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Emotional trade-offs of neural sensitivity to social threat and reward in adolescent girls

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Abstract

Contemporary affective neuroscience perspectives consider possible trade-offs of neural attunement to social cues for adolescent development. Integrating these perspectives with interpersonal theories emphasizing robust belonging needs during adolescence, this study examined whether exposure to naturally occurring interpersonal stressors was differentially associated with loneliness and depression contingent on adolescent girls' neural sensitivity to cues indicating social threat (non-belonging) vs. reward (belonging). Eighty-six adolescent girls (M_{age} = 16.31, SD = .84; 66.3% White) completed a social feedback task during an fMRI scan and reported on their loneliness and depression. Elevated interpersonal stress exposure was associated with more depression in girls who showed dampened but not heightened activation in the salience and social processing networks in response to threat (vs. reward). In the context of low interpersonal stress, however, dampened activation to threat (vs. reward) was associated with particularly low levels of depression. These effects were partially accounted for by self-reported loneliness. This research supports current trends towards developing a more refined perspective on the adaptational value of neural attunement to social cues for adolescent development, suggesting that the balance of social threat vs. reward sensitivity can confer emotional risks or benefits by shaping how adolescent girls navigate diverse social contexts.

Keywords: interpersonal stress; neural attunement; threat and reward sensitivity; loneliness; depression

Introduction

Belonging to a social group is one of the most basic human needs (Baumeister and Leary 1995). This need is intensified during adolescence, a stage during which a process of social reorientation (Nelson et al. 2005, Crone and Dahl 2012, Rudolph et al. 2016a, Galván 2021) heightens the salience of peer evaluation, connectedness, and alignment to peer group norms (Sebastian et al. 2010, Andrews et al. 2020, 2021) as well as exposure to interpersonal stressors, particularly in girls (Rudolph 2002). Negotiating this increasingly complex social landscape requires girls to strike a delicate balance between attending to social cues indicating non-belonging (social threat) vs. belonging (social reward). This study investigated the novel premise that the balance of neural attunement to social threat vs. reward cues confers emotional trade-offs—i.e. both benefits and risks—for adolescent girls' emotional adjustment, shaping whether they respond to their social contexts in healthy or unhealthy ways.

Emotional implications of attunement to social cues

According to the adaptive calibration model (ACM) of development (Ellis et al. 2017), stress-response systems filter information in ways that amplify or dampen environmental cues, both of which can have adaptational costs and benefits. Consistent with the ACM, heightened attunement to social cues may reflect either a sensitive profile, which allows for flexible attention and sensitivity to feedback and consequent strong self-regulation and positive engagement with the environment, or a vigilant withdrawn profile, which promotes (sometimes unfounded) attention to threat and consequent internalizing symptoms in girls. Likewise, blunted attunement to social cues can reflect either a buffered profile, which predicts lower internalizing symptoms, or an unemotional profile, which reflects insensitivity to threat, inhibition of social learning, and aloof relationships in girls (Ellis et al. 2017).

Consistent with these context-specific trade-offs of sensitivity to the environment, contemporary developmental affective neuroscience theories challenge prevailing views that cast activation in particular brain regions as either health-promoting or risk-enhancing (Pfeifer and Allen 2012, Schriber and Guyer 2016, Crone et al. 2020, Guyer 2020, Rudolph et al. 2020). During adolescence, a key developmental task is establishing a sense of belonging within the peer group. Being attuned to signs of non-belonging is therefore a key

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feature of adolescent development that can promote adaptive stress responses and motivate engagement in affiliative behaviours aimed at strengthening social bonds (Nelson et al. 2005, Andrews et al. 2020, 2021); however, this sensitivity to social threat cues also is implicated as a risk factor for emotional distress (Somerville 2013, Rudolph et al. 2016b). Accordingly, this study explored whether individual differences in patterns of neural sensitivity to social threat vs. reward can confer either mental health benefits or costs by moderating the impact of exposure to naturally occurring interpersonal stressors on adolescent girls' emotional adjustment (loneliness and depression).

Neural processing of social cues during adolescence

Two brain networks may be particularly relevant for understanding how adolescent girls navigate complex social dynamics. The salience network (e.g. amygdala, dorsal anterior cingulate cortex [dACC], and anterior insula [AI]) monitors internal states and changes in the environment (Uddin 2015, Seeley 2019), including tracking information about one's social standing (Kumar et al. 2019); it also engages other networks in the interests of goal pursuit (Chen et al. 2016). Salience network activation may mark cues of perceived non-belonging as particularly meaningful, thereby enhancing detection of, attention to, and efforts to address potential threats to belonging needs. The social processing network (e.g. medial prefrontal cortex [mPFC], temporoparietal junction [TPJ], posterior superior temporal sulcus [pSTS], precuneus, and posterior cingulate cortex [PCC]) is implicated in social reasoning, including mentally representing one's own and others' beliefs, emotions, and behaviour (Gunther Moor et al. 2010, Sebastian et al. 2010, Andrews et al. 2020, 2021). Social processing network activation may prompt deeper processing of social threat cues in efforts to attribute causality and understand their implications for one's status (Andrews et al. 2020) and may help to promote a sense of social connection (Delgado et al. 2023). Thus, the salience network may serve as a critical component of a detection and response selection system, alerting individuals to the need to attend to and address social cues and allowing flexible responding to these cues, whereas the social processing network may prompt individuals to reflect on the meaning of these cues. Growing evidence indicates enhanced sensitivity to social threat in these networks during adolescence (Tousignant et al. 2018, Cheng et al. 2020; for reviews, see Blakemore and Mills 2014, Cacioppo et al. 2013, Crone and Dahl 2012, Andrews et al. 2020, 2021), particularly in girls (Somerville 2013, Guyer et al. 2016).

Emotional trade-offs of neural sensitivity to social threat vs. reward

These maturational changes likely subserve several critical functions (Blakemore and Mills 2014, Andrews et al. 2020, 2021). Given the complexity of adolescent girls' relationships, which prioritize developing intimacy, trust, and reciprocal support (Rudolph and Dodson 2022), it is crucial to detect, carefully process, and flexibly respond to social threat cues indicative of non-belonging, allowing girls to better understand and learn from social situations and engage in motivated behaviours aimed at strengthening social ties (Andrews et al. 2020, Rudolph 2021). Salience network activation can alert girls to possible challenges to their group belonging, prompting them to generate strategies for re-inclusion. Indeed, research reveals heightened activation in the salience network (insula, dACC) when individuals' choices during a decision-making task are misaligned with group members; moreover, individual differences in this activation predict one's likelihood I'm sorry I'm not I am of initiating behaviour that re-aligns one's decisions with group members (Tomlin et al. 2013). Likewise, social processing network activation can enhance girls' understanding of nuanced social dynamics, allowing them to alter their behaviour in ways that facilitate successful integration into the peer group (Andrews et al. 2020, 2021). However, actively processing social reward cues indicative of group belonging also can contribute to feelings of intimacy and belonging within healthy relationships. For example, mentalizing about shared preferences can facilitate a sense of alignment with others that can enhance one's sense of social connection (Delgado et al. 2023). The adaptational value of engaging in heightened processing of social threat vs. reward cues may, therefore, vary for girls living in different social contexts, leading to either health-promoting or risk-enhancing effects. In particular, the match between adolescent girls' relative neural sensitivity to threat vs. reward cues and their social contexts (i.e. exposure to low vs. high levels of interpersonal stress) may help to shape individual differences in emotional well-being or ill-being.

Health-promoting effects

Successful navigation of social stressors (e.g. peer rejection, friendship conflict) requires cognitive efforts to understand the causes of stressors and perspectives of others as well as behavioural efforts to repair or form new relationships. Consistent with the ACM sensitive profile, heightened activation to threat cues may sometimes be an adaptive response within stressful contexts (Ellis et al. 2017), perhaps reflecting awareness of social norms and more advanced social-cognitive skills that can promote active and effective interpersonal coping (Masten et al. 2009). Specifically, stress-exposed girls who show more sensitivity to social threat (vs. reward) in salience and social processing regions may engage in deeper processing of social stressors; more flexible responding and enhanced understanding of stressors may, in turn, help them resolve relationship difficulties and better regulate their emotions (Andrews et al. 2020). Supporting the idea that heightened threat vs. reward sensitivity may promote behaviours that enhance social belonging, past studies of adolescents reveal that heightened dACC, insula, and mPFC activation during online social exclusion vs. inclusion is associated with more peer-reported popularity and acceptance (de Water et al. 2017) as well as higher parent-reported interpersonal competence, such as time spent with peers and involvement in social activities (Masten et al. 2009); this heightened engagement may protect girls from loneliness, which may then buffer them from depression (Mahon et al. 2006, Schinka et al. 2013).

In contrast, stress-exposed adolescent girls who show less activation to social threat (e.g. an unemotional profile) may lack awareness of social norms or have lower motivation or ability to flexibly resolve social stressors; instead, these girls may avoid social stressors, thereby undermining their engagement (Andrews et al. 2020) and enhancing risk for loneliness, which can put them at risk for further diminished social motivation (Delgado et al. 2023) and depression (Mahon et al. 2006, Schinka et al. 2013). Indeed, some research links reduced activation to social exclusion vs. inclusion in salience (e.g. dACC, subgenual ACC) and social processing (e.g. precuneus) regions to higher levels of depressive symptoms (Masten et al. 2011, Jankowski et al. 2018). Likewise, compared to non-depressed youth, clinically depressed youth show reduced activation in social processing regions to words conveying social status, a pattern of hypoactivity that is hypothesized to be associated with social withdrawal (Silk et al. 2017).

Risk-enhancing effects

On the other hand, consistent with the ACM vigilant withdrawn profile, girls in relatively low-stress environments may be at greater risk for loneliness and depression when they show higher salience

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and social processing network activation in response to social threat vs. reward. A recent meta-analysis revealed that intrinsic activation in the sgACC, mPFC, and PCC/precuneus is associated with rumination (Makovac et al. 2020). Moreover, precuneus activation during online social exclusion vs. inclusion is associated with more self-reported rejection sensitivity (Masten et al. 2009) and trait rumination (Yoon et al. 2023) in adolescents. In low-stress contexts, when girls likely encounter more favourable than threatening social cues, heightened sensitivity to threat vs. reward may lead adolescents to overthink relatively minor social issues, perhaps triggering rumination about actual or even perceived social slights; this excessive vigilance may prompt social avoidance (Ellis et al. 2017, Rudolph 2021, Davis et al. 2023) and interfere with the development or maintenance of healthy relationships, leading to loneliness, which may then heighten risk for depression (Mahon et al. 2006, Schinka et al. 2013).

Consistent with these risk-enhancing effects, research links activation in the salience (e.g. amygdala, ACC, anterior insula) and social processing (e.g. mPFC, PCC, and precuneus) networks during social exclusion/rejection (vs. inclusion/acceptance) with spending less time with friends during high school (Masten et al. 2012, contrary to Masten et al. 2009), lower levels of perceived connectedness with peers (Silk et al. 2023), and elevated depression (Masten et al. 2011, Silk et al. 2014, Rudolph et al. 2016b, Jankowski et al. 2018, Silk et al. 2023). Heightened activation and connectivity in salience (e.g. amygdala) and social processing (e.g. mPFC, TPJ) regions also have been associated with loneliness and social isolation (Spreng et al. 2020, Delgado et al. 2023). In contrast, adolescent girls in low-stress contexts who show relatively less activation to threat than reward (e.g. a buffered profile) may be better able to take advantage of their more optimal social contexts by engaging in positive interactions that protect them against loneliness and consequent depression.

Overview of the present research

Collectively, theory and research implicate both health-promoting and risk-enhancing effects of heightened activation in the salience and social processing networks in response to social threat vs. reward (Gu¨roğlu and Veenstra 2021). Recent efforts to explain such seemingly paradoxical findings consider how social experience interacts with threat vs. reward sensitivity to predict adjustment (Schriber and Guyer 2016, Rudolph et al. 2016b, Crone et al. 2020, Guyer 2020, Rudolph et al. 2020, Galván 2021, Pagliaccio et al. 2023). Studies examining such interactions in the context of social threat are scarce, and these studies also yield mixed findings. Whereas some research reveals that stress exposure predicts more internalizing symptoms in youth who show heightened activation to social threat in certain regions (e.g. anterior insula, dACC; Rudolph et al. 2016b, Rudolph et al. 2020, Pagliaccio et al. 2023), other evidence suggests that reduced activation in these and other regions intensifies the link between stress exposure and internalizing symptoms (Pagliaccio et al. 2023, Kirshenbaum et al. 2024), a pattern that has been interpreted as reflecting difficulty flexibly responding to stress. To further examine these context-dependent effects, this study examined whether the balance of neural sensitivity to social threat vs. reward moderates the link between adolescent girls' social experiences and emotional adjustment. We focused on adolescent girls given their heightened tendency to base their self-worth on peer belonging (O'Brien and Bierman 1988, Foulkes and Blakemore 2016), concerns about peer evaluation (Rudolph and Conley 2005), sensitivity to rejection (Sebastian et al. 2010, Somerville 2013, Guyer et al. 2014), and vulnerability to interpersonal stressors and depression (Rudolph 2009).

Social threat and reward were reflected, respectively, in peer feedback indicative of non-belonging in the peer group (feedback that one's preferences diverge from those of peers) vs. belonging in the peer group (feedback that one's preferences align with those of peers). Bonding over shared preferences that hold personal relevance can be rewarding by reinforcing social connections (Delgado et al. 2023)—particularly during adolescence when alignment with peer group norms is highly motivating—whereas diverging from peer group norms can threaten adolescents' sense of belonging (Tomova et al. 2021). Because misalignment with peer group norms can be addressed through strategic efforts aimed at realignment, this type of social threat may be perceived as more controllable than threat characterized by more global rejection or exclusion. Thus, adolescents who live in stressful environments but who are tuned into such cues and are motivated to engaged in efforts to realign with the peer group may be at a greater advantage than those who lack awareness of social threat cues or disengage in the face of stress. Given the nature of our social feedback task, we therefore hypothesized that: (a) more exposure to interpersonal stressors would be associated with elevated loneliness and depression in adolescent girls who showed dampened social threat (vs. reward) sensitivity; yet (b) heightened social threat (vs. reward) sensitivity would be detrimental within low-stress contexts. Moreover, we tested whether loneliness accounted for the interactive effects of interpersonal stressors and neural sensitivity on depression, and we examined whether these effects were specific to interpersonal versus noninterpersonal stressors. Finally, we conducted supplemental analyses to examine whether the proposed interactive effect of interpersonal stress and neural activation to threat (vs. reward) was specific to the *a priori* networks of interest.

Method

Participants and procedures

Participants were 86 girls (M_{age} = 16.31, SD = .84) who completed a functional magnetic resonance imaging (fMRI) scan in the summer following 9th, 10th, or 11th grade (see Supplement for additional sample information). Within three weeks, research staff administered life stress and diagnostic interviews. Participants were compensated $50 for the fMRI session and $25 for the interviews. Parents and youth provided written consent/assent. All procedures were approved by the university IRB.

Measures

Social feedback task

Adolescents completed the Social Feedback Task (Rudolph et al. 2021, Davis et al. 2023) during an fMRI scan (Fig. 1). This task provides feedback regarding girls' social belonging (their opinions align with those of peers) or non-belonging (their opinions diverge from those of peers). Girls were told that they would be selecting their preferences in different domains from two options and would receive feedback about whether other teens agreed or disagreed with them based on hundreds of teens who had previously completed the task. The task included a single run of 60 trials with three phases. First, girls were presented with two choices (e.g. rap vs. rock) within a variety of adolescent-relevant domains (e.g. music), and indicated their preference via a button press (*decision*); this phase lasted 5000 ms or until participants made a selection. Second, a fixation cross appeared on the screen during a 1365–2730-ms jitter, followed by a screen indicating the task was retrieving feedback (*anticipation*), which remained on the screen for 2000 ms. Third, after a 1365-2730 ms jitter, girls received

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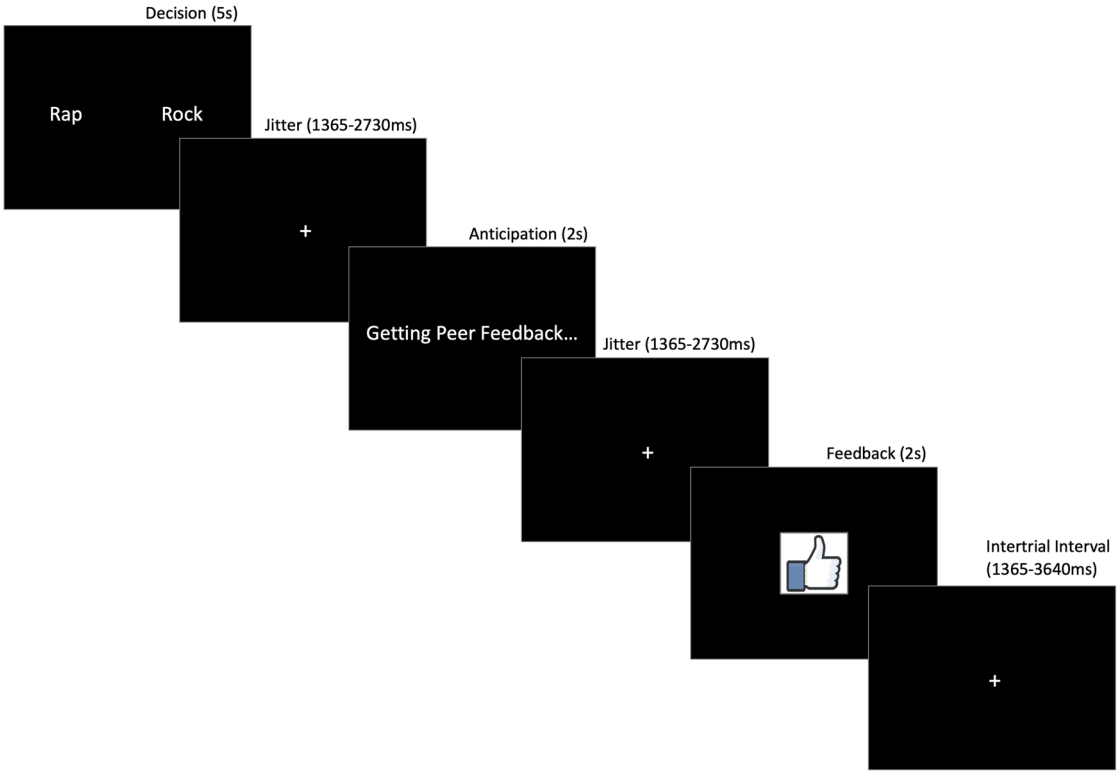

Figure 1. Social feedback task design.

feedback indicating whether other teens mostly agreed (thumbs up; belonging/reward feedback), mostly disagreed (thumbs down; non-belonging/threat feedback), or roughly half agreed/half disagreed (thumb to the side; neutral feedback) with their selection (*feedback*). Feedback was randomly generated such that girls received 20 trials of each type. Feedback remained on the screen for two seconds, followed by a 1365–3640-ms inter-trial interval. Analyses focused on the feedback stage and on the *Threat* vs. *Reward* contrast.

fMRI data acquisition and analysis

fMRI data were collected using a 3 Tesla Siemens Trio MRI scanner. T2*-weighted echoplanar images were collected during the task; structural scans consisted of a T2*weighted, matched-bandwidth high-resolution, anatomical scan and a T1* magnetization-prepared rapid-acquisition gradient echo (see Supplementary data for details). Data were preprocessed using statistical parametric mapping (SPM8; Wellcome Department of Cognitive Neurology). Images were spatially realigned to the mean and coregistered to the structural MPRAGE, which was then segmented into cerebrospinal fluid, gray matter, and white matter. Structural and functional images were transformed into standardized stereotactic space as defined by the Montreal Neurological Institute. Normalized functional data were smoothed using an 8 mm full-width-at-half-maximum Guassian kernel and filtered using high-pass temporal filtering with a cutoff of 128 s to remove low-frequency drift.

For each participant's data, a general linear model (GLM) was created using regressors that corresponded to each phase (*Decision, Feedback Anticipation, Feedback Receipt*) of the task and an unweighted regressor for trials with excessive head motion (over 2.5 millimetres overall motion). Inter-trial intervals and trials in which participants did not respond were not explicitly modelled and are included in the implicit baseline. The present analyses focused on activation to feedback receipt based on valence. To model feedback, separate regressors were created for reward, threat, and neutral feedback (20 trials each). Parameter estimates resulting from the GLM were then used to create linear contrasts. To assess relative activation to the receipt of threat vs. reward feedback, we extracted activation from several *a priori* regions of interest (ROIs) during the Threat vs. Reward contrast. The amygdala, dACC, anterior insula, mPFC, and PCC ROIs were created by combining across right and left anatomical regions as defined by the Wake Forest University PickAtlas (PCC; Maldjian et al. 2003) or Harvard-Oxford Atlas (amygdala, dACC, insula, mPFC; Frazier et al. 2005). To create bilateral TPJ and precuneus and right STS ROIs, we used functional brain masks developed through previous research identifying regions responsive in a theory of mind task (Dufour et al. 2013). Additional detail about these ROIs is presented in the Supplementary data.

Assessment and coding of interpersonal stressors

Using a revised version of the Youth Life Stress Interview (Rudolph and Flynn 2007), interviewers first asked an open-ended question about exposure to stressful events within the past three months, and then provided specific prompts and follow-up questions about events within key relationship domains (e.g. peer exclusion, end of friendships, conflicts with parents). Coders rated each event from 1 (*No stress*) to 5 (*Severe stress*). Interpersonal stress scores were calculated as the sum of the stress ratings for each interpersonal event with a rating above 1. To examine specificity of the results to interpersonal stress, we also calculated scores reflecting exposure to noninterpersonal stressors (e.g. academic difficulties, health issues, financial problems). One-way random-effects intra-class correlation coefficients (ICC) supported high reliability for the ratings of event impact (ICC = .94). High reliability also was found for categorization of events as interpersonal versus noninterpersonal (kappa = .91).

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Assessment and coding of depression

Interviewers administered a revised version (Agoston and Rudolph 2016) of the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID; Sheehan et al. 1998) to assess depressive symptoms within the past three months. Ratings for each symptom (0 = *Absent*, 1 = *Subthreshold*, 2 = *Clinically significant*) were summed within each diagnosis (e.g. Major Depressive Disorder [MDD], Persistent Depressive Disorder), across multiple MDD episodes, and across diagnostic categories to create a single continuous depression score. Inter-rater reliability was high (ICC = .94).

Loneliness

Participants completed a 20-item revised version (version 3; Russell 1996) of the UCLA Loneliness Scale (Russell et al. 1978, 1980), rating the extent to which they agreed with each statement (e.g. "How often do you feel left out?") on a 4-point scale (1 = *Never* to 4 = *Always*). Scores were calculated as the mean of the items (reverse-scoring as needed), with higher scores indicating more loneliness. This scale has established reliability and validity (Russell 1996, Vassar and Crosby 2008), with strong internal consistency in this sample (α = .91).

Analytic plan

SPSS version 28 was used to conduct the central analyses. First, we examined the intercorrelations among the ROIs within the salience (amygdala, dACC, anterior insula) and social processing (mPFC, PCC, precuneus, STS, TPJ) networks to support the creation of two composite scores reflecting the average of activation across regions within each network.

Second, we conducted hierarchical multiple regression analyses examining the interactive effect of stress and neural activation to threat (vs. reward) feedback on depression. Prior to analysis and calculation of the interaction terms, each variable was standardized. The main effects of stress and neural activation were entered at the first step, and the two-way Interpersonal Stress × Neural Activation interaction terms were entered at the second step. Separate analyses were conducted for the two networks. We graphed the interactions with R package ggplot2 (Wickham 2016) using a standard method recommended by Aiken and West (1991) by estimating simple slopes at low (-1 *SD*) and high (+ 1 *SD*) levels of neural activation (Aiken and West 1991). We also examined two indexes to determine whether findings were consistent with a plasticity model wherein the balance of sensitivity to threat vs. reward would have different implications for emotional adjustment depending on stress exposure (for additional information about these indexes, see Supplementary data; Roisman et al. 2012, Del Giudice 2017): (1) the Regions of Significance (RoS); and (2) the Proportion of Interaction (PoI).

Next, we conducted mediated-moderation analyses to determine whether loneliness accounted for the interactive effects of stress and neural activation on depression. Several conditions must be satisfied to demonstrate mediated moderation (Muller et al. 2005). Condition 1 requires that the magnitude of the overall effect of the independent variable (stress) on the dependent variable (depression) depends on the moderator (neural activation); Condition 2 requires that the mediator (loneliness) accounts for the overall moderation effect. For this to be the case, either the effect of stress on loneliness depends on neural activation and the average partial effect of loneliness on depression is significant (non-zero) and/or the partial effect of loneliness on depression depends on neural activation and the average effect of stress on loneliness is significant (non-zero). As a result, moderation of the residual direct effect of stress on depression is reduced compared to the overall moderated effect (for additional information about testing mediated moderation, see Supplementary data).

Results

Creation of composite scores and descriptive information

Correlational analyses revealed significant intercorrelations among the ROIs within the salience (rs = .56–.72, ps < .001) and social processing (rs = .56–.85, ps < .001) networks. We therefore created composite scores reflecting average activation within each network. Supplementary Table 1 presents descriptive information and correlations.

Interpersonal stress × neural activation contributions to depression

Salience network

Analyses revealed a significant effect of stress, a nonsignificant effect of neural activation, and a significant Interpersonal Stress × Neural Activation interaction (Table 1). As shown in Fig. 2a, decomposition of this interaction revealed that higher stress was significantly associated with depression in girls with low, B = 3.74, *SE* = 1.00, $t(86) = 3.73$, $p < .001$, but not high, B = 0.13, *SE* = 1.17, $t(86) = 0.11$, $p = .91$, salience network activation to threat vs. reward. The lower-bound and upper-bound RoS were at –2.90 *SD* and .84 *SD*, respectively. The PoI was 38% to the left of the crossover and 62% to the right of the crossover. At low stress, girls with high activation to threat vs. reward had depression scores *higher* than those with low activation to threat vs. reward. At high stress, girls with high activation to threat vs. reward had depression scores *lower* than those with low activation to threat vs. reward.

Social processing network

Analyses revealed a significant effect of stress, a nonsignificant effect of neural activation, and a significant Interpersonal Stress × Neural Activation interaction (Table 1). As shown in Fig. 2b, decomposition of this interaction revealed that higher stress was significantly associated with depression in girls with low, B = 4.24, *SE* = 1.21, $t(86) = 3.51$, $p = .001$, but not high, B = 0.93, *SE* = .99, $t(86) = 0.94$, $p = .35$, social processing network activation to threat vs. reward. The lower-bound and upper-bound RoS were at –2.89 *SD* and 2.77 *SD*, respectively. The PoI was 50% to the left of the crossover and 50% to the right of the crossover. At low stress, girls with high activation to threat vs. reward had depression scores *higher* than those with low activation to threat vs. reward. At high stress, girls with high activation to threat vs. reward had depression scores *lower* than those with low activation to threat vs. reward.

Interpersonal stress × neural activation contributions to loneliness

Salience network

Analyses revealed a nonsignificant effect of stress, a nonsignificant effect of neural activation, and a significant Interpersonal Stress × Neural Activation interaction (Table 2). As shown in Fig. 3a, decomposition of this interaction revealed that higher stress was significantly associated with loneliness in girls with low, B = 0.21, *SE* = .06, $t(86) = 3.34$, $p = .001$, but not high, B = –0.06, *SE* = .06, $t(86) = -1.00$, $p = .32$, salience network activation to threat vs. reward. The lower-bound and upper-bound RoS were at –.77 *SD* and .93 *SD*, respectively. The PoI was 53% to the left of the crossover and 47% to the right of the crossover. At low stress, girls with high activation to

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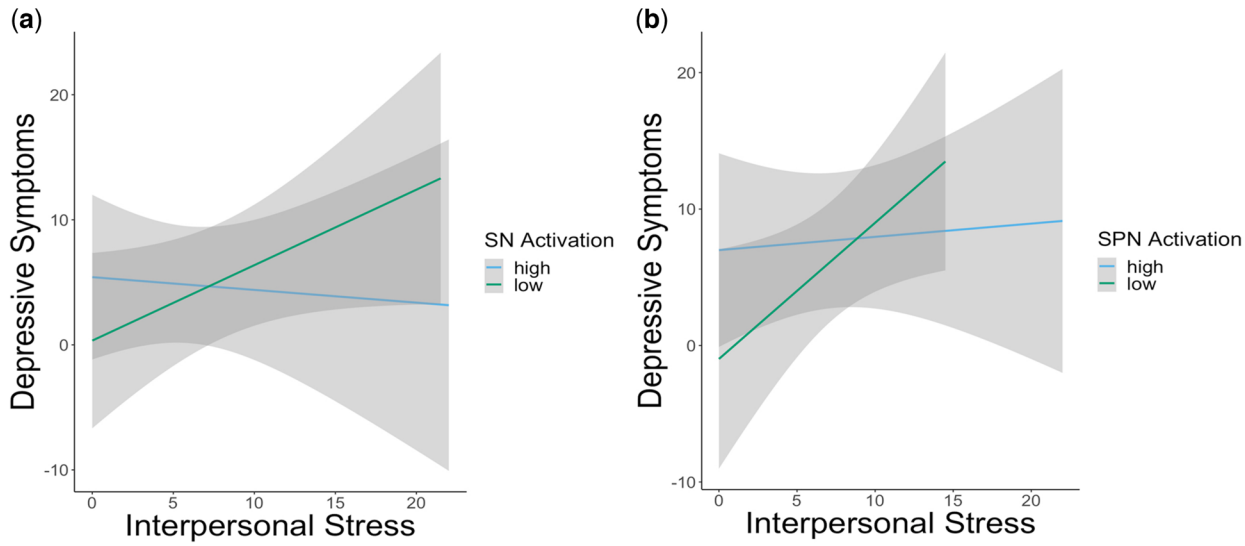

Figure 2. Predicting depression from the interactive contribution of interpersonal stress and: (a) salience network activation, and (b) social processing network activation in response to social threat vs. reward.
Note. SN = salience network. SPN = social processing network. Shaded areas represent 95% confidence intervals.

Table 1. Predicting depression from interpersonal stress and neural activation to social threat vs. reward.

	Salience network			Social processing network		
Predictors	**ß**	**t**	***p* (FWE)**	**ß**	**t**	***p* (FWE)**
Interpersonal stress	.26	2.53	.01 (.01)	.35	3.34	.001 (.002)
Neural activation	−.06	−.59	.56 (.99)	−.01	−.007	.99 (.99)
Stress × activation	−.24	−2.33	.02 (.04)	−.22	−2.11	.04 (.04)

Note. ßs represent standardized coefficients. FWE = family-wise error rate.

threat vs. reward had loneliness scores *higher* than those with low activation to threat vs. reward. At high stress, girls with high activation to threat vs. reward had loneliness scores *lower* than those with low activation to threat vs. reward.

Social processing network

Analyses revealed a significant effect of stress, a nonsignificant effect of neural activation, and a significant Interpersonal Stress × Neural Activation interaction (Table 2). As shown in Fig. 3b, decomposition of this interaction revealed that higher stress was significantly associated with loneliness in girls with low, B = 0.21, *SE* = .06, *t*(86) = 3.34, *p* = .001, but not high, B = −0.05, *SE* = .06, *t*(86) = −0.84, *p* = .40, social processing network activation to threat vs. reward. The lower-bound and upper-bound RoS were at −.08 *SD* and 2.26 *SD*, respectively. The PoI was 77% to the left of the crossover and 23% to the right of the crossover. At low stress, girls with high activation to threat vs. reward had loneliness scores *higher* than those with low activation to threat vs. reward. At high stress, girls with high and low activation to threat vs. reward had similar levels of loneliness.

Tests of mediated moderation

Salience network

Analyses revealed a significant effect of loneliness and a nonsignificant Loneliness × Neural Activation interaction (Table 3). The residual effect of the Interpersonal Stress × Neural Activation interaction on depression was no longer significant, suggesting that loneliness mediated the interactive contribution of stress and neural activation to depression. At low activation to threat vs. reward, we found a significant conditional indirect effect of stress on depression via loneliness (IE = 2.19, SE = 1.10, confidence interval [.35, 4.55]). The effect proportion revealed that loneliness accounted for 30.02% of the total effect of stress on depression in girls with low salience network activation. As expected, at high activation to threat vs. reward, the conditional indirect effect of stress on depression via loneliness was nonsignificant (IE = −.33, SE = .40, confidence interval [−1.16, .45]).

Social processing network

Analyses revealed a significant main effect of loneliness and a nonsignificant Loneliness × Neural Activation interaction (Table 3). The residual effect of the Interpersonal Stress × Neural Activation interaction on depression was no longer significant, suggesting that loneliness mediated the interactive contribution of stress and neural activation to depression. At low activation to threat vs. reward, we found a significant indirect effect of stress on depression via loneliness (IE = 2.45, SE = 1.54, confidence interval [.06, 6.01]). The effect proportion revealed that loneliness accounted for 34.94% of the total effect of stress on depression in girls with low social processing network activation. As expected, at high activation to threat vs. reward, the conditional indirect effect of stress on depression via loneliness was nonsignificant (IE = −.38, SE = .51, confidence interval [−1.40, .67]).

Summary

A summary of evidence for each condition required to support mediated moderation is available in the Supplementary data. Analyses examining the specificity of the results to interpersonal vs. noninterpersonal stress (Supplementary Tables 2–4) as well as to the networks of interest (Supplementary Tables 5–10) also are presented in the Supplementary data.

Discussion

Navigating increasingly complex social dynamics during adolescence can challenge girls' emotional adjustment (Rudolph 2009).

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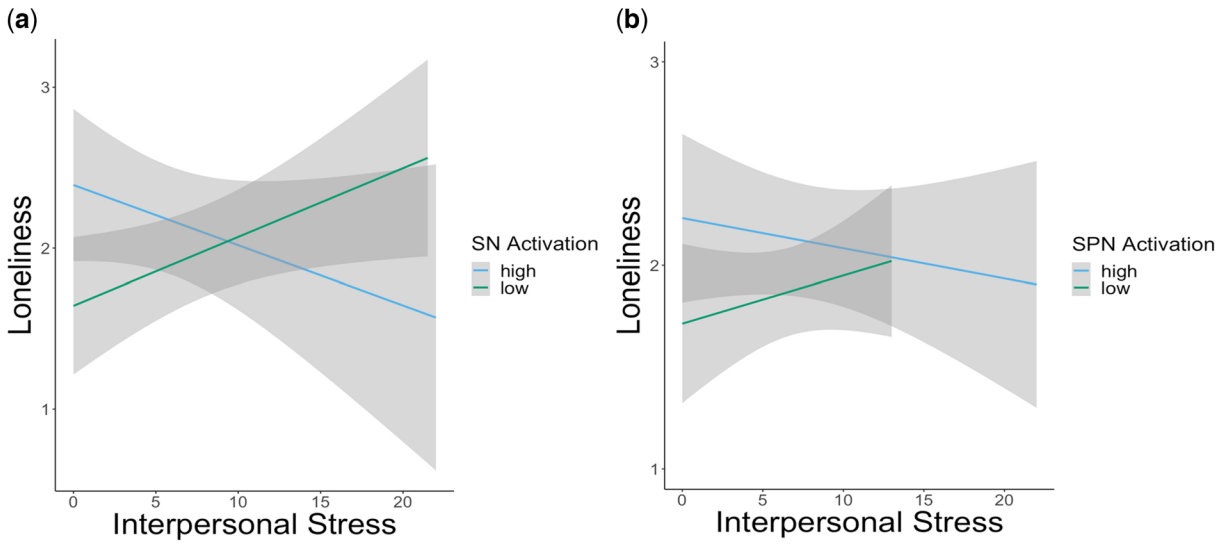

Figure 3. Predicting loneliness from the interactive contribution of interpersonal stress and: (a) salience network activation, and (b) social processing network activation in response to social threat vs. reward.
Note. SN = salience network. SPN = social processing network. Shaded areas represent 95% confidence intervals.

Table 2. Predicting loneliness from interpersonal stress and neural activation to social threat vs. reward.

	Salience network			Social processing network		
Predictors	***ß***	***t***	***p* (FWE)**	***ß***	***T***	***p* (FWE)**
Interpersonal stress	.16	1.54	.13 (.13)	.26	2.49	.02 (.03)
Neural activation	.02	.19	.85 (.85)	.17	1.66	.10 (.20)
Stress × activation	−.30	−2.82	.006 (.008)	−.28	−2.72	.008 (.008)

Note. ßs represent standardized coefficients. FWE = family-wise error rate.

Table 3. Predicting depression from interpersonal stress, neural activation to social threat vs. reward, and loneliness.

	Salience network			Social processing network		
Predictors	***ß***	***t***	***p* (FWE)**	***ß***	***t***	***p* (FWE)**
Interpersonal stress	.16	1.67	.10 (.10)	.22	2.18	.03 (.07)
Neural activation	−.07	−.71	.48 (.48)	−.08	−.87	.39 (.48)
Stress × activation	−.11	−1.09	.28 (.42)	−.08	−.82	.42 (.42)
Loneliness	.43	4.39	.001 (.001)	.45	4.52	.001 (.001)
Loneliness × activation	−.13	−1.32	.19 (.38)	−.06	−.60	.55 (.55)

Note. ßs represent standardized coefficients. FWE = family-wise error rate.

Supporting contemporary developmental neuroscience models that emphasize social context × neural activation interactions (Schriber and Guyer 2016, Rudolph et al. 2016b, Crone et al. 2020, Guyer 2020, Rudolph et al. 2020, Pagliaccio et al. 2023), this study revealed that successful negotiation of interpersonal stress is contingent on individual differences in adolescent girls' neural attunement to social cues. Specifically, the balance of neural sensitivity to threat vs. reward moderated the link between social experiences and adolescent girls' depression. Moreover, these effects were partially accounted for by their sense of loneliness, implicating fulfilment of—or threats to—belonging needs as a critical factor explaining the link between neural attunement to social cues and adolescent emotional health or ill-being. Consistent with interpersonal theories of adolescent depression (e.g. Rudolph 2009) and our focus on neural activation to social cues, supplemental analyses supported the specificity of these findings to girls' exposure to interpersonal, but not noninterpersonal, stressors as well as to activation of the salience and social processing networks, but not the primary visual cortex. Results predicting depression, but not loneliness, were similar for the ventral striatum, a region that has been implicated in processing of reward but also has been found to be relevant to processing threat and other aversive stimuli (Lindquist et al. 2016, Telzer 2016).

Interpersonal stress × neural sensitivity predicting loneliness and depression

Consistent with hypotheses, interpersonal stress exposure was associated with elevated loneliness and depression in girls with dampened activation in the salience and social processing networks in response to social threat vs. reward. During adolescence, maturation of salience and social processing networks allows for more sophisticated social-cognitive processes that likely form the basis for increasing positive engagement within the peer context (Nelson et al. 2005, Andrews et al. 2020). Heightened salience network activation in response to non-belonging may prompt girls living in high-stress contexts to attribute more motivational significance to threat feedback and foster increases in flexible goal pursuit, such as engagement in affiliative behaviours to regain social belonging. Indeed, prior research reveals that activation of the salience network in response to misalignment with a group predicts behaviours aimed at social realignment (Tomlin et al. 2013). Likewise, heightened activation of the social processing network in response to non-belonging may potentiate more sophisticated reasoning about social stressors, such as attempts to understand the intentions of peers or how one can align oneself better with peer norms, perhaps enhancing efforts to effectively resolve stressors. Supporting this idea, adolescents who perform better on mentalizing tasks, which are subserved by the social processing network, report less loneliness and peer rejection (Andrews et al. 2020). In contrast, girls with dampened threat vs. reward sensitivity may be less motivated or able to effectively process and flexibly engage with social stressors, contributing to feelings of loneliness and depression.

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However, dampened threat vs. reward sensitivity was associated with particularly low loneliness and depression in girls living in low-stress contexts. These girls have less of an inherent need to monitor their surroundings for social threats; indeed, they likely benefit from attending more to favourable social input. Thus, heightened neural attunement to threat vs. reward in these contexts may reflect oversensitivity to potential or perceived threats of non-belonging, resulting in unnecessary perseveration about one's status, unfounded rejection sensitivity, and social wariness as well as a failure to respond to favourable social cues, resulting in loneliness and depression. Consistent with this interpretation, unnecessary activation of the salience network may lead to overestimation of the importance of social stimuli and consequent over-mobilization of stress responses in non-threatening situations (Schimmelpfennig et al. 2023).

Contributions, limitations, and future directions

This study highlights the critical importance of refining developmental affective neuroscience theories of adolescent development to consider the context-specific implications of the relative balance of neural sensitivity to social threat vs. reward cues. Maturation in the salience and social processing networks likely plays a significant role in shaping how adolescent girls navigate rising social complexity and stressors during this developmental stage. Using a state-of-the-art comprehensive interview assessing exposure to naturally occurring interpersonal stressors along with analyses examining differential susceptibility to stress, this study reveals meaningful trade-offs associated with adolescent girls' threat vs. reward sensitivity, a pattern that generally replicated across the two networks. Thus, these results extend a small, but growing, body of evidence demonstrating that different aspects of social experience interact with neural sensitivity to social cues to predict emotional well-being (Rudolph et al. 2016b, Kim-Spoon et al. 2017, Jarcho et al. 2019, Rudolph et al. 2020, Pagliaccio et al. 2023), and they support an extension of the ACM (Ellis et al. 2017) to incorporate patterns of neural sensitivity to social cues.

The context-dependent adverse sequelae of both dampened and heightened threat vs. reward activation observed in this study are consistent with prior mixed findings yielded by research examining links between social threat vs. reward responsivity and depression, as described earlier, as well as with more general theoretical frameworks and empirical evidence regarding the psychological and physical impact of hypo- vs. hyperreactivity to stress (Carroll et al. 2017). Consistent with the ACM, observed links between heightened reactivity and depressive symptoms have been interpreted as indicative of overvigilance to threat, whereas observed links between blunted reactivity and depressive symptoms have been interpreted as indicative of failures in motivated engagement necessary to adapt to changing environmental demands (Carroll et al. 2017, Ellis et al. 2017), both of which may play a role in loneliness and depression. Given these opposing patterns, it will be important for future research to further elucidate when neural sensitivity to threat vs. reward confers emotional benefits vs. costs. Several factors beyond the recent social context in which adolescents live may alter the meaning of neural activation patterns.

First, these patterns of activation may have different implications depending on the nature of the social threat or reward. This study examined neural activation in response to one specific form of social feedback, namely information about whether girls fit in with peer group norms. This form of feedback may differ from social cues elicited by other social threat and reward paradigms, such as those involving direct exclusion vs. inclusion or rejection vs. acceptance with no clear indication of the reason. In day-to-day interactions, when adolescents receive feedback that their specific preferences diverge from peers, they can actively cope with this feedback through strategic efforts to increase their alignment with peers and sense of belonging or to search for new peer groups with similar preferences. Indeed, activation to feedback about misalignment from group norms predicts future efforts to realign with the group (Tomlin et al. 2013). However, a tendency to show heightened neural activation to less controllable social threats may serve to exacerbate emotional distress. Thus, it will be important to investigate whether this pattern of findings replicates using other social evaluation paradigms or is specific to circumstances in which adolescents may perceive some degree of control over their peer status.

Second, to fully understand why the same patterns of activation can confer benefits or risks, it will be important to elucidate the developmental origins of these patterns. According to the ACM (Ellis et al. 2017), more and less sensitive profiles stem from early experiences. Specifically, a sensitive profile develops in safe and supportive environments, whereas a vigilant profile develops in stressful contexts; similarly, a buffered profile develops in moderately stressful environments, whereas an unemotional profile develops in severely stressful or traumatic environments. The ramifications of heightened or dampened neural sensitivity to threat vs. reward may therefore depend not only on adolescents' current social contexts but also on their early life experiences. Moreover, the consequences of heightened or dampened threat sensitivity may change over time. Temporary increases in neural activation in response to social threats may prepare adolescents to cope with challenges. Yet, persistent activation across extended periods of time may eventually compromise emotional health. Future research therefore needs to examine these processes using long-term longitudinal designs to determine the antecedents of various neural profiles as well as to track neural activation and emotional adjustment across development.

Third, the advantages or disadvantages of neural activation to social cues may depend upon other attributes of adolescents. For example, adolescents with strong self-regulatory skills (e.g. Davis et al., in press) or social competencies may be able to channel heightened threat sensitivity in ways that help them repair their relationships or form new relationships in the face of interpersonal stress, but threat sensitivity may be detrimental for adolescents who are unable to translate heightened neural attunement to threat into effective behavioural efforts to regain a sense of belonging. Given some variability in the effects in the present study, as reflected in the confidence bands, it will be important to identify individual differences in the impact of different patterns of neural activation on adolescent girls' ability to cope effectively with interpersonal stressors. It also may be the case that there is variability in the extent to which adolescent girls view misalignment with peer group norms as a social threat as some girls may value individuality over conformity. The present study did not include ratings of perceived threat during the social feedback task, and thus we are unable to determine the role of subjective threat perceptions; it would be beneficial for future research to consider such perceptions to develop a more comprehensive understanding regarding feelings of belonging and non-belonging and their neural correlates in adolescent girls.

Continued refinement of developmental affective neuroscience theories of adolescent development also will require identifying various mechanisms that account for the emotional consequences of social context × neural activation interactions. For example, we speculated that dampened activation to threat vs. reward in high-stress contexts may exacerbate the effects of stress exposure by decreasing strategic efforts to engage with stressors and resolve

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relationship difficulties, whereas heightened activation to threat vs. reward in low-stress contexts may result in excessive vigilance and perseveration on perceived threats and failure to benefit from favourable social interactions and relationships. Future studies should directly investigate these and other relevant mechanisms.

Finally, this study focused on adolescent girls given their heightened vulnerability to social-evaluative concerns, interpersonal stressors, and depression (Rudolph and Conley 2005, Rudolph 2009, Somerville 2013, Guyer et al. 2014). Despite the particular relevance of these processes to adolescent girls, it will be important to examine whether this pattern of findings generalizes to boys or to girls at other developmental stages.

Conclusion

This study provides a novel perspective on neural markers of loneliness and depression in adolescent girls, suggesting that the relative balance of neural activation to social threat vs. reward shapes how adolescent girls negotiate stressful vs. favourable social environments. Specifically, findings implicate the adaptational value of a match between girls' social experiences and patterns of neural attunement to social cues. More broadly, this study illustrates the pressing need for more nuanced perspectives on the meaning and implications of activation in particular brain regions for adolescent development and risk for psychopathology as well as for research that directly examines processes through which emotional risk or resilience emerges.

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Author contributions

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Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest

None declared.

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Data Availability

Data are available from the first author upon reasonable request.

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