

# Neural sensitivity to peer feedback and depression symptoms in adolescents: a 2-year multiwave longitudinal study

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**Background:** Depression risk increases during adolescent development, and individual differences in neural sensitivity to peer feedback (rejection vs. acceptance) may be a key diathesis in understanding stress-related depression risk. **Methods:** At baseline, adolescents (12–14 years old;  $N = 124$ ) completed clinical interviews and self-report symptom measures, and the Chatroom Task while MRI data were acquired. The majority of participants provided usable MRI data ( $N = 90$ ; 76% female), which included adolescents with no maternal depression history (low risk  $n = 64$ ) and those with a maternal depression history (high risk  $n = 26$ ). Whole-brain regression models probed group differences in neural sensitivity following peer feedback, and whole-brain linear mixed-effects models examined neural sensitivity to peer feedback by peer stress interactions relating to depression symptoms at up to nine longitudinal assessments over 2 years. **Results:** Whole-brain cluster-corrected results indicated brain activation moderating the strong positive association between peer interpersonal stress and depression over time. This included activation in the anterior insula, cingulate, amygdala, and striatum during anticipation and receipt of feedback (i.e., rejection vs. acceptance). Moderation effects were stronger when examining peer interpersonal (vs. non-interpersonal) stress and in relation to depression (vs. social anxiety) symptoms. **Conclusions:** Neural responses to peer feedback in key social and incentive processing brain regions may reflect core dispositional risk factors that interact with peer interpersonal stressors to predict adolescent depression symptom severity over time. **Keywords:** Adolescence; depression; social stress; Chatroom Task; social processing; insula.

## Introduction

Peer relationships are increasingly salient during adolescence (Blakemore & Mills, 2014; Somerville, 2013), coinciding with a period of increased depression risk (Avenevoli, Knight, Kessler, & Merikangas, 2008; Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015; Kessler, Avenevoli, & Merikangas, 2001; Merikangas et al., 2010). Although affiliative focus is developmentally normative, adolescents vary in their sensitivity to peer evaluation (e.g., acceptance vs. rejection) and thus, peer-related stress. Diathesis-stress models of depression suggest that predisposing risk factors, or diatheses, may prime adolescents for depressive symptoms following interpersonal stressors, particularly peer-related stress (Abela & Sullivan, 2016; Beck, 2008; Colodro-Conde et al., 2018; Hammen et al., 1995; Rudolph, Flynn, & Abaied, 2008). Diatheses relating to psychological (Chango, McElhaney, Allen, Schad, & Marston, 2012) and neural sensitivity (Oppenheimer et al., 2019) to social rejection may confer increased depression risk among adolescents. However, there is limited research

prospectively testing neural response to peer feedback as a potential diathesis contributing to depression following peer-related interpersonal stress.

Earlier work examining neural sensitivity to peer evaluation has largely focused on Cyberball paradigms, indicating that social exclusion elicits activation overlapping with physical pain circuits, for example, anterior insula (AI) and anterior cingulate cortex (ACC; Cacioppo et al., 2013; Eisenberger, 2012). Among youth, social exclusion and rejection tasks also engage the medial and ventrolateral prefrontal cortex (PFC), posterior cingulate, and ventral striatum (Vijayakumar, Cheng, & Pfeifer, 2017). These findings include recent research utilizing Chatroom Tasks with more ecologically valid peer feedback (Guyer, McClure-Tone, Shiffrin, Pine, & Nelson, 2009; Silk et al., 2012) and links to real-world social functioning (Sequeira et al., 2021; Silk et al., 2012, 2022). Chatroom Tasks generally include separable task phases (e.g., anticipation and receipt of peer feedback), which can isolate different cognitive processes and engage different brain circuits. Collectively, these findings highlight the potential of probing neural sensitivity to peer feedback to understand affective disturbances during a critical period of socioemotional development.

Conflict of interest statement: See Acknowledgments for full disclosures.

Neuroimaging work on social rejection has largely focused on increased amygdala responses in pediatric anxiety (Guyer et al., 2008; Lau et al., 2011; Rappaport & Barch, 2020; Spielberg et al., 2015). Pediatric anxiety research also has highlighted increased insula rejection response (Lau et al., 2011) and blunted nucleus accumbens (NAcc; within the ventral striatum) response to anticipation of feedback (Spielberg et al., 2015). Anxiety-related differences often manifest in response to peers that participants were not interested in (i.e., low-value peers; Beer et al., 2016; Guyer et al., 2008; Spielberg et al., 2015), c.f. (Jarcho et al., 2015). Less research has probed neural responses to peer feedback to understand depression risk. However, adolescents with depression showed increased brain activation to rejection compared with healthy youth in the amygdala, subgenual ACC, AI, and NAcc (Silk et al., 2014), with subgenual ACC response may be particularly predictive of change in depression symptoms over time (Masten et al., 2011; Silk et al., 2022). Furthermore, maternal depression history relates to blunted response to peer acceptance in unaffected offspring, including in the amygdala (Tan et al., 2014), NAcc, ACC, and inferior frontal gyrus (IFG; Olino, Silk, Ostertter, & Forbes, 2015). The majority of findings on depression have implicated receipt rather than anticipation of peer feedback. Yet, as striatal hypoactivation is noted in depression during both phases of processing of monetary rewards (Borsini, Wallis, Zunszain, Pariante, & Kempton, 2020; Keren et al., 2018), parsing anticipatory versus consummatory alterations is critical to understand the pathophysiology of depression (Rizvi, Pizzagalli, Sproule, & Kennedy, 2016; Winer, Jordan, & Collins, 2019).

To clarify whether neural response to peer rejection increased longitudinal risk for depression symptoms, psychiatrically healthy 12- to 14-year-olds (a subset at elevated depression risk given maternal depression history) completed a Chatroom Task while fMRI data were acquired; interpersonal peer stress and psychiatric symptoms were probed over the subsequent 2 years. This early to middle adolescence transition represents an important period prior to the peak of MDD onset (Avenevoli et al., 2008, 2015; Kessler et al., 2001; Merikangas et al., 2010). We hypothesized that peer stress would relate to increased depression symptoms, and critically, that baseline brain function (anticipation and receipt of peer feedback) would moderate within-person associations between peer stress and depressive symptoms. First, we hypothesized that blunted amygdala and NAcc response when anticipating feedback from high-value peers would magnify stress-related depression risk. Second, we hypothesized that heightened subgenual ACC and left AI response to rejection and blunted NAcc and IFG response to acceptance would potentiate stress-related depression risk.

## Materials and methods

### Participants

Adolescents (12- to 14-year-olds) and their birth mothers were recruited from the Boston area (Auerbach et al., 2017; Belleau et al., 2020; Kumar et al., 2019; Lincoln et al., 2019). Mothers either had no lifetime depression history (low risk) or had experienced 1+ episodes of major depression (high risk; half additionally met criteria for recurrent depression). Adolescents were right-handed and English fluent. Adolescents were excluded at baseline for a diagnosis of any lifetime mental disorder, current psychotropic medication, major medical or neurological illnesses, or MRI contraindication. The Partners IRB approved this study. Adolescents assented, and mothers provided informed written consent. Clinical interviews (see Appendix S1) assessed lifetime mental disorders for mothers (First, Spitzer, Gibbon, & Williams, 2002) and adolescents (Kaufman et al., 1997).

Adolescent-mother dyads ( $N = 149$ ) completed baseline assessments, and 124 adolescents completed MRI scanning. Ninety adolescents provided usable Chatroom Task data (Figure S1), as 12 were excluded for artifacts, poor quality, or incomplete task data and 22 had excessive head motion during scanning. Four participants did not provide any clinical follow-up data.

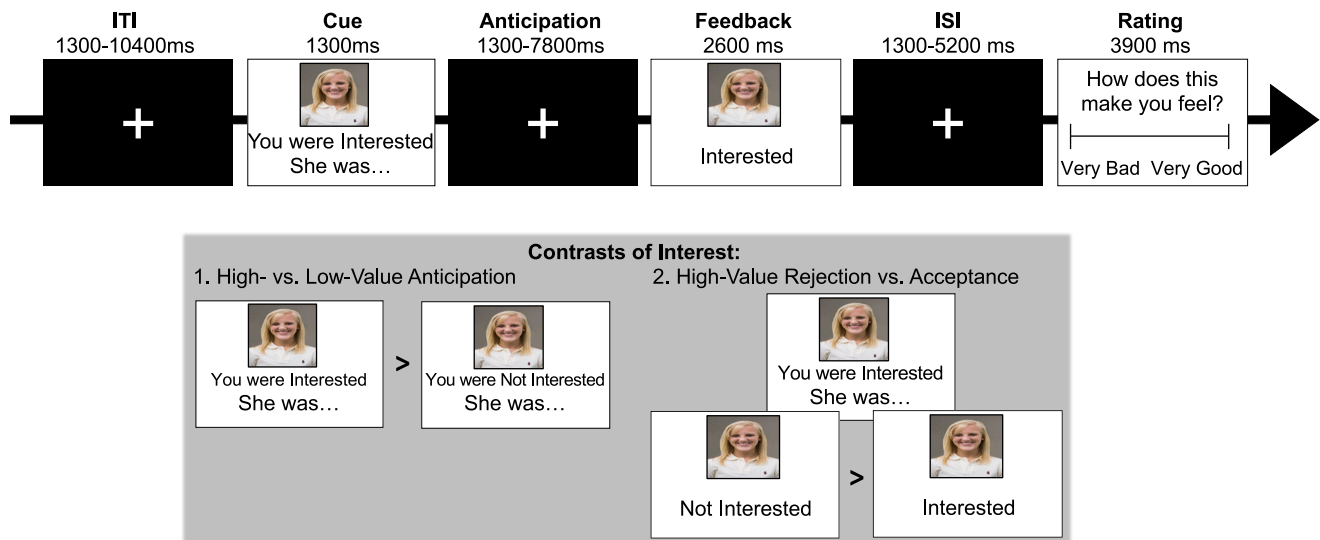
### Adolescent self-report

At baseline, adolescents reported on their pubertal development (Tanner & Davies, 1985). Youth completed symptom questionnaires at baseline and every 3 months over 2 years [ $n$  participants responding at months: 1 ( $n = 77$ ), 3 ( $n = 73$ ), 6 ( $n = 67$ ), 9 ( $n = 61$ ), 12 ( $n = 62$ ), 15 ( $n = 46$ ), 18 ( $n = 54$ ), 21 ( $n = 45$ ), and 24 ( $n = 59$ )]. All efforts were made, within reason, to complete assessments within 1–2 weeks of the scheduled follow-up. The 33-item Mood and Feelings Questionnaire (MFQ; Angold, Costello, Messer, & Pickles, 1995) assessed past 2-week depression severity (Cronbach's  $\alpha$  across assessments = .86 to .93). From the 39-item Multidimensional Anxiety Scale for Children (MASC; March, Parker, Sullivan, Stallings, & Conners, 1997), we examined the nine-item social anxiety subscale (Cronbach's  $\alpha = .80$ –.90). The 57-item Adolescent Life Events Questionnaire (ALEQ; Hankin & Abramson, 2002) assessed past week frequency of stressful events (from 0 = never to 4 = always). We focused on a 15-item peer interpersonal stress subscale, for example, 'You got into a fight or argument with your friends' (Auerbach, Bigda-Peyton, Eberhart, Webb, & Ho, 2011). A 13-item non-interpersonal stress subscale, including financial (e.g., 'A close family member (parent, sibling) lost their job') and academic stressors (e.g., 'You did poorly on or failed a test or class project'), was used to probe specificity to interpersonal peer stress versus non-interpersonal stress.

### Chatroom Task

The Chatroom Task (Guyer et al., 2008; Guyer et al., 2009) was completed over two visits. At baseline, participants were told that they were participating in a multisite study on adolescent interactions in online chatrooms. Participants created profiles including their likes/dislikes and a photograph taken in the lab; they were told that other participants would review their profile and indicate interest (peer acceptance) or not (peer rejection) in chatting. Next, participants viewed photographs of 60 same-sex peers and selected 30 that they were 'interested' (high value) and 30 that they were 'not interested' (low value) in chatting with online following MRI.

On each of 60 trials during MRI scanning (~1–2 weeks later; Figure 1), a peer photograph was displayed with a reminder of participants' prior choice: 'You were [not] interested' (cue),



**Figure 1** Chatroom Task schematic. This figure summarizes a sample trial from the chatroom MRI task. Outside of the scanner, participants see an array of 60 same-sex peer photographs and are asked to select half that they would be interested in chatting with following the scan. Approximately 70% of peers were Caucasian and 30% were Black, Hispanic, Asian, or mixed race. During fMRI, participants complete 60 trials. On each trial, participants see one of the peer photos and are first cued with a reminder of their initial selection (interested or not interested in chatting with that peer). This is followed by a jittered anticipation period, and then participants review peer feedback (that the peer is interested or not interested in chatting with them). After another jittered fixation cross display (ISI = inter-stimulus interval), participants rate how that feedback made them feel on a visual analog slider scale (0 [not very interested] to 100 [very interested]). A fixation cross is displayed between trials for a jittered intertrial interval (ITI). A schematic of the contrasts of interest in the main text analyses is presented. The (1) high- versus low-value anticipation contrast examines activity during the cue+anticipation periods comparing trials when the participant expressed interest versus not (during the out of scanner rating). The (2) high-value rejection versus acceptance contrast examines activity during the feedback period on a subset of trials when participants were interested and then received either rejection (not interested) or acceptance (interested) feedback

followed by a fixation cross for a jittered inter-stimulus interval (ISI; anticipation). Next, peer acceptance or rejection feedback was displayed: 'Interested' or 'Not Interested' (feedback), followed by a second jittered ISI. Finally, participants rated their emotional response (rating). Participants received 30 acceptance and 30 rejection trials (split by participant interest, e.g.,  $n = 15$  when participants were interested and accepted), pseudorandomized with no more than three sequential acceptances/rejections. After MRI scanning, participants were debriefed on the deception and completed a brief questionnaire about their experience.

### MRI data acquisition and processing

MRI data were acquired on a Siemens Tim Trio 3 T scanner. The Chatroom Task was acquired in one run during T2\*-weighted functional imaging (TR = 1,300 ms; 2 mm isotropic voxels; multiband acceleration factor = 8; 834 volumes). Data were checked for quality using MRIQC (Esteban et al., 2017) and processed using fMRIPrep v1.5.1rc2 (Esteban et al., 2019; see Supporting Information).

### MRI analysis

AFNI (Cox, 1996; Cox & Hyde, 1997) was used to rescale, smooth (4 mm FWHM), and mask data. First-level GLMs (3dDeconvolve) were constructed with eight regressors with boxcars of fixed (GAM) or variable duration (dmBLOCK) convolved with a gamma hemodynamic response function: (1–2) Anticipation, split by participant interested or not (high- vs. low-value), variable duration (1,300 ms Cue +1,300–7,600 ms ISI); (3–6) Feedback, four conditions split by participant and peer interest (e.g., *high-value acceptance*: participant was interested and peer was interested), 2,600 ms duration; (7) ISI, 1,300–5,200 ms duration; (8) Rating, 3,900 ms

duration. Models were fit with restricted maximum likelihood estimation of temporal auto-correlation structure (3dREML).

Steps were taken to mitigate head motion-related artifacts (see Supporting Information). GLMs regressed 24 temporally filtered (Fair et al., 2019; Gratton et al., 2019) head motion and 8 cerebral spinal fluid and white matter regressors. Volumes with time-series outliers and/or framewise displacement >0.3 mm were regressed out. Participants with outliers on >30% of frames were excluded.

### Analysis

Analyses were performed in R v4.0.3 (Team, 2015). Sample characteristics and group differences were summarized using the *scipub* package (Pagliaccio, 2020). Linear mixed-effects (LME) models (*lme4*; Bates, Mächler, Bolker, & Walker, 2014) probed depression symptoms as a repeated measure across baseline and follow-up. Group, assessment time point (months of assessment from baseline to 24 months [0, 1, 3, 6, 9, 12, 15, 18, 21, 24]), and peer stress were fixed effects of interest, controlling for age, sex, and a random effect for participant. Standardized  $\beta$  coefficients and  $\eta_p^2$  effect sizes (Lüdtke, 2018b) are presented.

### Whole-brain voxel-wise analyses

We utilized LME models to examine voxelwise brain activation by stress interactions with depression symptoms as the outcome variable, including age, sex, risk group, head motion, time point (months of assessment from baseline to 24 months), activation by time point as fixed effects covariates and participant as a random effect. Minor edits were made to AFNI's *3dLMEr* (Chen, Saad, Britton, Pine, & Cox, 2013) to examine voxelwise activation as an independent variable and clinical outcomes as the dependent variable (<https://github.com/>



dpagliaccio/3dLMERx). In supplementary analyses, we examined risk group differences in voxelwise activation (AFNI 3dtttest++) covarying age, sex, and head motion (% frames censored). Whole-brain 3D results are available at: <https://github.com/dpagliaccio/ChatroomResults>.

Analyses focused on anticipation of feedback from high- versus low-value peers (i.e., those that the participant was vs. was not interested in) and high-value rejection > acceptance (i.e., feedback from peers that the participant was interested in). Voxelwise analyses were performed within gray matter where >90% of participant had usable data (Figure S2) and corrected for multiple comparisons using AFNI's 3dFWMx (voxelwise  $p < .001$  [chi-squared > 13.816];  $k > 49$ ) to maintain a highly stringent analysis level  $p < .0001$  false-positive rate (see Supporting Information).

Average contrast activation was extracted from whole-brain significant clusters for post hoc testing and visualization (Lüdtke, 2018a). Johnson–Neyman analyses were performed (Long, 2019) to determine peer stress levels with significant brain–depression associations. Difference-score contrasts were parsed by examining interactions with the constituent conditions > baseline (e.g., rejection > baseline) using the same LME model. To probe specificity to peer interpersonal stress, LME models examined activation by non-interpersonal stress interactions. To test symptom specificity, LME models examined social anxiety instead of depression symptoms as the outcome.

## Results

### Sample characteristics

Risk groups did not differ on demographics, depression symptoms, or stress (Table 1, Table S1). However, high-risk adolescents exhibited greater anxiety. Participants excluded from the Chatroom Task analysis for any reason ( $n = 34$ ) did not differ from those included ( $n = 90$ ) other than greater head motion (Table S2). Trial-level analysis of chatroom ratings is summarized in the Supporting Information; notably, high-risk adolescents expressed less positive feelings about acceptance.

### Clinical follow-ups over 2 years

Figure S3 visualizes individual-level depression and peer stress data. In an LME model, greater peer interpersonal stress was strongly related to greater, concurrent depression symptoms across visits (Table 2;  $\beta = 0.34$ ,  $t(626) = 10.02$ ,  $p < .001$ ,  $\eta_p^2 = .14$ ). This did not interact with visit, that is, stress-related risk did not increase/decrease linearly with time since baseline. See Supporting Information for follow-up analyses and associations with Chatroom Task ratings.

### Anticipation

Across the sample, there was a robust response to anticipation (vs. baseline) in the bilateral AI, caudate, IFG, MTG, and SPL, and deactivation in the bilateral MFG, amygdala, and mPFC (Figure S4). The high-value > low-value peer contrast (participant was vs. was not interested) yielded significant negative contrast activation predominantly in visual regions (Figure 2, Figure S4). No whole-brain cluster-corrected group differences were observed between high-risk and low-risk adolescents.

LME models revealed significant high- versus low-value anticipation (interested > not interested contrast) by peer stress interactions relating to depression symptoms over time in hypothesized regions, including the bilateral caudate, a cluster spanning the right putamen to AI, left amygdala, and rostral ACC/mPFC as well as large medial and superior frontal gyrus clusters, strong fusiform gyrus effects, and other regions (see Supporting Information for additional effects, Table S3, Figure S5). Several regions exhibited positive interaction effects, for example, in the left amygdala and hippocampus (Figure 2A); positive associations between stress and

**Table 1** Sociodemographic and clinical sample characteristics

	Low risk ( $N = 64$ )	High risk ( $N = 26$ )	Group difference	p	Effect size
Age (years)	13 (0.8)	13.04 (0.82)	$t = 0.20$	.84	$d = 0.05$
Sex (female)	40 (62.5%)	18 (69.23%)	$\chi^2 = 0.13$	.72	OR = 1.35
Tanner mean score	3.15 (0.53)	2.99 (0.6)	$t = -1.14$	.26	$d = -0.27$
Race (White)	55 (85.94%)	20 (76.92%)	$\chi^2 = 0.53$	.47	OR = 0.55
Parental marital status (married)	59 (92.19%)	21 (80.77%)	$\chi^2 = 1.42$	.23	OR = 2.77
Parent education (completed college)	58 (90.62%)	23 (88.46%)	$\chi^2 = 0.00$	1.00	OR = 1.26
Family income (>\$75 k)	50 (78.12%)	22 (84.62%)	$\chi^2 = 0.17$	.68	OR = 1.53
MFQ	6.17 (5.5)	9.27 (8.33)	$t = 1.75$	.09	$d = 0.44$
MASC total	34.06 (11.93)	43.15 (13.35)	$t = 3.02$	.004	$d = 0.72$
MASC social	8.25 (4.68)	11.19 (5.65)	$t = 2.35$	.02	$d = 0.57$
ALEQ total	19.88 (14.18)	20.96 (16.79)	$t = 0.29$	.77	$d = 0.07$
ALEQ peer interpersonal	5.33 (4.66)	6.15 (4.71)	$t = 0.76$	.45	$d = 0.18$
ALEQ non-interpersonal	7.09 (4.34)	7.62 (5.71)	$t = 0.42$	.68	$d = 0.10$
Frames censored (%)	8.35 (7.08)	9.06 (8.07)	$t = 0.39$	.70	$d = 0.09$
N longitudinal assessments	6.91 (2.51)	6.15 (3.00)	$t = -1.13$	.27	$d = -0.27$

Mean (standard deviation) values are presented for continuous variables along with count (%) values for categorical variables. Differences between low-risk and high-risk groups based on maternal depression history are denoted by  $t$ -test for continuous or chi-squared ( $\chi^2$ ) test for categorical variables along with the accompanying effect size, Cohen's  $d$  or odds ratio (OR), respectively.

ALEQ, Adolescent Life Events Questionnaire; MASC, Multidimensional Anxiety Scale for Children; MFQ, Mood and Feelings Questionnaire.

**Table 2** Linear mixed-effects models predicting depression symptoms over time

	<i>b</i>	<i>t</i>	<i>b</i>	<i>t</i>	<i>b</i>	<i>t</i>	$\eta_p^2$
<b>Fixed effects</b>							
Age	−0.07	−0.95	−0.07	−0.95	−0.07	−0.97	.02
Sex (female)	0.15	0.93	0.14	0.86	0.14	0.88	<.001
Visit	0.05	2.05*	0.04	1.90	0.05	1.83	<.001
Group (high risk)	0.33	1.95	0.30	1.75	0.30	1.75	.04
ALEQ Peer	0.34	10.02***	0.26	6.48***	0.27	6.53***	.15
Group × ALEQ Peer	–	–	0.21	3.00**	0.21	2.90**	.01
Visit × ALEQ Peer	–	–	0.02	0.92	0.01	0.39	<.001
Visit × Group	–	–	−0.02	−0.41	−0.03	−0.54	<.001
Visit × Group × ALEQ Peer	–	–	–	–	0.04	0.78	<.001
<b>Random effects</b>							
$\sigma^2$	0.31		0.30		0.31		
$\tau_{00}$	0.45 <sub>ID</sub>		0.46 <sub>ID</sub>		0.45 <sub>ID</sub>		
ICC	0.59		0.60		0.60		
df	626		623		622		
Marginal $R^2$ /Conditional $R^2$	.179/.666		.185/.674		.185/.672		
AIC	1,296.39		1,300.01		1,311.40		

Linear mixed-effects models were run in the  $N = 90$  sample of adolescents included in the MRI sample. Regression coefficient ( $b$ ) and associated  $t$ -statistics ( $t$ ) are presented for each predictor. Partial eta squared effect sizes are presented for the final model ( $\eta_p^2$ ). The base model examined associations between peer stress (Adolescent Life Events Questionnaire [ALEQ]) and depression symptoms (Mood and Feelings questionnaire [MFQ]) over the longitudinal follow-ups. This included  $n = 634$  individual self-report observations. Subsequent models added interactions between visit (time point of assessment), stress, and risk group. Models exhibit potential non-normality of residuals. Log-transforming MFQ values help minimize this. Robust SE can also be estimated (*robustlmm::rlmer*). Neither method to address normality substantively affected the effect of peer stress ( $\eta_p^2 = .14$ ). \* $p < .05$ ; \*\* $p < .01$ ; \*\*\* $p < .001$ .

depression were attenuated among participants with lower activation to high-value peers (interested) and/or higher activation to low-value peers (not interested) (Figure 2B). Most regions, including the right caudate, exhibited a negative interaction (Figure 2C), whereby stress–depression associations were attenuated among participants with greater response to low-value peers.

### Feedback

High-value rejection > acceptance elicited left AI activation and deactivation (i.e., greater activation to acceptance > rejection) in the bilateral caudate/accumbens and mPFC (Figure 3D, Figure S6). Figures S7 and S8 display activation for low-value and all peer feedback. No whole-brain cluster-corrected group differences were observed between high-risk versus low-risk adolescents.

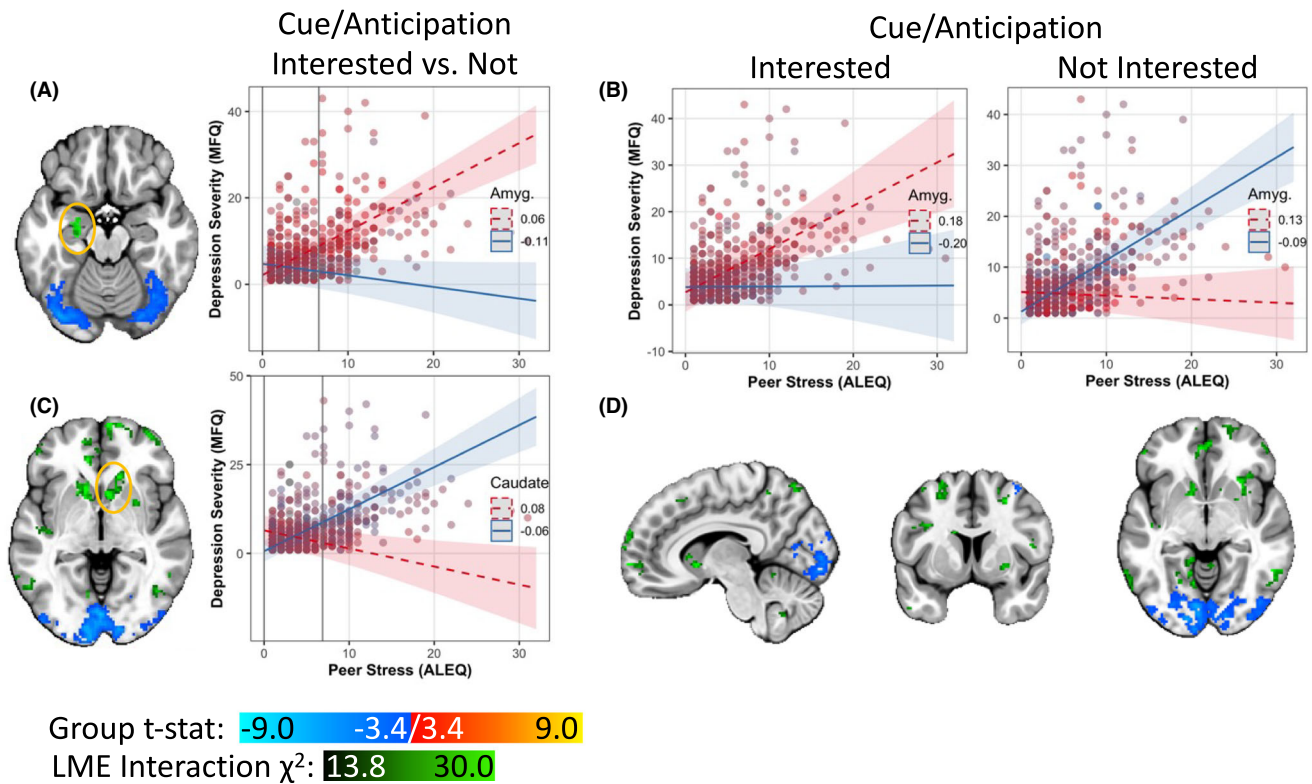
LME models revealed significant high-value rejection > acceptance feedback by peer stress interactions relating to depression over longitudinal follow-up including several hypothesized regions—bilateral AI extending in right PI, bilateral caudate, dACC, right putamen, and left amygdala—as well as bilateral MFG and SFG, and dorsal ACC (see Supporting Information for additional effects, Table S4, Figures 3D, Figure S9). The majority of regions displayed positive interactions, for example, in the left AI (Figure 3A), positive associations were observed between stress and depression with greater high-value rejection > acceptance activation. Attenuation of stress–depression associations was driven

primarily by lower response to high-value rejection > baseline in the left AI (Figure 3B). Fewer regions, including the IFG (Figure 3C) and angular gyrus, exhibited negative interaction effects, such that positive associations between stress and depression were strongest with the lowest high-value rejection > acceptance activation.

### Post hoc testing for anticipation and feedback

Johnson–Neyman analyses determined the range of peer interpersonal stress values with a significant brain–depression association. For both anticipation and feedback contrasts, all regions identified in the above LME models indicated significant associations between brain activation and depression only at higher levels of stress. Furthermore, very few regions exhibited any crossover interaction, that is, with significant brain–depression association at low stress values (See Tables S3 and S4).

For both contrasts, activation by *non-interpersonal* stress interactions relating to depression were non-significant or weaker than activation by peer interpersonal stress interactions, despite the correlation between peer and non-interpersonal stress ( $r = .44$ ,  $t(632) = 12.23$ ,  $p < .001$ ). Similarly, for both contrasts, activation by peer stress interactions relating to social anxiety were nonsignificant or weaker than those relating to depression, despite the strong depression and social anxiety association ( $r = .55$ ,  $t(632) = 16.69$ ,  $p < .001$ ). Figure S10 displays whole-brain results that indicate notably fewer regions exhibited feedback contrast by peer stress



**Figure 2** Neural activation to anticipation. Several significant clusters/effects of interest are highlighted here for the high-value cue/anticipation contrast (interested vs. not interested). The main effect of task (one-sample *t*-test across the full sample; blue–red color scale) is presented to highlight areas activated by this contrast along with the contrast by peer stress interaction from linear mixed-effects (LME; green color scale) models relating to depression symptoms over all time points. Scatterplots are presented to parse positive (A; hippocampus/amygdala) and negative (C; caudate) interaction effects in sample regions. Simple slope lines are presented at the min (blue) and max (red) values of contrast activation with their 95% confidence interval band. Dark gray vertical lines indicate the Johnson–Neyman intervals for the interactions; associations between brain activation and depression symptoms were significant outside of this band (at higher levels of peer stress). Panel C further parses the interaction in the amygdala by presenting simple slopes from the interaction between peer stress and anticipation when interested or not interested >baseline separately relating to depression symptoms. Panel D displays additional clusters of interest, including deactivation in the visual cortex and interaction effects in the right putamen, anterior insula, and mPFC. Full results are presented in the Supporting Information

interactions related to social anxiety versus depression symptoms. Figure S11 displays overlap in supplementary analyses examining low-value and all feedback trials.

## Discussion

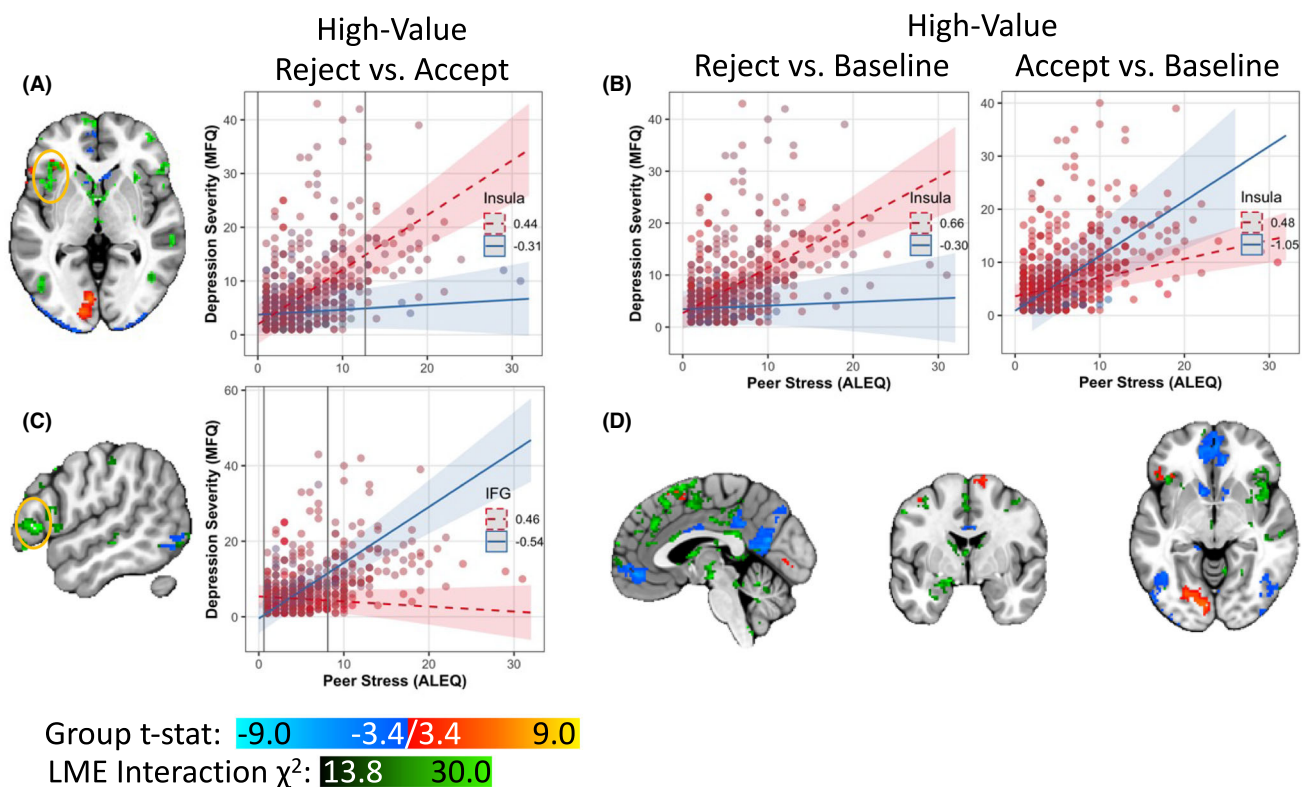
Peer-related stress is a strong risk factor for adolescent depression symptoms, and our results suggest that this effect may be moderated by individual differences in neural responses to peer feedback in key social and incentive processing brain regions. Results were particularly salient for ‘high-value’ peers—peers that participants expressed interest in interacting with following the scan. Furthermore, we observed relative specificity to depression symptoms (vs. social anxiety) and interpersonal peer stress (vs. non-interpersonal stress). Thus, consistent with diathesis-stress models, there is compelling evidence for neural processing of peer feedback as a critical risk factor for adolescent depression.

Core brain regions implicated in social processing and peer rejection include the AI, ACC, mPFC, striatum, and amygdala (Rappaport & Barch, 2020).

We found convergent task effects—left AI activation to high-value rejection > acceptance and greater activation to acceptance > rejection in bilateral caudate/accumbens and mPFC. Interestingly, mPFC and striatal responses were similar to low-value (or across all) peers, whereas left AI rejection response was more robust to high-value peers. Critically, there was little spatial overlap between regions robustly activated at the group-average level and those moderating peer stress effects (Figures 2 and 3). This is often expected, as regions showing consistent activation across individuals have less inter-individual variability that is key to individual difference analyses, which is important to consider in future work, particularly for region of interest selection. Response to rejection > acceptance yielded the most robust moderation, but anticipation also was key to consider. Future work could aim to parse the relative value of these contrasts and potential prediction of differential outcomes.

These current results are in line with the diathesis-stress framework—ordinal interactions by which neural diatheses only increase depression risk when stress occurs. Prior work has noted similar





**Figure 3** Neural activation to high-value peer feedback. Several significant clusters/effects of interest are highlighted here for the high-value reject > accept contrast. The main effect of task (one-sample *t*-test across the full sample; blue–red color scale) is presented to highlight areas activated by this contrast along with the contrast-by-peer stress interaction from linear mixed-effects (LME; green color scale) models relating to depression symptoms over all time points. Scatterplots are presented to parse positive (A; anterior insula) and negative (B; inferior frontal gyrus) interaction effects in sample regions. Simple slope lines are presented at the min (blue) and max (red) values of contrast activation with their 95% confidence interval band. Dark gray vertical lines indicate the Johnson–Neyman intervals for the interactions; associations between brain activation and depression symptoms were significant outside of this band (at higher levels of peer stress). Panel C further parses the interaction in the anterior insula by presenting simple slopes from the interaction between peer stress and rejection or acceptance feedback > baseline separately relating to depression symptoms. Panel D displays additional clusters of interest, including deactivation in the medial prefrontal cortex and caudate as well as interaction effects in the right insula, left amygdala, and anterior cingulate cortex; full results are presented in the Supporting Information

diathesis–stress interactions between interpersonal stress (e.g., peer victimization) and right AI region of interest response to peer feedback in relation to suicidal ideation (Oppenheimer et al., 2019). Most regions herein showed no significant cross-over effects. Functionally, this indicated little differentiation based on activation when peer stress was low (i.e., lines converging near zero in Figures 2 and 3), but significant brain–depression associations emerged when peer stress was experienced. This is notable as disordinal/cross-over interactions require less power to detect, and thus, mass-univariate testing is biased toward finding such interactions, even when the true interaction is ordinal (Chavez & Wagner, 2017). Alternative stress models would predict cross-over interactions, e.g., differential susceptibility (Belsky & Pluess, 2009) or biological sensitivity to context models (Boyce & Ellis, 2005; Ellis & Boyce, 2008). These hypothesize high-reactivity phenotypes that are detrimental in negative circumstances but adaptive in positive circumstances versus low-reactivity phenotypes that are context insensitive (instead of risk vs. resilience phenotypes). Our ability to differentiate diathesis–stress and differential susceptibility

interactions may be bounded by current focus on negative factors (peer stress, depression). Future work should expand on this by considering neural interactions with positive environmental factors (e.g., peer support) and associations with adaptive outcomes.

Importantly, we also observed the relative specificity of results to depression versus anxiety symptoms. Clusters identified based on whole-brain depression analyses exhibited weaker or nonsignificant links with anxiety, potentially driven by collinearity between depression and anxiety. Furthermore, whole-brain analyses (Figure S10) yielded very few cluster-corrected results where high-value rejection > acceptance moderated peer stress effects on anxiety symptoms. Results may be shaped by leveraging a sample at-risk for depression given maternal history; relatedly, anxiety effects may be more apparent at clinically severe levels. Anxiety also has been related to differences in task-based connectivity (PPI, e.g., Beer et al., 2016; Guyer et al., 2008; Jarcho et al., 2015; Spielberg et al., 2015), which could be examined in the future.

Findings should be interpreted in the context of several limitations. First, our sample size high-risk

youth may have limited power to identify risk-related differences or higher level interactions with risk group (e.g., group-by-brain-by-stress), which were not significant (see [Supporting Materials](#)). That said, we do find that high-risk youth felt less positively about peer acceptance. Nonetheless, our overall sample ( $N = 90$ ) was relatively large, particularly in comparison to prior research using this task (Guyer et al., 2008; Lau et al., 2011; Olino et al., 2015; Oppenheimer et al., 2019; Platt et al., 2015; Silk et al., 2014; Spielberg et al., 2015; Tan et al., 2014). Furthermore, repeated longitudinal assessment of peer interpersonal stress and depression improved our power to understand moderation by baseline brain function. Third, we excluded a relatively large number of participants for head motion during the scan. Although this may decrease power, it is critical to include only high-quality, low-motion data to avoid artifacts. The current task was run across one long scan block, and thus, future research should consider dividing the task across multiple blocks to reduce motion-related issues. Last, although our sample was well-divided by sex, most participants identified as White and had relatively high family income. Different sociodemographic groups likely experience different types, salience, and frequency of stressors that can contribute to depression (e.g., peer stress, socioeconomic deprivation, discrimination; Benner et al., 2018; Britt-Spells, Slebodnik, Sands, & Rollock, 2018; Respress, Morris, Gary, Lewin, & Francis, 2013; Richardson, Westley, Gariépy, Austin, & Nandi, 2015). Future work should expand on this with broader sociodemographic sampling.

Peer stress is a critical risk factor for depression. We highlight individual differences in brain response to peer feedback as a key neural factor moderating stress-related risk for depression. This builds on work showing self-reported rejection sensitivity as an important moderator of the link between relational stressors and adolescent depression (Chango et al., 2012). Other biological work suggests that stress system functioning also moderated effects of peer stress on depression in youth (Rudolph, Troop-Gordon, & Granger, 2011). Nonetheless, neural measures have yet to be well integrated into our diathesis–stress models. Collectively, our findings underscore the importance of characterizing different stages of social processing—anticipation and feedback—to elucidate vulnerability to depression following peer stress.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

### Appendix S1. Methods.

**Table S1.** Debrief characteristics among low- and high-risk participants.

**Table S2.** Differences among participants included versus excluded.

**Table S3.** Whole-brain linear mixed-effects model results: cue + anticipation interest versus not contrast.

**Table S4.** Whole-brain linear mixed-effects model results: high-value reject versus accept contrast.

**Figure S1.** Participant inclusion/exclusion diagram.

**Figure S2.** Whole-brain analysis mask.

**Figure S3.** Longitudinal trajectories of depression and stress.

**Figure S4.** Whole-brain cue + anticipation activation.

**Figure S5.** Whole-brain cue + anticipation  $\times$  peer stress predicting depression symptoms.

**Figure S6.** Whole-brain high-value rejection versus acceptance feedback contrast.

**Figure S7.** Whole-brain low-value rejection versus acceptance feedback contrast.

**Figure S8.** Whole-brain all rejection versus acceptance feedback contrast.

**Figure S9.** Whole-brain high-value feedback  $\times$  peer stress predicting depression symptoms.

**Figure S10.** Whole-brain high-value feedback  $\times$  peer stress predicting depression versus anxiety.

**Figure S11.** Whole-brain feedback subtypes  $\times$  peer stress predicting depression symptoms.

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## Key points

- Interpersonal and peer stress is a major risk factor for depression in adolescence.
- Neural response in key social and incentive processing brain regions in the context of anticipating and receiving peer feedback moderates stress-related risk for depression symptoms.
- Findings provide support for considering social neural risk factors in diathesis–stress models of adolescent depression.

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