exposure was moderated by the RewP, such that increases in depressive symptoms over the two-year study period were evident only for youth exhibiting a blunted RewP.

These results are consistent with diathesis-stress models of depression (Monroe & Simons, 1991) insofar as acute life stressors appeared to be particularly depressogenic for youth with blunted reward processing. These findings are also consistent with prior

Table 2. Correlations among the main study variables

	1.	2.	3.	4.	5.	6.	7.
Baseline age	1						
Baseline RewP	0.12*	1					
Baseline depressive symptoms (CDI)	0.24**	0.06	1				
Lifetime total stressor exposure (STRAIN)	0.29**	−0.01	0.48**	1			
Lifetime chronic stressor exposure (STRAIN)	0.30**	0.01	0.48**	0.91**	1		
Lifetime acute stressor exposure (STRAIN)	0.25**	−0.03	0.42**	0.95**	0.72**	1	
Follow-up depressive symptoms (CDI)	0.31**	0.02	0.60**	0.58**	0.27**	0.50**	1

STRAIN, Stress and Adversity Inventory; RewP, Reward Positivity; CDI, Children's Depression Inventory.
**$p < 0.001$. *$p < 0.05$. Pearson's r correlations are reported.

Table 3. Regression results using depressive symptoms at follow up as the dependent variable predicted from lifetime acute stressor exposure, lifetime chronic stressor exposure, baseline age, RewP, depressive symptoms, the lifetime acute stressor exposure × baseline RewP interaction, and the lifetime chronic stressor exposure × baseline RewP interaction

	b			
Predictor	b	95% CI [LL to UL]	VIF	Model fit
(Intercept)	6.59**	[6.00 to 7.19]	–	
Baseline RewP	−0.06	[−0.16 to 0.04]	1.06	
Baseline age	0.31^	[−0.05 to 0.66]	1.15	
Baseline depressive symptoms (CDI)	0.38**	[0.28 to 0.49]	1.36	
Lifetime acute stressor exposure (STRAIN)	0.06	[−0.07 to 0.19]	2.18	
Lifetime chronic stressor exposure (STRAIN)	0.44**	[0.26 to 0.62]	2.33	
Lifetime acute stressor exposure × baseline RewP	−0.02*	[−0.05 to −0.001]	2.14	
Lifetime chronic stressor exposure × baseline RewP	0.01	[−0.02 to 0.04]	2.13	
				$F(7, 237) = 33.37$**
				$R^2 = 0.482$**
				95% CI [0.35, 0.53]

RewP, Reward Positivity; CDI, Children's Depression Inventory; STRAIN, Stress and Adversity Inventory; b, unstandardized regression weights; CI, 95% confidence interval; LL and UL indicate the lower and upper limits of the CI, respectively; VIF, Variance Inflation Factor. ^ = $p < 0.10$; * = $p < 0.05$; ** = $p < 0.01$.

Table 4. Simple slopes of the relation between lifetime acute stressor exposure (STRAIN) and depression severity (CDI) scores two years later at different levels of baseline RewP

Lifetime acute stressor exposure × RewP	b	Lower CI	Upper CI	p
RewP (−1 s.d.)	0.22	0.02	0.41	0.031***
RewP (M)	0.06	−0.07	0.19	0.372
RewP (+1 s.d.)	−0.10	−0.30	0.11	0.357

RewP, Reward Positivity; CI, 95% confidence interval.
***$p < 0.001$.
Note: Beta coefficients are adjusted for baseline depressive symptoms and baseline age.

studies, which have found that life stress and the RewP interact to predict depression (Burani et al., 2021; Goldstein et al., 2020). Our results add to this prior work by suggesting that this interaction between life stressor exposure and reward functioning may be evident only for acute stressors occurring over the life course. The RewP may thus be a stress vulnerability marker insofar as individuals with a blunted RewP exhibit less responsivity to reward and reward-seeking behavior (Bress & Hajcak, 2013), which may lead to a greater impact of acute stressor exposure through less engagement with rewarding activities and stimuli in the environment.

One possible biological pathway by which stressor exposure may impact reward processing leading to depression involves the HPA axis. When activated, the HPA axis produces corticotropin-releasing factor (CRF) and glucocorticoids. Several brain regions implicated in reward processing are rich in receptors for CRF and glucocorticoids, including the prefrontal cortex, the ventral striatum, and the ventral tegmental area (Novick et al., 2018; Van Pett et al., 2000). Increased CRF in the reward system may in turn attenuate dopamine transmission leading to reduced reward-related behavior (Bryce & Floresco, 2016). A second possibility involves the immune system. Greater lifetime stressor exposure has been found to predict higher levels of inflammatory activity (Byrne et al., 2021), and a core biobehavioral effect of inflammation involves the reduction of reward-related neural signaling and behavior (Felger et al., 2016; Slavich, 2020, 2022). Additional research is needed to investigate these and other biological pathways that may link greater lifetime stressor exposure with reward-related neural function and depression.
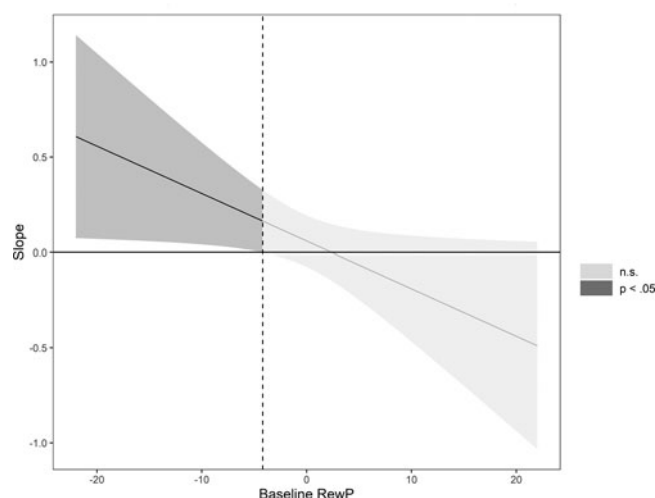
Fig. 2. Conditional effect of lifetime acute stressor exposure (STRAIN) on follow-up depressive severity (CDI). Johnson-Neyman plot of the Lifetime Acute Stressor Exposure × Reward Positivity interaction predicting depressive symptom scores on the Children's Depression Inventory at follow up. The dotted line indicates the value of the RewP where the confidence intervals cross zero. Lifetime Acute Stressor Exposure predicted depressive symptom scores at follow up at amplitudes of RewP below the dotted line. The shaded area represents the confidence interval of the conditional effect, with the dark gray area representing values of Baseline RewP for which the effect is significant, and the light gray area representing values of Baseline RewP for which the effect is non-significant. Baseline RewP, Age, CDI scores and Lifetime Chronic Stressor Exposure were included as covariates ($N = 245$).

Consistent with prior research, these results also demonstrate that a robust RewP may potentially confer resilience to stress (Burani et al., 2021; Goldstein et al., 2020; Pegg et al., 2019). Individuals with greater acute lifetime stressor exposure did not exhibit increases in depressive symptoms two years later if they had a larger RewP response to reward. This finding suggests that youth who respond to rewarding stimuli robustly may be relatively protected against the depressogenic effects of life stress. Importantly, hypersensitivity to rewards may also function as a risk factor for other forms of psychopathology. Increased reward processing, for example, could lead to excessive approach-related affect that is characteristic of hypomania and mania (Alloy & Nusslock, 2019; Nusslock, Young, & Damme, 2014). Nevertheless, future research may benefit from developing interventions that aim to enhance reactivity to pleasant stimuli/rewards among those with a blunted RewP, which may increase resiliency – something that is currently done in cognitive behavior therapy (e.g. promoting behavioral activation, scheduling pleasurable activities) but which could be perhaps further emphasized for those with deficient reward system functioning.

Several limitations of this study are worth noting. First, we only sampled adolescent girls given their relatively high risk for developing depression during this developmental period. Moreover, this sample was largely White. Future research should thus examine if these results generalize across both sexes and genders as well as to older adolescents, adults, and racially and ethnically diverse populations. This is particularly important as the nature of depressive symptoms differs across ethnicities (Assari & Moazen-Zadeh, 2016; Wight, Aneshensel, Botticello, & Sepúlveda, 2005) as well in adolescents v. adults, who display higher levels of anhedonia (Rice et al., 2019). Therefore, the age range and racial/ethnic composition of this sample may limit

the depressive symptoms that were assessed. Along these same lines, additional research is needed to examine the possibility that any sex and/or gender differences detected in the future may vary as a function of biological and/or social factors that have been associated with depression. Second, participants were recruited from the community and thus exhibited relatively few major life stressors and depressive symptoms. It should be noted that even modest elevations in depressive symptoms in this age range are strong predictors of subsequent increases in depressive symptoms or onset of MDD (Klein, Shankman, Lewinsohn, & Seeley, 2009). Nevertheless, future studies are needed to study these processes in at-risk and depressed populations. Specifically, recruiting individuals who have experienced more lifetime stressors, or who are at risk for developing depression, would permit an examination of whether such stressors interact with blunted reward processing to predict caseness of MDD, rather than increases in depressive symptoms. In addition, future studies could investigate whether the timing of acute or chronic stressors interacts with the RewP to predict depressive symptoms.

Third, future studies are needed to examine the time course characteristics of both lifetime acute stressor exposure and blunted reward processing, and how they interact to impact the development of depressive symptoms. Fourth, we used baseline RewP as predictor of changes in depressive symptoms over time. This approach has both limitations and benefits. Regarding the limitations, although clinical interview data suggest that this sample was relatively healthy, it is unknown whether these adolescents experienced depressive symptoms prior to the baseline visit that may have impacted their RewP. Future longitudinal research is thus needed to examine this issue. Fifth, retrospective self-reporting of life stressors can be biased by depressive symptoms, which can make it difficult to determine if high lifetime stressor scores are attributable to experiencing more stressors v. having more depressive symptoms (Harkness & Monroe, 2016). We addressed this issue by using an instrument for assessing stressor exposure (i.e. the STRAIN), which is not sensitive to negative mood or social desirability (Slavich & Shields, 2018).

Notwithstanding these points, the present study is the first to demonstrate that greater lifetime acute stressor exposure interacts with the RewP to predict longitudinal increases in depressive symptoms over a two-year period. Framed in terms of resilience, individuals with an increased RewP appeared to be protected from the depressogenic effects of acute life stressor exposure. In contrast with our prior work, we did not find a main effect of RewP in prospectively predicting increases in depressive symptoms (Nelson et al., 2016). However, the present study differed in several ways, including a different age range and different symptom measures (i.e. interview-based v. self-report), and a longer duration between baseline and follow up. In doing so, the present study extends our understanding of how the RewP interacts with lifetime stressor exposure to predict changes in depression over time. Collectively, these data provide novel evidence regarding possible pathways to depression, insofar as they suggest that adolescents who experience greater acute stressor burden over the lifespan, and who do not exhibit a strong neural response to reward, may be at the greatest risk of developing depression.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291722001386.

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