Altered reward processing following an acute social stressor in adolescents

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Abstract

Altered reward processing is a transdiagnostic factor implicated in a wide range of psychiatric disorders. While prior animal and adult research has shown that stress contributes to reward dysfunction, less is known about how stress impacts reward processing in youth. Towards addressing this gap, the present study probed neural activation associated with reward processing following an acute stressor. Healthy adolescents (n = 40) completed a clinical assessment, and fMRI data were acquired while participants completed a monetary guessing task under a no-stress condition and then under a stress condition. Based on prior literature, analyses focused on a priori defined regions-of-interest, specifically the striatum (win trials) and dorsal anterior cingulate cortex [dACC] and insula (loss trials). Two main findings emerged. First, reward-related neural activation (i.e., striatum) was blunted in the stress relative to the no-stress condition. Second, the stress condition also contributed to blunted neural response following reward in loss-related regions (i.e., dACC, anterior insula); however, there were no changes in loss sensitivity. These results highlight the importance of conceptualizing neural vulnerability within the presence of stress, as this may clarify risk for mental disorders during a critical period of development.

Introduction

Adolescence is characterized by heightened reward sensitivity [1], increased stress exposure [2], and high rates of mental disorders [3]. Aberrant reward processing is implicated in a range of mental disorders including major depressive disorder [4, 5], post-traumatic stress disorder [6], and schizophrenia [7], and prior research also has demonstrated that stress robustly predicts the onset and severity of these disorders [8]. Building on these findings, recent research has sought to clarify how stress may impact reward functioning to improve our understanding of disorder etiology [9–11].
In animal studies testing the impact of physical stress (e.g., foot shock), results showed that rats exhibited reduced consummatory (i.e., decreased saccharine consumption; [12] and exploratory [13, 14] behaviors. Similarly, acute social stress (e.g., social defeat) led to a decrease in reward seeking behavior in adolescent rats [15]. In humans, early life adversity has been associated with reward dysfunction, as evidenced by blunted activation during both reward anticipation in the dorsal striatum [16, 17] and reward receipt in the ventral striatum [18–20]. The impact of chronic stress through active military service also contributed to reduced nucleus accumbens (i.e., ventral striatum) activation during reward receipt [21]. Using a physical stressor (cold pressor), Porcelli and colleagues (2012) demonstrated that acute stress decreased activation to monetary reward in the dorsal striatum and orbitofrontal cortex among healthy adults [22]. Collectively, animal and human studies show an association between stress and blunted behavioral and neural response to reward anticipation and consumption. However, these studies operationalize reward dysfunction following stress without considering baseline levels of reward processing. Probing changes in reward processing—by examining patterns of reward function before and after acute stress—may afford new insights into the development of mental disorders.

Towards addressing this gap, Kumar and colleagues administered a monetary incentive delay task to healthy adults while acquiring functional magnetic resonance imaging (fMRI) data under no-stress and stress conditions [23]. After the initial task administration, participants received acute negative feedback and then, completed the task a second time. Results showed reduced activation in the putamen and caudate during reward receipt following stress relative to no-stress, suggesting that stress can elicit anhedonic-like activation patterns. Although this study expands past research, little is known about how stress may elicit changes in reward function among adolescents. This downward extension is particularly important, as adolescence is a sensitive period for identifying emerging individual differences in reward functioning. Namely, adolescence marks a period of substantial changes in incentive-seeking behavior, characterized by a greater drive to approach pleasant experiences and potentially greater engagement in risk-taking behaviors [24]. Moreover, adolescence also constitutes a period of greater reliance on peer relationships [25] and greater sensitivity to peer rejection [26]. Taken together, understanding changes in reward processing as a function of social stressors may clarify potential vulnerability to the emergence of psychiatric symptoms.

The present study tested whether acute social stress negatively impacted reward-related neural functioning in healthy adolescents. Participants completed a monetary reward task [27, 28] under no-stress and stress conditions. Additionally, we implemented an ecologically valid social task [29, 30] in which participants believed they were being accepted or rejected by peers. This task was used as an acute social stressor, as participants were informed they were rejected more than other teens participating in the study. Consistent with prior research probing baseline reward function, (e.g., [31, 32]) we hypothesized that following acute social stress, adolescents would exhibit reduced activation in regions that have been found to respond to win feedback (e.g., stratum). Additionally, previous research has shown that loss feedback is associated with dACC and anterior insula activation [33–35], and therefore, we hypothesized that adolescents would exhibit increased activation in loss-related regions following stress.

Materials and method

Participants

The original sample included 61 adolescents from the greater Boston area. Data from 21 adolescents were excluded due to: (a) head movement (> 2 mm) or artifacts (n = 13), (b) < 10% change in affect following stress (n = 4), or (c) scanner malfunction (n = 4). The final sample...
included 40 adolescents (75% female) aged 12–14 years (M = 13.20, SD = 0.72; Tanner Stage: M = 3.22, SD = 0.48). The ethnic distribution was: 82.5% Caucasian, 7.5% Asian, 7.5% multiracial, and 2.5% Black or African American. Participants were right-handed, native English speakers, with normal or corrected to normal vision. Exclusion criteria included lifetime mental disorders, loss of consciousness (> 5 minutes), a neurological disease, or MRI contraindication. Excluded participants did not differ from the final sample on sex, or ethnicity (ps > .14). Relative to the final sample, excluded participants were younger (t(60) = -2.87, p = .006).

Procedure

The Partners Institutional Review Board approved study procedures. Adolescents assented and legal guardians provided written consent in accordance with the Declaration of Helsinki. The baseline assessment included two study visits, occurring within 1–2 weeks of each other (M = 7.30 days, SD = 3.48). During the initial study visit, participants completed a clinical interview and self-report assessments of pubertal status. Adolescents also completed the first part of the Chatroom Task. Eligible participants completed a second visit in which fMRI data were acquired while completing the Guessing Task. In the scanner, participants completed one run of the Guessing Task (no-stress condition), followed by the Chatroom Task (the social stressor), and then a second administration of the Guessing Task (stress condition).

Clinical instruments

The Kiddie-Schedule for Affective Disorders and Schizophrenia-Present (K-SADS-PL; [36]) is a semi-structured interview assessing lifetime DSM-IV disorders in youth. Interviews were recorded, and 20% of interviews were randomly selected to assess inter-rater reliability (κ = 1.00).

The Tanner Staging Questionnaire (TSQ; [37]) is a 5-item self-report assessment of physical development.

Experimental task

The Guessing Task [27] is designed to assess neural response to win and loss feedback and has been shown to reliably activate reward- and loss-related regions. For each trial, there was a jittered intertrial interval, which showed a fixation cross for 1300–9100 ms. Then, participants were presented with two identical doors and were instructed to select which door (left or right) they thought contained a prize as quickly as possible by pressing the left or right button on the response box, respectively, (doors presented up to 3900 ms). After the selection, a jittered fixation cross appeared for 1300–7800 ms, and then, feedback was presented for 1300 ms: (a) green “↑” for win or (b) red “↓” for loss. On each trial, the participant either won $0.50 or lost $0.25, and the participant was informed that they would keep the sum earned from the experiment. Unbeknownst to the participant, the outcome was fixed, as they won 24 trials and lost 24 trials in pseudorandom order, completing a total of 48 trials. For the current study, participants completed the Guessing Task under both no stress and stress conditions.

Stress manipulation

The Chatroom Task [29, 30] was designed to simulate adolescent social interactions and to probe differential response to peer feedback (i.e., acceptance versus rejection). E-Prime (Psychological Software Tools, Pittsburgh, PA) software was used to present stimuli and record responses. In Phase 1, participants were led to believe they were participating in a study of how adolescents interact in online chatrooms. First, they created an online profile (i.e., indicating
likes, dislikes) and then, accompanying photographs of the participants were taken. Next, they viewed 60 photographs of same-aged adolescents and selected 30 adolescents they were interested and 30 they were not interested in chatting with online following a neuroimaging scan 1–2 weeks later. Participants were informed that peers from collaborating institutions would review their profiles and indicate whether they were interested (i.e., peer acceptance) or not interested (i.e., peer rejection) in chatting online with them. Of note, female participants were only presented with female peers to select, and similarly, males could only select male peers.

For Phase 2, participants received peer feedback from the 60 adolescents allegedly participating in the nationwide study while fMRI data were acquired. During each trial, the participant viewed the photograph of a “participating adolescent” (1300 ms), and a photograph caption displaying interested or not interested was used to remind the participant about the prior selection. Then, a jittered fixation cross (1300–7600 ms) was presented, followed by the peer feedback under the photograph (2600 ms). After the feedback, a jittered fixation cross (1300–5200 ms) was displayed, and the participant received a prompt, “How does this make you feel?” and was instructed to provide a rating on a visual analogue scale ranging from 0 (very bad) to 100 (very good). Feedback was provided in pseudorandom order with no more than 3 trials of the same response provided consecutively. Unbeknownst to participants, feedback was fixed, as everyone received the same number of acceptance (30 interested trials) and rejection (30 not interested trials) trials.

The stressor included two components. First, at the completion of the Chatroom Task, the screen displayed the following non-veridical feedback, “Individual Performance: Peer Acceptance (38%), Peer Rejection: 62%; Average Participant Performance: Peer Acceptance: 64%, Peer Rejection: 36%.” In addition to reading this statement aloud through the scanner intercom, study staff stated the following, “Based on the breakdown from today, it seems like you’re accepted by fewer teens compared to other teens completing the task. Additionally, you are being rejected more than other teens that have completed the selection process.” Second, to provide a rationale as to why it was necessary to repeat the Guessing Task, study staff also read the following statement to participants, “Unfortunately, your performance in the Guessing Task was below average. Remember, you earned only $12 out of a possible $24. For the data to be usable, a participant needs to earn more than $14. Thus, we’re going to need to redo this task. Please try to focus.” To determine whether the stress manipulation was effective, participants completed visual analogue scales probing affect ratings prior to entering the scanner and following the two-pronged stressor. Participants rated positive (i.e., happy, joyful) and negative (i.e., sad, upset, and discouraged) items from the Positive and Negative Symptom Schedule (PANAS; [38]) using a sliding scale ranging from 0 (not very true of me) to 100 (very true of me). To determine whether the stress manipulation was effective a participant needed to exhibit a 10% increase in negative affect or a 10% decrease in positive affect from pre- to post-stress; participants who did not exhibit changes in negative or positive affect were excluded (n = 4). On average, participants’ negative affect increased 30.6% and positive affect decreased 19.8% following the stressor (Table 1) (Fig 1). In a repeated measures ANOVA, a Time x Affect interaction emerged (Table 1) (Fig 1). In a repeated measures ANOVA, a Time x Affect interaction emerged $F(1,39) = 138.05, p = 2.20 \times 10^{-14}, \eta^2 = 0.78$. Results show that following stress, positive affect significantly decreased ($p = 3.29 \times 10^{-10}, \eta^2 = 0.89$) and negative affect

| Table 1. Positive and negative affect before and after stress (n = 40). |
|-----------------|-----------------|-----|-----|
|                  | No-Stress       | Stress | F    | p    |
|                  | M (SD)          | M (SD) |     |      |
| Positive Affect  | 78.26 (14.13)   | 57.94 (16.04) | 138.05 | 2.20 $\times 10^{-14}$ |
| Negative Affect  | 9.14 (13.73)    | 39.79 (16.51)   |  | |

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significantly increased ($p = 2.99 \times 10^{-13}$, $\eta^2 = 0.23$). Imaging data from this social stressor task will be reported in future manuscripts.

**Image acquisition and processing**

Functional MRI data were acquired on a Siemens Tim Trio 3.0 Tesla MR scanner using a 32-channel head coil at the McLean Imaging Center. For functional scans, data were acquired in an interleaved fashion using T2*-weighted gradient echo planer images (EPI), with the following parameters TR/TE: 1300/32.2ms; FOV: 212 mm; phase partial Fourier 6/8; echo spacing = 0.69ms; matrix: 64x64; 72 slices; in-plane resolution: 2mm; flip angle = 66˚; voxels 2 x 2 x 2 mm. Data were preprocessed and analyzed using SPM12 (Statistical Parametric Mapping [SPM]; http://fil.ion.u-cl.ac.uk/spm/). Preprocessing steps included: distortion and motion correction, slice timing, realignment to the mean image, coregistration to the structural image, normalization to the MNI template, and smoothing with a 4mm Gaussian kernel. The Artifact Detection Toolbox (ART; http://www.nitrc.org/projects/artifact_detect/) was
used to identify outlier scans in global signal (> ±2 SD) and movement (> 2.5 mm of movement or 2 degrees of rotation from the previous volume. Participants for whom more than 15% of the 491 volumes were removed due to movement, in either the pre-stress or post-stress run of the monetary reward task, were excluded ($n = 13$) [39]. General linear models were defined at the single-subject level with regressors corresponding to anticipation cue, decision cue, win feedback, and loss feedback trials. Contrast maps were constructed for win feedback > fixation and loss feedback > fixation. In order to reduce the influence of outliers, we chose to winsorize outlier data for each ROI; data were winsorized at 2.5 standard deviations from the mean. Approximately 2% of the data for the ROIs were winsorized.

To test a priori hypotheses that neural response to wins would decrease after stress, five 10-mm spherical regions of interest (ROIs) were created around MNI coordinates in regions previously implicated in reward processing. There are several methods by which ROIs are defined, including both anatomical and functional definitions. Anatomically defined ROIs have two significant challenges. First the specified regions may be much larger than the actual area of activation by the task. Second anatomically defined ROIs assume functional homogeneity across the region, which in many cases is an erroneous assumption [40]. These concerns would be particularly problematic with regions like the dACC and the insula included in our analyses. In order to avoid these problems, we used functional ROIs identified from prior studies of reward related regions [27, 41]. Within the ventral striatum, the left ($x = -14, y = 10, z = -8$) and right ($x = 10, y = 6, and z = -4$) ROIs were obtained from a prior publication using the same task [27]. In the dorsal striatum, coordinates for the left ($x = -16, y = 20, z = 2$) and right caudate ($x = 12, y = 20, z = 4$) were obtained [27]. The putamen did not emerge in Carlson et al., (2011), but was a region of interest in this study due to its role in stress and reward processing [32]. Thus, coordinates for the left putamen were obtained from a meta-analysis of reward related-neural networks in adults [41] and adolescents [32]. The right putamen did not emerge in the meta-analysis as a brain area commonly activated in reward-related processing, and thus was not used as an ROI in the present study. Using MarsBar [42] the left putamen ROI was defined as a 10-mm radius sphere centered at ($x = -24, y = 4, z = 6$) [41] (Fig 2A). There is approximately a 24 voxel overlap between the right ventral striatum and the right caudate, and a 54 voxel overlap between the left ventral striatum and the left caudate. No other ROIs overlap.

To probe regions associated with loss and rejection, the dorsal anterior cingulate cortex (dACC) and anterior insula ROIs were created from the same meta-analysis of regions implicated in neural networks associated with loss [41]. The dACC was defined as a 10-mm radius sphere centered at ($x = 6, y = 24, z = 34$). The left anterior insula was defined as a 10-mm radius sphere centered at ($x = -28, y = 24, z = -8$), and the right anterior insula as a 10-mm radius sphere centered at ($x = 36, y = 20, z = -6$) (Fig 2B).

**Data analytic overview**

Statistical analyses were conducted using IBM SPSS Statistics Version 21.0. In no stress and stress conditions, parameter estimates were extracted from the win > fixation contrast and loss > fixation contrast using MarsBar. To create win > loss contrasts (for both stress conditions), parameter estimates from loss > fixation were subtracted from win > fixation. For our primary analyses, a **Condition** (No-Stress, Stress) x **Valence** (Win, Loss) repeated measures analysis of variance (RMANOVA) probed whether reward processing for each ROI differed as a function of stress and included eta-squared effect sizes ($\eta^2$) where: (a) .02 – .12 = small, (b) .13 – .25 = medium, and (c) $\geq .26$ = large. Significant interactions were then decomposed. A Benjamini Hochberg correction for False Discovery Rate (FDR) applied for all tests ($q = .015$).
Results

Impact of stress on reward regions

**Left and right ventral striatum.** The Condition x Valence interaction for the left [$F(1,39) = 0.83, p = .368, \eta^2 = 0.02$] and right [$F(1,39) = 3.62, p = .064, \eta^2 = 0.09$] ventral striatum were non-significant (Table 2)(Fig 3).

**Left caudate.** A Condition x Valence interaction emerged for the left caudate [$F(1,39) = 4.47, p = .041, \eta^2 = 0.10$]; however, this analysis does not survive our FDR correction. Nevertheless, exploratory post-hoc results show that activation following wins was greater than losses in both the no-stress ($p = 1.20 \times 10^{-5}, \eta^2 = 0.39$) and stress condition ($p = .008, \eta^2 = 0.17$).

Table 2. Win- and loss-related neural activation before and after stress ($n = 40$).

| Reward-Related Regions | No-Stress Win M (SD) | No-Stress Loss M (SD) | Stress Win M (SD) | Stress Loss M (SD) | F    | p     |
|-------------------------|----------------------|-----------------------|-------------------|--------------------|------|-------|
| **Ventral Striatum**    |                      |                       |                   |                    |      |       |
| Left                    | 1.10 (0.68)          | 0.15 (0.81)           | 0.65 (0.74)       | -0.11 (0.65)       | 0.83 | .368  |
| Right                   | 0.91 (0.70)          | -0.03 (0.69)          | 0.38 (0.85)       | -0.22 (0.73)       | 3.62 | .064  |
| **Caudate**             |                      |                       |                   |                    |      |       |
| Left                    | 1.17 (0.63)          | 0.59 (0.60)           | 0.84 (0.83)       | 0.58 (0.70)        | 4.47 | .041  |
| Right                   | 1.35 (0.71)          | 0.68 (0.76)           | 1.03 (1.07)       | 0.65 (0.91)        | 2.65 | .112  |
| **Putamen**             | 0.66 (0.74)          | 0.59 (0.80)           | 0.48 (0.76)       | 0.65 (0.75)        | 2.22 | .144  |
| **Loss-Related Regions**|                      |                       |                   |                    |      |       |
| dACC                    | 2.02 (1.21)          | 2.16 (1.39)           | 1.23 (1.37)       | 2.05 (1.40)        | 8.29 | .006  |
| **Anterior Insula**     |                      |                       |                   |                    |      |       |
| Left                    | 0.84 (0.68)          | 0.70 (0.82)           | 0.24 (0.68)       | 0.49 (0.74)        | 7.48 | .009  |
| Right                   | 2.18 (1.37)          | 2.27 (1.29)           | 0.82 (1.11)       | 1.38 (1.16)        | 3.15 | .084  |

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Interestingly, within-valence effects show a decrease in activation for wins following the stressor ($p = .032, \eta^2 = 0.11$), but no change in response to loss ($p = .892, \eta^2 < .01$) (Table 2).

**Right caudate.** The $\text{Condition \times Valence}$ interaction in the right caudate [$F(1,39) = 2.65, p = .112, \eta^2 = 0.06$] was non-significant.

**Left putamen.** The $\text{Condition \times Valence}$ interaction in the left putamen [$F(1,39) = 2.22, p = .144, \eta^2 = 0.05$] was non-significant.

**Effect of stress on loss regions**

**dACC.** A $\text{Condition \times Valence}$ interaction emerged in the dACC [$F(1,39) = 8.29, p = 0.006, \eta^2 = 0.18$]. Post hoc results show that activation following win was not significantly different than activation following loss ($p = .51, \eta^2 = .01$) in the no-stress condition; however, activation to loss was significantly greater than win ($p = 2.69 \times 10^{-4}, \eta^2 = 0.30$) following stress. Within-valence effects suggest that this interaction was driven by a decrease in activation to win following stress ($p = .001, \eta^2 = 0.23$); contrary to our hypothesis, there was no significant increase in dACC response to loss after stress ($p = .54, \eta^2 = 0.06$) (Table 2).

**Left and right anterior insula.** There was a $\text{Condition \times Valence}$ interaction in the left anterior insula [$F(1,39) = 7.48, p = .009, \eta^2 = 0.16$]. There was no significant difference ($p = .237, \eta^2 = .04$) between activation following wins relative to activation following loss in the no-stress condition. While not significant, activation for loss trended toward greater than win ($p = .090, \eta^2 = 0.17$) following stress. Within-valence effects show a significant decrease in activation for win after stress ($p = .001, \eta^2 = 0.34$), but not a significant increase in activation to loss ($p = .121, \eta^2 = 0.06$) (Table 2). By contrast, the $\text{Condition \times Valence}$ interaction in the right anterior insula [$F(1,39) = 3.15, p = .084, \eta^2 = 0.08$] was non-significant.
In a RMANOVA with the win regions (left and right Caudate, left Putamen, and left and right ventral striatum), we see a main effect of Condition (no-stress, stress), $F(1,39) = 85.035$, $p = 0.000062$, $\eta^2 = 0.686$, with neural activity higher in both win and loss trials in the no-stress, relative to stress conditions. When we conducted comparable analyses in the loss regions (dACC, left and right insula), we see a main effect of Condition (no-stress, stress), $F(1,39) = 6.457$, $p = 0.015$, $\eta^2 = 0.142$, with neural activity higher in the loss trials in the no-stress, relative to stress conditions.

**Discussion**

The present study tested whether social stress impacted neural activation of regions implicated in processing wins and losses in adolescents, and two principal findings emerged. First there was a blunted pattern of neural activity in the striatum in both win and loss trials during the stress condition compared to the no-stress condition. Second, in contrast to our hypothesis, acute stress did not potentiate neural responses to losses, but instead decreased neural responses to wins in loss and rejection related regions (dACC, left anterior insula). Additionally, relative to the no-stress condition, the stress condition elicited blunted neural responses to wins in the dorsal striatum, though this finding did not survive our correction for multiple tests.

Consistent with previous research in adults [23], we found blunted striatal response to reward receipt and loss during the stress relative to no-stress condition in adolescents. This change in reward receipt and loss in response to stress may be indicative of a stress-elicited anhedonic-like pattern of neural activation. More broadly, this suggests that the experience of stress, particularly social stress, may cause diminished neural responsivity in reward-related regions, which may be a factor for diminished positive affect that often characterizes adolescent depression [43].

In regions that have been implicated with responses to losses (i.e., dACC, anterior insula), no differences emerged in neural activation following losses and wins in the no-stress condition. In contrast, following stress, we observed a greater response to loss relative to win conditions. A closer examination revealed that following stress, this effect was driven by a blunted response to wins as opposed to greater sensitivity to loss. This finding suggests that this potential vulnerability may not be a byproduct of loss sensitivity, but rather, a consequence of reduced responsiveness to positive experiences, which is broadly consistent with prior work implicating disruption of positive affective processes in stress-related disorders [43]. Moreover, this finding suggests that diminished responsivity to rewards may not be restricted to the typical neural circuitry of reward (e.g., striatum), but also may affect the responsivity within frontal regions in adolescents.

Though exploratory, acute stress contributed to blunted patterns of activation in the left dorsal striatum, a region implicated in reward-related learning [44], which is in line with prior stress exposure findings probing striatal activation in the context of stress exposure [22]. Prior research suggests that caudate activation is strongest to unpredictable rewards that are contingent on an individual’s actions [45]. Our findings of the left dorsal striatum—despite not surviving the Type I correction—may indicate a decrease in the reinforcement of goal-directed actions following stress. This interpretation would be consistent with prior work demonstrating a weaker caudate response to reward receipt in individuals with stress-related disorders (i.e., major depressive disorder) relative to healthy controls [4].

This study builds on previous investigations of stress and reward-related dysfunction in two ways. First, this study expands previous findings in adults [23] to adolescents. Prior research with adults shows that acute stressors result in decreased sensitivity to reward in reward-related regions (e.g., dorsal striatum, ventral striatum)[22, 23]. Given the heightened saliency of reward during adolescence, significant social stressors, and increased rates of
psychiatric disorders, testing the relationship between reward and interpersonal stress in adolescence is critical for understanding the development of psychopathology. Additionally, in contrast to previous work testing early life adversity or chronic stress, the pre-post study design allows us to identify changes in neural response as a direct result of interpersonal stress. Our findings provide a model by which stress may expose a vulnerability to reward-related dysfunction, thus increasing risk for psychopathology. These findings are consistent with studies demonstrating that an increase in cortisol, a marker of stress, is associated with a blunted reward-related response in healthy adults [46].

Prior research suggests that adolescents’ make poorer decisions when exposed to social or cognitive stressors. This impaired decision-making appears to be an exaggeration of their individual risk-taking profiles under no-stress conditions, thus suggesting both an individual differences and environmental effect on decision-making in adolescents [47]. Our findings extend this literature by suggesting that in adolescents, there may be changes in reward- and loss-responsivity under stress.

Findings should be interpreted in light of a few limitations. First, the ethnic distribution within this sample limits the generalizability of the findings. Additionally, the age range was restricted to 12 to 14 years old in order to reduce putative age-related effects. However, this restricted range may also limit the generalizability of these findings to younger or older youth. Second, the Guessing Task uses a fixed random sequence design, which prohibits evaluating reinforcement learning in response to reward feedback. Thus, in this study, changes in behavioral response to stimuli (e.g., response time) were not collected. However, these data could have provided additional information in regard to behavioral changes pre- and post-stress. Lewis and colleagues [48] found that when engaged in a learning condition paradigm, adults under physical stress showed a blunted response in the striatum in response to monetary gains, relative to adults in a no-stress condition. Given that these findings are in contrast to our own, it would be important to investigate learning conditions in a similar paradigm with adolescents, as there may be developmentally differences in neural response to rewards under stress during learning. Additionally, this study would have benefited from a physiological measure of stress responsivity rather than relying on self-reported changes in affect alone. Finally, the study design required the use of the Guessing Task in both the no-stress and stress conditions, leaving open the possibility of task habituation. Randomization of the task conditions was not possible in this particular design. While the repetition of this task was a critical part of our study design, it is possible that there could be a general dampening of response to the second presentation of the stimuli. Without the counterbalance it is impossible for us to know whether there were specific carryover effects.

Summary
In sum, the current findings identify how neural response to reward may change following social stress in adolescents. Building on prior work in experimental animals [12–15] and human adults [23], we illustrate the importance of conceptualizing adolescent neural vulnerability within the presence of stress, as this may clarify risk for mental disorders during a critical developmental period.

Supporting information
S1 Reward Data. Reward Data. The reward data file contains all data included in the analyses for this paper.
(SAV)
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References

1. Galvan A. The Teenage Brain: Sensitivity to Rewards. Current Directions in Psychological Science. 2013; 22(2):88–93. https://doi.org/10.1177/0963721412454137
2. Eiland L, Romeo RD. Stress and the developing adolescent brain. Neuroscience. 2013; 249:162–71. https://doi.org/10.1016/j.neuroscience.2012.10.048 PMID: 23123820
3. Merikangas KR, He JP, Burstein M, Swanson SA, Avenevoli S, Cui L, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication—Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry. 2010; 49(10):980–9. https://doi.org/10.1016/j.jaac.2010.05.017 PMID: 20855043
4. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry. 2009; 166(6):702–10. https://doi.org/10.1176/appi.ajp.2008.08081201 PMID: 19411368
5. Webb CA, Auerbach RP, Bondy E, Stanton CH, Foti D, Pizzagalli DA. Abnormal neural responses to feedback in depressed adolescents. J Abnorm Psychol. 2017; 126(1):19–31. https://doi.org/10.1037/abn0000228 PMID: 27935729
6. Sailer U, Robinson S, Fischmeister FP, Konig D, Oppenauer C, Lueger-Schuster B, et al. Altered reward processing in the nucleus accumbens and mesial prefrontal cortex of patients with posttraumatic stress disorder. Neuropsychologia. 2008; 46(11):2836–44. https://doi.org/10.1016/j.neuropsychologia.2008.05.022 PMID: 18597797
7. Strauss GP, Waltz JA, Gold JM. A review of reward processing and motivational impairment in schizophrenia. Schizophr Bull. 2014; 40(Suppl 2):S107–16.
8. Hammen C. Stress sensitivity in psychopathology: mechanisms and consequences. J Abnorm Psychol. 2015; 124(1):152–4. https://doi.org/10.1037/abn0000040 PMID: 25688441
9. Auerbach RP, Admon R, Pizzagalli DA. Adolescent depression: stress and reward dysfunction. Harv Rev Psychiatry. 2014; 22(3):139–48. https://doi.org/10.1097/HRP.0000000000000034 PMID: 24704785
10. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology. 2010; 35(1):4–26. https://doi.org/10.1038/npp.2009.129 PMID: 19812543
11. Pizzagalli DA. Depression, stress, and anhedonia: toward a synthesis and integrated model. Annual review of clinical psychology. 2014; 10:393–423. https://doi.org/10.1146/annurev-clinpsy-050212-185606 PMID: 24471371
12. Van Dijken HH, Van der Heyden JA, Mos J, Tilders FJ. Inescapable footshocks induce progressive and long-lasting behavioural changes in male rats. Physiol Behav. 1992; 51(4):787–94. PMID: 1594677
13. Enkel T, Spanagel R, Vollmayr B, Schneider M. Stress triggers anhedonia in rats bred for learned helplessness. Behav Brain Res. 2010; 209(1):183–6. https://doi.org/10.1016/j.bbr.2010.01.042 PMID: 20122969
14. Pijlman FT, Wolterink G, Van Ree JM. Physical and emotional stress have differential effects on preference for saccharine and open field behaviour in rats. Behav Brain Res. 2003; 139(1–2):131–8. PMID: 12642184
15. Rygula R, Abumaria N, Flugge G, Fuchs E, Ruther E, Havemann-Reinecke U. Anhedonia and motivational deficits in rats: impact of chronic social stress. Behav Brain Res. 2005; 162(1):127–34. https://doi.org/10.1016/j.bbr.2004.06.016 PMID: 15922073

16. Mehta MA, Gore-Langton E, Golembi N, Colvert E, Williams SC, Sonuga-Barke E. Hyporesponsive reward anticipation in the basal ganglia following severe institutional deprivation early in life. J Cogn Neurosci. 2010; 22(10):2316–25. https://doi.org/10.1162/jocn.2009.21394 PMID: 19929329

17. Dillon DG, Holmes AJ, Birk JL, Brooks N, Lyons-Ruth K, Pizzagalli DA. Childhood adversity is associated with left basal ganglia dysfunction during reward anticipation in adulthood. Biol Psychiatry. 2009; 66(3):206–13. https://doi.org/10.1016/j.biopsych.2009.02.019 PMID: 19358974

18. Hanson JL, Hariri AR, Williamson DE. Blunted Ventral Striatum Development in Adolescence Reflects Emotional Neglect and Predicts Depressive Symptoms. Biol Psychiatry. 2015; 78(9):598–605. https://doi.org/10.1016/j.biopsych.2015.05.010 PMID: 26092778

19. Kamkar NH, Lewis DJ, van den Bos W, Morton JB. Ventral striatal activity links adversity and reward processing in children. Dev Cogn Neurosci. 2017; 26:20–7. https://doi.org/10.1016/j.dcn.2017.04.002 PMID: 28436832

20. Hanson JL, Albert D, Iselin AM, Carre JM, Dodge KA, Hariri AR. Cumulative stress in childhood is associated with blunted reward-related brain activity in adulthood. Soc Cogn Affect Neurosci. 2016; 11(3):405–12. https://doi.org/10.1093/scan/nsv124 PMID: 26443679

21. Admon R, Lubin G, Rosenblatt JD, Stem O, Kahn I, Assaf M, et al. Imbalanced neural responsivity to risk and reward indicates stress vulnerability in humans. Cereb Cortex. 2013; 23(1):28–35. https://doi.org/10.1093/cercor/bhs369 PMID: 22291028

22. Porcelli AJ, Lewis AH, Delgado MR. Acute stress influences neural circuits of reward processing. Front Neurosci. 2012; 6:157. https://doi.org/10.3389/fnins.2012.00157 PMID: 22315822

23. Kumar P, Berghorst LH, Nickerson LD, Dutra SJ, Goer FK, Greve DN, et al. Differential effects of acute stress on anticipatory and consummatory phases of reward processing. Neuroscience. 2014; 266:1–12. https://doi.org/10.1016/j.neuroscience.2014.01.058 PMID: 24508744

24. Somerville LH, Jones RM, Casey BJ. A time of change: behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. Brain Cogn. 2010; 72(1):124–33. https://doi.org/10.1016/j.bandc.2009.07.003 PMID: 19695759

25. Larson R, Richards MH. Daily companionship in late childhood and early adolescence: changing developmental contexts. Child Dev. 1991; 62(2):284–300. PMID: 2055123

26. Blakemore SJ, Mills KL. Is adolescence a sensitive period for sociocultural processing? Annu Rev Psychol. 2014; 65:187–207. https://doi.org/10.1146/annurev-psych-010213-115202 PMID: 24016274

27. Carlson JM, Foti D, Mujica-Parodi LR, Harmon-Jones E, Hajcak G. Ventral striatal and medial prefrontal BOLD activation is correlated with reward-related electrocortical activity: a combined ERP and fMRI study. Neuroimage. 2011; 57(4):1608–16. https://doi.org/10.1016/j.neuroimage.2011.05.037 PMID: 21624476

28. Dunning JP, Hajcak G. Error-related negativities elicited by monetary loss and cues that predict loss. Neuroreport. 2007; 18(17):1875–8. https://doi.org/10.1097/01.wnr.0b013e3282f05b0 PMID: 18090330

29. Guyer AE, McClure-Tone EB, Shiffrin ND, Pine DS, Nelson EE. Probing the neural correlates of anticipated peer evaluation in adolescence. Child Dev. 2009; 80(4):1000–15. https://doi.org/10.1111/j.1467-8624.2009.01313.x PMID: 19630890

30. Guyer AE, Choate VR, Pine DS, Nelson EE. Neural circuitry underlying affective response to peer feedback in adolescence. Soc Cogn Affect Neurosci. 2012; 7(1):81–92. https://doi.org/10.1093/scan/nss043 PMID: 21828112

31. Wake SJ, Izuma K. A common neural code for social and monetary rewards in the human striatum. Soc Cogn Affect Neurosci. 2017; 12(10):1558–64. https://doi.org/10.1093/scan/nsx092 PMID: 28985408

32. Silverman MH, Jedd K, Luciana M. Neural networks involved in adolescent reward processing: An activation likelihood estimation meta-analysis of functional neuroimaging studies. NeuroImage. 2015; 122:427–39. https://doi.org/10.1016/j.neuroimage.2015.07.083 PMID: 26254587

33. Holroyd CB, Nieuwenhuis S, Yeung N, Nystrom L, Mars RB, Coles MG, et al. Dorsal anterior cingulate cortex shows fMRI response to internal and external error signals. Nature neuroscience. 2004; 7(5):497–8. https://doi.org/10.1038/nn1238 PMID: 15097995

34. Gehring WJ, Willoughby AR. The medial frontal cortex and the rapid processing of monetary gains and losses. Science. 2002; 295(5563):2279–82. https://doi.org/10.1126/science.1066893 PMID: 11910116

35. Galvan A, Hare TA, Davidson M, Spicer J, Glover G, Casey BJ. The role of ventral frontostriatal circuitry in reward-based learning in humans. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2005; 25(38):8650–6.
36. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997; 36(7):980–8. https://doi.org/10.1097/00004583-199707000-00021 PMID: 9204677

37. Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr. 1985; 107(3):317–29. PMID: 3875704

38. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol. 1988; 54(6):1063–70. PMID: 3397865

39. Fassbender C, Mukherjee P, Schweitzer JB. Minimizing noise in pediatric task-based functional MRI; Adolescents with developmental disabilities and typical development. NeuroImage. 2017; 149:338–47. https://doi.org/10.1016/j.neuroimage.2017.01.021 PMID: 28130195

40. Poldrack RA. Region of interest analysis for fMRI. Soc Cogn Affect Neurosci. 2007; 2(1):67–70. https://doi.org/10.1093/socneu/nsm006 PMID: 18985121

41. Liu X, Hairston J, Schrier M, Fan J. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. Neuroscience and biobehavioral reviews. 2011; 35(5):1219–36. https://doi.org/10.1016/j.neubiorev.2010.12.012 PMID: 21185861

42. Brett M, Anton, J., Valabregue, R., Polie, J. Region of interest analysis using an SPM toolbox. International Conference on Functional Mapping of the Human Brain; June 2–6, 2002; Sendai, Japan2002.

43. Forbes EE, Dahl R. E. Altered reward function in adolescent depression: What, when, and how? J Child Psychol Psychiatry. 2012; 53(1):3–15. https://doi.org/10.1111/j.1469-7610.2011.02477.x PMID: 22117893

44. Delgado MR. Reward-related responses in the human striatum. Annals of the New York Academy of Sciences. 2007; 1104:70–88. https://doi.org/10.1196/annals.1390.002 PMID: 17344522

45. Tricomi EM, Delgado MR, Fiez JA. Modulation of caudate activity by action contingency. Neuron. 2004; 41(2):281–92. PMID: 14741108

46. Montoya ER, Bos PA, Terburg D, Rosenberger LA, van Honk J. Cortisol administration induces global down-regulation of the brain’s reward circuitry. Psychoneuroendocrinology. 2014; 47:31–42. https://doi.org/10.1016/j.psyneuen.2014.04.022 PMID: 25001954

47. Johnson SB, Dariotis JK, Wang C. Adolescent risk taking under stressed and nonstressed conditions: conservative, calculating, and impulsive types. J Adolesc Health. 2012; 51(2 Suppl):S34–40.

48. Lewis AH, Porcelli AJ, Delgado MR. The effects of acute stress exposure on striatal activity during Pavlovian conditioning with monetary gains and losses. Front Behav Neurosci. 2014; 8:179. https://doi.org/10.3389/fnbeh.2014.00179 PMID: 24904331