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Girls' challenging social experiences in early adolescence predict neural response to rewards and depressive symptoms

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ABSTRACT

Developmental models of psychopathology posit that exposure to social stressors may confer risk for depression in adolescent girls by disrupting neural reward circuitry. The current study tested this hypothesis by examining the relationship between early adolescent social stressors and later neural reward processing and depressive symptoms. Participants were 120 girls from an ongoing longitudinal study of precursors to depression across adolescent development. Low parental warmth, peer victimization, and depressive symptoms were assessed when the girls were 11 and 12 years old, and participants completed a monetary reward guessing fMRI task and assessment of depressive symptoms at age 16. Results indicate that low parental warmth was associated with increased response to potential rewards in the medial prefrontal cortex (mPFC), striatum, and amygdala, whereas peer victimization was associated with decreased response to potential rewards in the mPFC. Furthermore, concurrent depressive symptoms were associated with increased reward anticipation response in mPFC and striatal regions that were also associated with early adolescent psychosocial stressors, with mPFC and striatal response mediating the association between social stressors and depressive symptoms. These findings are consistent with developmental models that emphasize the adverse impact of early psychosocial stressors on neural reward processing and risk for depression in adolescence.

Abbreviations: BA, Brodmann Area; BOLD, blood-oxygen-level-dependent; EPI, echo planar imaging; fMRI, functional magnetic resonance imaging; LN, natural log transformation; mPFC, medial prefrontal cortex; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; PGS, Pittsburgh Girls Study; PGS-E, Pittsburgh Girls Study-Emotions Substudy; ROI, region of interest; TE, echo time; TR, repetition time.

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1. Introduction

Depression is a leading cause of global disease burden with a 16.6% lifetime prevalence (Kessler et al., 2005; World Health Organization, 2008). Although the prevalence of depression during childhood is less than 3% (Fleming and Offord, 1990), rates of depression increase sharply during adolescence with the first onset occurring between the ages of 12 and 19 years in 20% of individuals who experience depression during their lifetimes (Kessler et al., 2005). Rates of depression are particularly high in adolescent girls (cumulative prevalence of 20.8%), who are twice as likely to become depressed compared to adolescent boys (Kessler, 1993). Because depression is a recurrent disorder, experiencing depression for the first time in childhood or adolescence, compared with onset later in life, results in greater lifetime depression-related disability (Kovacs, 1997). Thus, studies that examine risk factors for the development of depression in adolescent girls are particularly relevant for prevention and intervention efforts.

Parent and peer relationships are both important to adolescent development, and stressors in either social domain can increase risk for psychopathology. There is a large body of research documenting the impact that parenting behaviors, such as emotional responsiveness and warmth, have on children's emotional development broadly (Eisenberg et al., 1998; Morris et al., 2007), and on depressive symptoms specifically (McLeod et al., 2007). Additional data from longitudinal studies indicate that low parental warmth increases risk for depression in children and adolescents (Ge et al., 1994, 1996; Hipwell et al., 2008) and decreases resilience in adolescents with a high genetic and socioeconomic risk for the disorder (Brennan et al., 2003; Masten et al., 1999). Early adolescence in particular is characterized by decreases in parent–child relationship quality (Loeber et al., 2000; McGue et al., 2005), which could contribute to the higher risk for psychopathology during this developmental period relative to childhood.

Although parents continue to be important sources of social support and play a role in adolescents' mental health, peer relationships become increasingly important as adolescents individuate from parents and form social hierarchies with peers. Stressful interactions with peers, including emotional exclusion and aggression, are particularly difficult experiences for adolescents (Nelson et al., 2005; O'Brien and Bierman, 1988), and approximately 50% of sixth and seventh graders experience these forms of peer victimization (Wang et al., 2009). Peer victimization is also associated with increased risk for depression. A meta-analysis of cross-sectional studies indicated that peer victimization during childhood or adolescence was moderately associated with depression, and had a stronger relationship with depression than other negative psychosocial outcomes such as anxiety (Hawker and Boulton, 2000). Peer victimization also predicted later depressive symptoms in several longitudinal studies of children and adolescents (Keenan et al., 2010b; Sweeting et al., 2006; Vuijk et al., 2007).

Although there is substantial evidence that low parental warmth and peer victimization are both associated with risk for depression, few studies have examined the potential neural mechanisms of these effects. Several developmental models of depression have focused on the interface between adolescent social development and brain development in conceptualizing vulnerability to depression (Davey et al., 2008; Forbes and Dahl, 2005; Nelson et al., 2005). In this view, adolescent development of neural reward circuitry is a key process in the etiology of depression and depressive anhedonia. Furthermore, stressors that occur during adolescence may disrupt the development of reward-related circuitry, such as the medial prefrontal cortex (mPFC) – a region implicated in self-relevant and social processing as well as reward function (Amodio and Frith, 2006; Northoff and Hayes, 2011) – and the ventral striatum – a region implicated in motivation to obtain rewards (Berridge and Robinson, 1998). Consistent with these neurodevelopmental models of depression, neural response during reward anticipation and following rewarding outcomes is disrupted in adolescents and adults with depression (Forbes et al., 2009; Knutson et al., 2008; Pizzagalli et al., 2009; Steele et al., 2007). There is also evidence that exposure to early life stress, such as childhood maltreatment, is associated with reductions in reward-directed behavior (Guyer et al., 2006), and maternal deprivation produces anhedonic behaviors (e.g., decreased sucrose preference) in rodents and non-human primates (Pryce et al., 2005), behaviors that are supported by neural reward circuitry (Berridge and Robinson, 1998).

The aim of the present paper was to examine the relationship between social stressors experienced in early adolescence and neural response to rewards and depressive symptoms in later adolescence. Low parental warmth, peer victimization, and depressive symptoms were assessed at ages 11 and 12 and used to predict neural response during reward anticipation at age 16 in a large sub-sample of adolescent girls from the ongoing Pittsburgh Girls Study (PGS). Depressive symptoms were also assessed at age 16 and used to test associations with neural response to potential rewards in areas that were also associated with early adolescent social stressors. Based on previous studies showing increased mPFC response during reward anticipation in depressed adolescents (Forbes et al., 2009) and adults (Knutson et al., 2001), we expected that low parental warmth, peer victimization, and depressive symptoms would be associated with increased mPFC response during reward anticipation. We also expected that low parental warmth, peer victimization, and depressive symptoms would be associated with decreased ventral striatum response to potential rewards, consistent with other studies that found decreased striatal response to rewards in clinically depressed samples (Forbes et al., 2009; Pizzagalli et al., 2009; Steele et al., 2007). Finally, we hypothesized that neural response to potential rewards in the mPFC and ventral striatum would mediate the association between early adolescent social stress and depressive symptoms at age 16, even after controlling for early adolescent depressive symptoms.

2. Materials and methods

2.1. Participants

Participants were girls and their birth mothers recruited from the longitudinal Pittsburgh Girls Study (Keenan et al., 2010a). The PGS sample was formed following an enumeration of households with girls between the ages of 5 and 8 in the city of Pittsburgh. Of the 2992 eligible families, 2451 (85%) were successfully re-contacted and agreed to participate in a prospective study. Girls in the current fMRI study were participants in the ongoing longitudinal PGS Emotions sub-study (PGS-E), a study of precursors to depression beginning with laboratory assessments of girls and their mothers at age 9 years. PGS-E participants were drawn from the youngest participants in the PGS who either screened high on measures of depressive symptoms at age 8, or who were included in a random selection from the remaining 8-year old PGS girls. Girls whose scores fell at or above the 75th percentile by their own report on the Short Moods and Feelings Questionnaire (Angold et al., 1995) and/or by their mother's report on the Child Symptom Inventory (Gadow and Sprafkin, 1997) comprised the screen-high group ($N = 135$). There were significantly more African American than European American girls in the screen-high group. Thus, the girls selected from the remainder were matched to the screen-high group on race. Of the 263 families eligible to participate in the PGS-E, 232 (88.2%) agreed to participate and completed the first laboratory assessment when the girls were nine years of age. Retention in each year was above 95%.

At age 16, 194 participants completed the annual PGS-E assessment and 147 completed the reward task and fMRI scan (22 refused to be scanned or could not be scheduled, 25 were ineligible for scanning at the time of the study due to pregnancy, braces, or other scanning exclusions). An additional 27 participants who completed the scan were excluded from analyses. Reasons for exclusion included <80% striatum coverage ($n = 12$), >2 mm or 2° average movement in any direction during the scan ($n = 6$), poor quality scan ($n = 2$), incidental findings ($n = 1$), <80% response rate on the reward task ($n = 2$), and not understanding the reward task ($n = 4$). Subsequently, data from 120 participants were available for analyses. Of this sample, 65% were Black, 27% were White, and 8% were multi-racial. Sixty percent of the study families received some form of public assistance when the girls were between the ages of 9 and 12, with 26% of the families receiving public assistance continuously during that period. The mean number of years that participants' families received public assistance was 0.43 ($SD = 0.42$), indicating that participants' families received public assistance slightly less than 2 out of 4 years (ages 9–12) on average. The study distribution for race and public assistance was representative of the full PGS-E sample.

2.2. Questionnaires and interviews

Low parental warmth was assessed by parent report using six items from the Parent–Child Rating Scale (Loeber et al., 1998). Items (e.g., "How often have you wished [your daughter] would just leave you alone") were scored on a three-point scale (1 = 'almost never' to 3 = 'often'). Higher scores were indicative of lower parental warmth. Cronbach's α for low parental warmth items ranged from 0.75 (age 11) to 0.76 (age 12). Scores at ages 11 and 12 were correlated with one another (Pearson's $r = 0.59$, $p < 0.001$) and were averaged for analysis ($M = 8.71$, $SD = 2.09$).

Peer victimization was assessed using nine items from the Peer Experiences Scale (Vernberg et al., 1999). Items assessed victimization by physical aggression and social exclusion on a five-point scale (0 = 'never' to 4 = 'a few times per week'). Cronbach's α for the nine victimization items ranged from 0.85 (age 11) to 0.83 (age 12). Scores at ages 11 and 12 were correlated with one another (Pearson's $r = 0.63$, $p < 0.001$) and were averaged for analysis ($M = 3.33$, $SD = 4.30$).

Current symptoms of depression (i.e., past month) were measured in each year using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (Kaufman et al., 1997), a semi-structured psychiatric diagnostic interview, which was administered separately to the mother and the girl by research assistants who were trained and monitored by a licensed clinical psychologist (KK). Each of the nine symptoms of depression was assessed on a three-point scale (1 = 'not present', 2 = 'subthreshold', 3 = 'threshold') regardless of whether disturbance in mood or anhedonia were endorsed, thereby providing a continuous measure of depression symptom counts. Thirteen percent of the girls' interviews were randomly selected and coded for assessing interrater reliability. For youth-report data, the average intraclass correlation coefficient for total number of symptoms was 0.92. For caregiver report, the intraclass correlation coefficient for total number of symptoms was 0.58. A symptom was considered present if it was endorsed by either informant. At each wave of data collection the alpha coefficient for the nine depression symptoms based on the combined informants was above 0.55.

2.3. Reward task

Participants performed a reward-guessing task with a slow event-related design during fMRI acquisition. This task was designed to index brain activation during anticipation of monetary incentives. Previous studies show that this task reliably elicits activation in neural reward circuitry (Forbes et al., 2009, 2010).

Participants were instructed to guess whether the value of a visually presented card, with possible value from 1 to 9, would be greater than or less than five. Each trial began with the presentation of a blank card. Participants had 4 s to guess the value of the card via button press. The type of trial was then displayed for 6 s using an image with hands shuffling cards overlaid on an upward facing yellow arrow to indicate potential reward trials or a downward facing yellow arrow to indicate potential loss trials. This was followed by presentation of the "actual" value of the card for 500 ms, feedback on the trial outcome for 500 ms (a green upward-facing arrow for win, a red downward-facing arrow for loss, or a yellow circle for a no-change outcome), and a crosshair was displayed for 9 s. There were

24 trials, 20 s each, administered over a single 8 min run. Trials were presented in pseudorandom order and outcomes were predetermined with a balanced number of trial types (12 possible-win, 12 possible-loss; 6 win, 6 loss, and 12 neutral outcomes). This number of trials was previously shown to be adequate to elicit a robust BOLD response in our regions of interest (Forbes et al., 2009). Participants were told that they would receive their winnings after the scan; in fact, all participants received $10.

2.4. MRI acquisition, processing, and analysis

Neuroimaging was conducted on a Siemens 3.0 T Tim Trio scanner. BOLD functional images were acquired using a gradient echo planar imaging (EPI) sequence that included 39 axial slices (3.1 mm wide) beginning at the cerebral vertex and extending across the entire cerebrum and most of the cerebellum (TR/TE = 2000/28 ms, field of view = 20 cm, matrix = 64 × 64). Scanning parameters were selected to optimize BOLD signal quality while maximizing whole brain coverage. A reference EPI scan was acquired before fMRI data collection to visually inspect for artifacts (e.g., ghosting) and ensure adequate signal across the entire volume. In addition, a 160-slice high-resolution sagittally acquired T1-weighted anatomical image was collected for co-registration and normalization of functional images (TR/TE = 2300/2.98 ms, field of view = 20 cm, matrix = 256 × 240).

Preprocessing and analysis of imaging data were conducted using Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm). Anatomical images were auto-segmented in SPM8 prior to analysis. Functional image preprocessing included spatial realignment to the first volume in the time series to correct for head motion, spatial normalization to Montreal Neurological Institute (MNI) stereotaxic space using a 12-parameter affine model, and image smoothing using a Gaussian filter set at 6 mm full-width half-maximum to minimize noise and individual differences in gyral anatomy. Voxel-wise signal was ratio-normalized to the whole-brain global mean. Preprocessed data were inspected prior to second-level analysis to ensure that all participants had good whole brain coverage, ventral striatum coverage of at least 80%, and less than 2 mm or 2° average movement in any direction during the scan.

Second-level random effects models were used to estimate neural response to rewards while accounting for scan-to-scan and between-participant variability. For each participant, condition effects were calculated at each voxel using paired *t*-tests for reward anticipation > baseline. Reward anticipation was defined as the 12 potential-win intervals that included the 6 s potential-win arrow, 500 ms number presentation, 500 ms arrow feedback and the first second of fixation (8 s total). The reward anticipation period extended 2 s beyond the potential-win arrow to account for the delay in hemodynamic response relative to neural activity and capture as much of the reward anticipation response as possible while avoiding substantial overlap with BOLD response to reward outcome events. The last 3 s of fixation for all 24 trials served as the baseline condition. By averaging the last 3 s of fixation across all trial outcomes (6 reward, 6 loss, 12 neutral), the baseline condition served as a relatively neutral comparison for contrasts with reward anticipation (Forbes et al., 2009, 2010).

Analysis of imaging data focused on four regions of interest (ROIs): striatum, mPFC, orbitofrontal cortex (OFC), and amygdala. ROIs were defined using PickAtlas 3.0.3 (http://fmri.wfubmc.edu/software/PickAtlas). The striatal ROI was defined as a sphere with a 20 mm radius, centered on the Talairach coordinates of $x = 0$, $y = 10$ and $z = -10$, and encompassing the ventral striatum (including nucleus accumbens) and dorsal striatum bilaterally. The mPFC ROI was defined as a sphere with a 25 mm radius, centered on Talairach coordinates $x = 0$, $y = 42$, $z = 18$, and encompassing BA32 and medial regions of BA9 and BA10. Spheres were used for the striatal and mPFC ROIs because this approach focuses analyses on the striatum and medial regions of BAs 9 and 10 more precisely than atlas-based anatomical masks of those regions (especially for mPFC, which includes medial sections of large prefrontal regions such as BA10). The OFC was defined as BA11 and BA47, and the amygdala was defined using the human PickAtlas label. AlphaSim (http://afni.nimh.nih.gov/afni/) cluster extent thresholds were calculated *a priori* to determine the minimum cluster size necessary to maintain a corrected $p < 0.05$ for each ROI (cluster extent thresholds: striatum = 189 voxels, mPFC = 178 voxels, OFC = 62 voxels, amygdala = 62 voxels).

Regression analyses were performed in SPM8 to determine whether low parental warmth and peer victimization were associated with reward anticipation across participants. Using results of these analyses, a second set of regression analyses were conducted to determine whether current depressive symptoms were associated with neural response during reward anticipation in regions that were also associated with low parental warmth or peer victimization. To accomplish this, functional masks were created based on significant clusters yielded by regressions of BOLD response on early adolescent social stressors for each of the four anatomical ROIs. These functional masks were saved and used as functional ROIs for regressions of depressive symptoms on BOLD response. Because scores for low parental warmth, peer victimization, and depressive symptoms were positively skewed, these scores were log-transformed prior to analysis to better approximate a normal distribution. A constant was added to the peer victimization and depression scores prior to log-transformation because raw scores included values of zero. To account for the potential relationship between early depressive symptoms and neural response to rewards at age 16, all regression analyses included depressive symptom count averaged across ages 9–12 as a covariate. To address potential contributions of SES to development of reward circuitry, regression analyses also included, as a covariate, the average number of years that participants' families received public assistance across ages 9–12. Regression weights and confidence intervals for significant clusters of activation were computed in SPSS using extracted SPM beta values for the average BOLD response across each significant cluster.

Finally, for each region that was significantly associated both with early adolescent social stressors and current

depressive symptoms, mediation analyses were used to examine whether neural response during reward anticipation accounted for a significant portion of the association between early adolescent social stress and later depressive symptoms. To accomplish this, a second set of functional masks was created based on significant clusters yielded by regressions of BOLD response on current depressive symptoms for each functional ROI described above. These functional masks were saved and used as functional ROIs for regressions of low maternal warmth on BOLD response and peer victimization on BOLD response. Average BOLD response beta values across each significant cluster were extracted from these regressions, and tested as a mediator of the relationships between low maternal warmth and depressive symptoms, and peer victimization and depressive symptoms. Mediation analyses were implemented using the bootstrap method with the SPSS PROCESS macro (Hayes, 2013). Average depressive symptom count from ages 9 to 12 and average years of family public assistance from ages 9 to 12 were included as covariates in mediation analyses.

3. Results

3.1. Participant characteristics and clinical outcomes

Of the 120 girls with analyzable fMRI data, 3 met criteria for current major depressive disorder and an additional 7 met criteria for minor depressive disorder at age 16. The point prevalence of major depression in the sample (2.5%) is consistent with the point prevalence of depression in epidemiologic studies of adolescents (3.37 [95% CI: 1.35, 5.39]; Lewinsohn et al., 1993). The mean number of depressive symptoms at age 16 was 1.18 ($SD = 1.35$). The mean number of depressive symptoms across ages 9–12 was 2.06 ($SD = 1.57$). One-tailed Pearson's correlations indicated that depressive symptoms at age 16 were positively associated with low parental warmth ($r = 0.42$, $p < 0.001$) and peer victimization ($r = 0.37$, $p < 0.001$) in early adolescence. Low parental warmth and peer victimization were modestly associated with each other ($r = 0.17$, $p = 0.03$).

3.2. Association between early adolescent social stressors and reward-related BOLD response

Lower levels of parental warmth were associated with increased response in the dorsal and rostral mPFC ($R^2 = 0.10$, beta = 0.26, 95% CI: 0.14, 1.02, $p = 0.01$), ventral striatum ($R^2 = 0.11$, beta = 0.28, 95% CI: 0.21, 1.11, $p = 0.004$), and amygdala ($R^2 = 0.11$, beta = 0.25, 95% CI: 0.10, 0.76, $p = 0.012$) during reward anticipation. Higher levels of peer victimization were associated with decreased response in the dorsal and rostral mPFC during reward anticipation ($R^2 = 0.10$, beta = −0.26, 95% CI: −0.27, −0.04, $p = 0.007$). OFC response during reward anticipation was not associated with either low parental warmth or peer victimization. Detailed SPM8 regression results are presented in Table 1 and Fig. 1.

3.3. Association between reward-related BOLD response and depressive symptoms

Higher levels of concurrent depressive symptoms were associated with increased response in regions of the rostral mPFC ($R^2 = 0.07$, beta = 0.19, 95% CI: −0.01, 0.33, $p = 0.06$) and ventral striatum ($R^2 = 0.06$, beta = 0.22, 95% CI: 0.01, 0.32, $p = 0.04$) that were also positively associated with low parental warmth. Detailed SPM8 regression results are presented in Table 2 and Fig. 2. In addition, bootstrap tests of mediation indicated that BOLD response in both the mPFC (ES = 0.15, 95% CI: 0.004, 0.40, $p < 0.05$) and ventral striatum (ES = 0.14, 95% CI: 0.001, 0.41, $p < 0.05$) significantly mediated the association between low parental warmth and depressive symptoms. Depressive symptoms were not significantly associated with neural response during reward anticipation in regions that were also associated with peer victimization.

4. Discussion

The results of the present study indicate that social stressors experienced by girls in early adolescence are associated with neural response to anticipated rewards at age 16. Low parental warmth at ages 11 and 12 had particularly robust associations with neural response to reward at age 16, with large clusters of increased activation in the mPFC and ventral striatum during reward anticipation. In contrast, the relationship between peer victimization at ages 11 and 12 and neural response to reward was more modest and in the opposite direction. Greater peer victimization was associated with *decreased* mPFC activation during reward anticipation, and it did not predict reward response in other reward-related ROIs. These results suggest that in early adolescence, low parental warmth may have a greater influence than peer victimization on later adolescent neural response to reward, and that different types of social stressors may influence reward circuitry in different ways. Of note, low parental warmth is likely to be more stable across child development than peer victimization (Loeber et al., 2000; Wang et al., 2009). Girls who experience low parental warmth at ages 11 and 12 may have experienced similar parenting behaviors at multiple time points in development, with cumulative influence on their brain development. Peer groups, in contrast, tend to shift frequently during adolescence (Hardy et al., 2002). Therefore, the experience of social exclusion or aggression may be more normative, inconsistent, and time-limited, with less robust influence than parental warmth on adolescent brain function.

We also found that regions of the mPFC and striatum that were correlated with early adolescent parental warmth were also positively related to depressive symptoms at age 16. In fact, neural response to potential rewards in the mPFC and striatum mediated the relationship between low parental warmth and depressive symptoms. The associations of early adolescent parental warmth and subsequent depressive symptoms with mPFC reward anticipation response were in the predicted direction: lower warmth predicted greater dorsal and rostral mPFC response, and higher depressive symptoms predicted

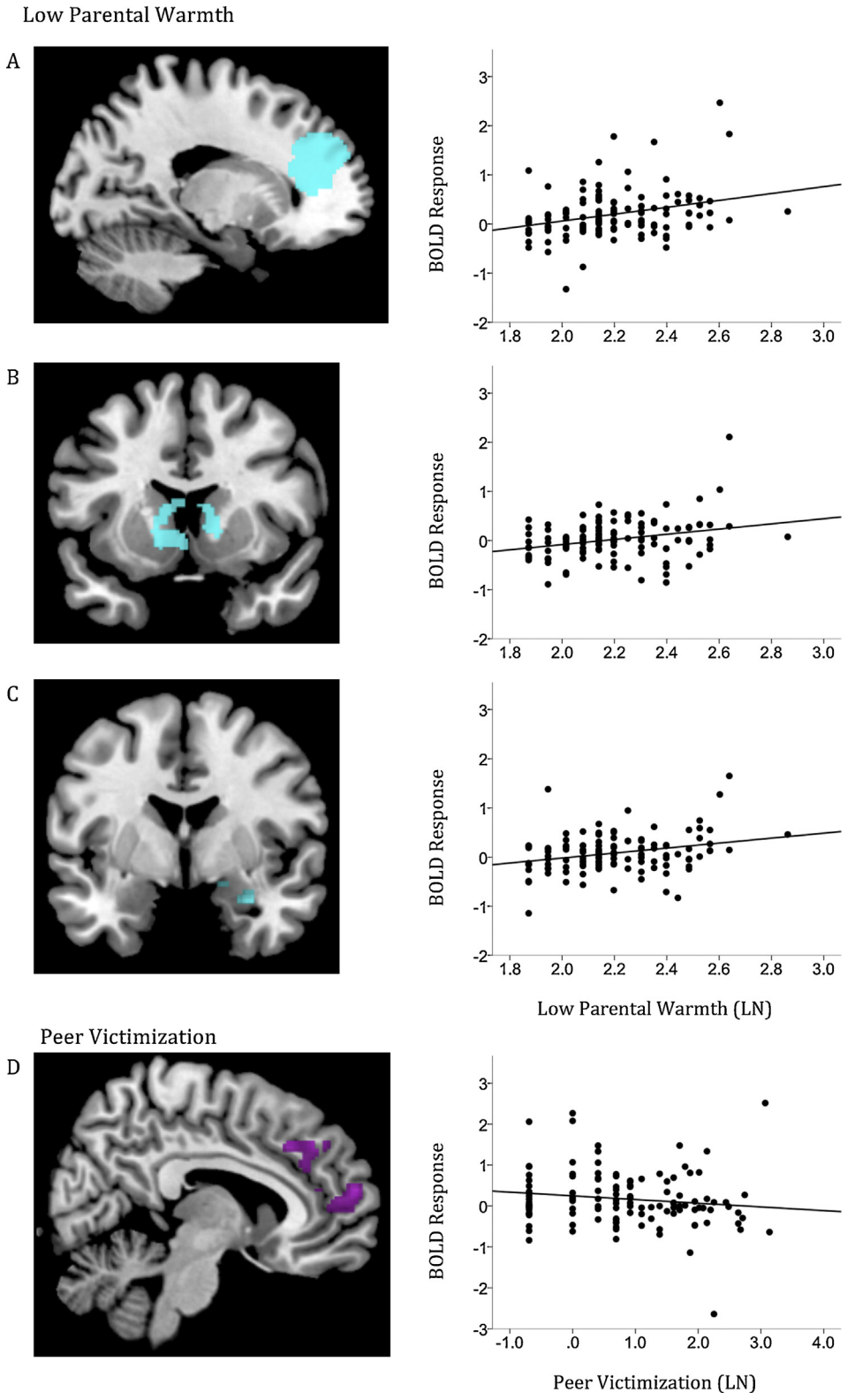

Fig. 1. Association between social stressors and blood-oxygen-level-dependent (BOLD) response during reward anticipation. Low parental warmth was positively associated with BOLD response in the dorsal and rostral mPFC (A; $R^2 = 0.10$), ventral striatum (B; $R^2 = 0.11$), and amygdala (C; $R^2 = 0.11$). LN = natural log transformation. Peer victimization was negatively associated with BOLD response in the rostral mPFC (D; $R^2 = 0.10$).

Table 1
Low parental warmth and peer victimization as predictors of BOLD response during reward anticipation.

Region	MNI coordinates			Cluster size	t (df = 115)
	x	y	z		
Low parental warmth associated with increased reward response					
mPFC (BA 9, 10, 32)	−18	56	30	2278	3.74**
Caudate head, caudate body, nucleus accumbens	10	6	16	1389	3.20*
Right amygdala	32	−2	−22	117	2.97
Peer victimization associated with decreased reward response					
mPFC (BA 10, 32)	0	50	10	372	3.19
mPFC (BA 8, 9, 32)	4	26	40	253	2.56

Note: Alpha Sim corrected $p < 0.05$ for all contrasts. BA, Brodmann Area; BOLD, blood-oxygen-level-dependent.
* $p < 0.05$ corrected for family-wise error at the cluster-level.
** $p < 0.01$ corrected for family-wise error at the cluster-level.

Table 2
Depressive symptoms predicting increased BOLD response during reward anticipation in regions that are also associated with low parental warmth.

Region	MNI coordinates			Cluster size	t (df = 116)
	x	y	z		
Caudate body, caudate head	−10	2	12	469	3.32
mPFC (BA 9)	16	54	28	146	2.33

Note. Alpha Sim corrected $p < 0.05$ for all contrasts. BA, Brodmann Area, BOLD, blood-oxygen-level-dependent.

greater rostral mPFC response. This is consistent with previous studies that found increased mPFC reward anticipation response in depressed participants (Forbes et al., 2009; Knutson et al., 2001). The mPFC is instrumental to evaluating the relative value of rewards and coordinating reward-related behavior (Rushworth and Behrens, 2008) as well as self-relevant and social processing (Amodio and Frith, 2006; Northoff and Hayes, 2011). Increased response in this region in individuals who have experienced low parental warmth or have higher depressive symptoms may reflect increased evaluation of personal performance on the task in light of previous experience or the imagined performance of others. Given that the rostral mPFC is also involved in self-related processing and internal monitoring

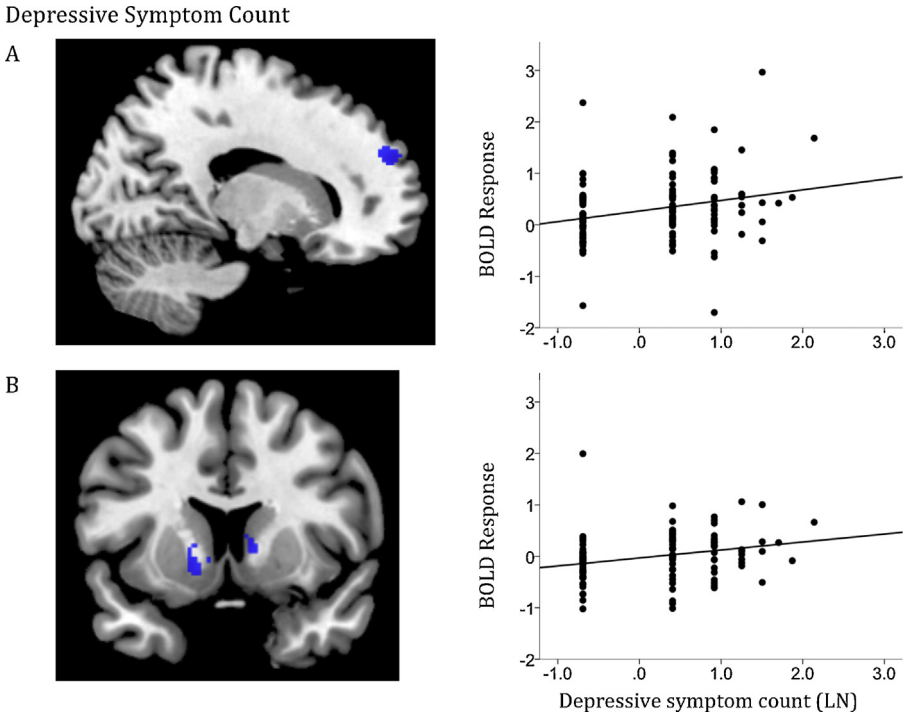

Fig. 2. Association between depressive symptoms and reward-related BOLD response in regions that were also associated with low parental warmth. Depressive symptoms were positively associated with BOLD response in the rostral mPFC (A; $R^2 = 0.07$) and ventral striatum (B; $R^2 = 0.06$) during reward anticipation. LN = natural log transformation.

(Amodio and Frith, 2006), increased response to reward in the mPFC could also reflect difficulty disengaging from this internal self-focus during the task.

In the present study, low parental warmth and higher levels of depressive symptoms were each independently associated with *increased* ventral striatal response during reward anticipation. This pattern was in the opposite direction to our prediction given the existing research in which *decreased* striatal response in depressed participants was observed relative to controls (Forbes et al., 2009; Pizzagalli et al., 2009; Steele et al., 2007). In those previous studies, however, participants were clinically depressed and samples were comprised of both males and females. The present study also measured reward anticipation response and depressive symptoms when the girls were 16, while other studies have assessed reward response in middle-aged adults (Pizzagalli et al., 2009; Steele et al., 2007) or across wider age ranges (8–17 in Forbes et al., 2009). Neurons in the mPFC and striatum undergo dramatic pruning and reorganization during adolescence (Andersen and Teicher, 2008; Davey et al., 2008; Spear, 2013). Therefore, sample differences could reflect the developmental phase of our fMRI and depressive symptom assessment.

Another possible explanation for this inconsistency with the extant literature is that different depression phenotypes will yield different neural signatures. The striatum is involved in coding the incentive salience, or motivational value, of rewards (Berridge and Robinson, 1998). Although we cannot tease apart depression sub-types in the current study, it may be that for depression characterized by anhedonia and low positive emotion one would expect blunted striatal activity in anticipation of reward. Depression characterized by dysphoria or irritability may be more reactive to reward opportunities. Similarly, predictable and consistent low parental warmth in the parent–child relationship may confer different risks for atypical neural processing of rewards than inconsistent or unpredictable parenting behavior. Differentiating patterns of brain activity among different depression phenotypes and risk contexts is a critical component to the development of brain-based algorithms for optimizing interventions. Our results suggest that there may be different patterns of neural activity within the broad domain of depression and contextual risks.

This is one of the first studies to use longitudinal data on early adolescent social stressors to predict brain reward processing and depressive symptoms later in adolescence, and it is the first study of social stress and reward processing in an all-female sample. Adverse parent and peer relationships may be especially influential for girls because girls are more likely than boys to value social cooperation, rely on social support to cope with stressors, attribute negative events to themselves, over-empathize with others, and suppress negative emotions to comply with the others' expectations (Keenan and Hipwell, 2005). For example, girls who have parents who are cold or punishing may blame themselves for their parents' behavior and go to great lengths to comply with their parents' wishes at the expense of their own emotional expression and desire for social support. Furthermore, early-adolescent girls report greater declines in the quality of their relationships with their parents (McGue et al., 2005) and have higher rates of relational victimization (Wang et al., 2009) than boys. The high value that girls place on social cooperation and support, combined with the decrease in the quality of parent–child relationships and high rate of relational victimization during the transition from childhood to adolescence, may partially account for girls' relatively greater risk for later depression. Other strengths of this study include the large sample size and the inclusion of participants who are at high risk for adverse psychosocial outcomes due to low socioeconomic status.

Conversely, because this study included an all-female sample, the relationship between low parental warmth, peer victimization, and neural reward processing in boys remains to be determined. Likewise, because many of the girls in the study were from low-income, urban neighborhoods, the results presented here may not generalize to girls from other socioeconomic backgrounds or environments. Although we included years of public assistance as a covariate in our analyses to control for the effect of poverty on reward response, we were not able to include a comprehensive indicator of socioeconomic status, such as income-to-needs, because complete income information was not provided by all participants. While possibly less fine-grained a measure of SES, public assistance represents an objective measure of family financial difficulty and indicates which of our generally low-SES participants were particularly burdened with poverty. Childhood SES has been reported to influence dorsal mPFC response to reward in adults (Gianaros et al., 2011) as well as emotional processing (Gianaros et al., 2008) and PFC function (Sheridan et al., 2012). Financial stress may also weaken parents' caregiving resources and the ability of children to cope with psychosocial stressors such as low parental warmth and peer victimization (McLoyd, 1990). Additional research that examines the synergistic effects of socioeconomic status, parenting behavior, and peer stressors could delineate the neural mechanisms by which different stressors impact brain function during adolescence.

Additional study limitations include the cross-sectional fMRI assessment, the circumscribed assessment of psychosocial stress through two self-report measures, and the limited number of trials in the Reward Guessing Task. First, although our design is longitudinal and prospective, we did not assess brain functioning earlier in adolescence, and thus cannot infer that early adolescent social stressors caused disruptions in later neural response to reward. Causality has been established in animal studies, which show that early social stress produces anhedonic behavior in rodents and non-human primates (Pryce et al., 2005), and these behaviors depend on brain reward circuitry (Berridge and Robinson, 1998). However, a number of other factors could explain the association between early social stressors and brain reward response in the present study. In particular, girls' depressive symptoms and/or altered reward responsiveness may influence parenting and peer relationships (e.g., Hipwell et al., 2008). Furthermore, while some parental psychopathology is likely reflected by our measure of low parental warmth, we did not include a separate index of parent/family psychopathology in our analyses, nor did we include other measures of parenting

that could moderate the association between warmth and reward and warmth and depression symptoms. In addition, self-reported data have some limitations, and observational measures of adolescents' relationships with their parents and peers may provide a clearer picture of the relationship between social stress and neural response to reward. Finally, the limited number of trials in the Reward Guessing Task (12 potential win) may have reduced the signal-to-noise ratio in analyses of reward anticipation response. Notably, including too many trials and thereby extending the duration of the task also has disadvantages due to risk of task habituation, fatigue, and movement. We limited the number of trials in the Reward Guessing Task to balance these risks and because we've previously found that 12 reward anticipation trials is an adequate number to elicit a robust BOLD response in our regions of interest (Forbes et al., 2009).

Despite these limitations, this study is consistent with the idea that early social stress affects the neurodevelopment of reward circuits and thereby increases risk for depressive symptoms. The results of this study, particularly the divergent directions of association between neural response to reward and the two types of psychosocial stressors studied here, indicate that the influence of specific psychosocial stressors may be differentially weighted in the brain. Future studies of psychosocial stress and reward processing during adolescence should carefully consider the relative impact of parent, peer, and other stressors and their developmental timing on systems involved in the pathophysiology of depression. Furthermore, there is some evidence that neural response to monetary and social rewards differs between females and males: monetary and social rewards elicit similar patterns of striatum response in females, while men are more responsive to monetary rewards and less responsive to social rewards than women (Guyer et al., 2009; Spreckelmeyer et al., 2009). Given the pronounced sex differences in the incidence of depression during adolescence and the influence of psychosocial stressors, it will be important for future studies to examine the influence of psychosocial stressors on reward processing in both sexes. Ultimately, these studies may lead to developmentally-appropriate and sex-specific interventions for reward-related brain function and other neural and behavioral precursors of depression in adolescence.

Conflicts of interest statement

There are no conflicts of interest to report in submission of this manuscript.

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