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Disrupted amygdala-prefrontal connectivity during emotion regulation links stress-reactive rumination and adolescent depressive symptoms

Carina H. Fowler[a,1], Michelle E. Miernicki[b,1], Karen D. Rudolph[b], Eva H. Telzer[a,*]

[a] University of North Carolina at Chapel Hill, Department of Psychology and Neuroscience, 235 E Cameron Ave, Chapel Hill, NC 27599, USA
[b] University of Illinois at Urbana-Champaign, Department of Psychology, 603 E. Daniel St, Champaign, IL 61820, USA

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ABSTRACT

Rumination in response to stress (stress-reactive rumination) has been linked to higher levels of depressive symptoms in adolescents. However, no work to date has examined the neural mechanisms connecting stress-reactive rumination and adolescent depressive symptoms. The present work attempted to bridge this gap through an fMRI study of 41 adolescent girls (M_{age} = 15.42, SD = 0.33) – a population in whom elevated levels of depressive symptoms, rumination, and social stress sensitivity are displayed. During the scan, participants completed two tasks: an emotion regulation task and a social stress task. Using psychophysiological interaction (PPI) analyses, we found that positive functional connectivity between the amygdala and ventrolateral prefrontal cortex (VLPFC) during the emotion regulation task mediated the association between stress-reactive rumination and depressive symptoms. These results suggest that stress-reactive rumination may interfere with the expression and development of neural connectivity patterns associated with effective emotion regulation, which may contribute, in turn, to heightened depressive symptoms.

1. Introduction

The adolescent brain is particularly sensitive to emotionally salient and stressful stimuli (Spear, 2009), and rates of depressive symptoms increase during this developmental period, particularly in girls (Hankin and Abramson, 2001). Theory and research implicate rumination—repetitive, uncontrolled, negative thoughts—as a key factor in both the onset of depressive symptoms and gender differences in depressive symptoms that emerge in adolescence (Johnson and Whisman, 2013; Nolen-Hoeksema and Girgus, 1994). Although a wealth of evidence supports a connection between emotion-focused rumination and depression in youth (for a review, see Rood et al., 2009), less research has examined stress-reactive rumination in this group, and no research to date has explored the neurobiological mechanisms that link stress-reactive rumination to adolescent depression. The present study bridges this gap by examining the role of amygdala-ventrolateral prefrontal cortex (VLPFC) connectivity in explaining the association between stress-reactive rumination and depression in adolescent girls.

Rumination involves repeatedly focusing on the same negative thoughts, particularly about one's feelings of depression, their significance, and their cause (Nolen-Hoeksema, 1991). Research defines two distinct types of rumination: emotion-focused rumination and stress-reactive rumination. Emotion-focused rumination is a trait-level process in which individuals focus repetitively on a negative emotional state, such as feelings of depression (Nolen-Hoeksema, 1991), whereas stress-reactive rumination is a state-level process during which individuals fixate on negative thoughts about any everyday stressful event (Robinson and Alloy, 2003). Measures of emotion-focused rumination are often confounded with measures of depression (Treynor et al., 2003) because an individual who possesses trait-level emotion-focused rumination engages repeatedly in negative, uncontrolled thoughts, which may already be symptomatic of depression (Nolen-Hoeksema, 1991). In contrast, stress-reactive rumination is not related to repetitive depressive thought content, but rather to perseveration on a particular stressful, negative event. However, while stress-reactive rumination is a state-level process that occurs in response to a specific stressor, individuals may develop a tendency to respond to stressful events with stress-reactive rumination—an inclination that has been linked to increased risk for depressive symptoms in youth (Skitch and Abela, 2008). Thus, understanding the neural correlates of stress-reactive rumination may be particularly important for understanding the emergence of depressive symptoms because it is not so closely related to concurrent depressive symptomatology.

Adolescent females are a particularly important population among

* Corresponding author.
E-mail address: ehtelzer@unc.edu (E.H. Telzer).
[1] These authors contributed equally.

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whom to study the connection between stress-reactive rumination and depressive symptoms. In childhood, rates of depression are similar between the sexes, but depressive symptoms increase among girls starting in adolescence and remain higher for females throughout the lifespan (Johnson and Whisman, 2013). Adolescent females are also particularly likely to engage in rumination (Nolen-Hoeksema and Girgus, 1994) and are highly susceptible to stress, particularly social stress (Rudolph, 2002). Moreover, experiencing interpersonal and peer-related stress predicts depressive symptoms in adolescent girls (Hankin et al., 2007; Rudolph et al., 2009).

Emerging evidence has identified a link between stress-reactive rumination and depression in adolescents (Rood et al., 2012; Skitch and Abela, 2008), but no research to date has identified the neural mechanisms underlying this association. At the behavioral level, the connection between stress-reactive rumination and depression may be explained by poor emotion regulation. Rumination is an emotion regulation strategy—albeit an ineffective one—and ruminating prevents individuals from engaging in effective forms of emotion regulation that are linked to reduced depressive symptoms (Aldao et al., 2010; Gross and John, 2003; Ward et al., 2003). Given this connection between stress-reactive rumination, poor regulation of negative emotion, and depression at the behavioral level, it seems likely that poor emotion regulation at the neural level may connect stress-reactive rumination and depressive symptoms.

Two neural regions implicated in emotion regulation are the amygdala and ventrolateral prefrontal cortex (VLPFC). The amygdala is important in processing negative emotional responses (Phelps, 2006; Whalen, 1998), while effective emotion regulation tends to involve recruitment of the VLPFC (Dolcos and McCarthy, 2006; Lieberman et al., 2007; Ochsner et al., 2012). Heightened VLPFC activation down-regulates the amygdala when viewing aversive or emotional stimuli (Lieberman et al., 2007; Ochsner et al., 2004; Wager et al., 2008). One way to examine connections between the amygdala and PFC is through functional connectivity analyses, which demonstrate regions of the brain that are temporally interconnected (Greicius, 2008). Developmental neuroimaging research across children, adolescents, and adults has found that children display a pattern of positive functional connectivity between the amygdala and PFC. Developmentally, this connectivity switches in valence, such that by adulthood there is negative functional connectivity between the amygdala and PFC (Gee et al., 2013; Silvers et al., 2015). This developmental shift from positive to negative amygdala-PFC connectivity is thought to be indicative of neural maturity and improved emotion regulation, where the PFC effectively down-regulates the amygdala in response to a stressor (Gee et al., 2013). In contrast, positive connectivity reflects a more immature pattern, and thus may be an indicator of poor emotion regulation. Indeed, in adolescents, more negative connections between the VLPFC and subcortical regions that include the amygdala predict improved self-control, an important component of emotion regulation (Lee and Telzer, 2016). Therefore, repeatedly engaging in the state of stress-reactive rumination may prevent the development and expression of connectivity associated with effective emotion regulation, as evidenced by the VLPFC failing to down-regulate the amygdala. In turn, given the connection between poor emotion regulation and depression, this inability at the neural level to engage in effective emotion regulation may lead to higher depressive symptoms.

In the current study, we examined whether ineffective emotion regulation at the neural level, as evidenced by positive functional connectivity between the amygdala and VLPFC, explains the link between stress-reactive rumination and depression in adolescent girls. During an fMRI brain scan, participants completed an emotion regulation task during which they labeled the emotion of positive and negative emotion faces. This task is rooted in evidence demonstrating that putting feelings into words has a regulatory impact on emotion at the neural and behavioral level (Lieberman et al., 2007; Lieberman et al., 2011). The task involves both the regulation of positive and negative emotion. Because stress-reactive rumination involves processing of negative emotion, individuals who engage in stress-reactive rumination should only express disrupted regulation of negative emotion. Further, although there are some situations in which it can be beneficial to down-regulate positive emotion, most examples of this behavior are conscious, voluntary choices and thus do not involve ruminative responses (i.e., involuntary, repetitive negative thoughts).

We induced stress-reactive rumination *in vivo* using Cyberball (Williams and Jarvis, 2006) to create a salient social stressor. Cyberball is an online ball-tossing game that leads the participant to believe that two peers have socially rejected her. Because adolescent females are particularly vulnerable to social stress (Rudolph, 2002), social rejection is a relevant and ecologically valid stressor. Although prior research has explored stress-reactive rumination by inducing stress and measuring consequent rumination *in vivo* (Glynn et al., 2002; Hilt and Pollak, 2012; Key et al., 2008), this is the first neuroimaging study to examine how stress-reactive rumination is associated with emotion regulation at the neural level. In sum, we tested the following hypotheses: (1) stress-reactive rumination in response to an *in vivo* stressor (i.e., Cyberball) would be associated with greater depressive symptoms; (2) greater stress-reactive rumination would be associated with greater positive functional connectivity between the amygdala and VLPFC during an emotion regulation task; (3) positive functional connectivity between the amygdala and VLPFC during an emotion regulation task would be associated with greater depressive symptoms; (4) the association between stress-reactive rumination and depressive symptoms would be explained (i.e., mediated) by positive functional connectivity between the amygdala and VLPFC during emotion regulation. Given that stress-reactive rumination involves processing of negative emotions, we hypothesized that the above links would be found for the regulation of negative, but not positive, emotions.

2. Methods

2.1. Participants

Of the 50 participants in the overall sample, 6 participants were excluded due to change in design of the emotion regulation task, and 3 participants were excluded due to missing behavioral data. The final sample therefore included 41 adolescent girls (M_{age} = 15.42 years, *SD* = 0.33).All participants were recruited from a larger longitudinal study of youth from 2nd-9th grade (for more details on this longitudinal study, please see Rudolph et al., 2014). Exclusion criteria for study participation included MRI contraindications (e.g., metal implanted in the body), braces, and claustrophobia. Participants were not excluded for left handedness or medication use. 12.19% of participants were left-handed, and 17.07% of participants reported prescription medication use. No participants took psychotropic medication on the day of the scan. Participants were 70.7% European-American, 22% African-American, 2.4% Latina, and 4.9% other. Participants and their guardians provided written assent and consent, respectively, following the University's Institutional Review Board guidelines.

2.2. Procedure

2.2.1. Emotion regulation task

In the scanner, participants first completed an emotion regulation task modified from Lieberman et al. (2007) known as affect labeling. During the task, participants viewed negative (e.g., angry, sad, fearful) and positive (e.g., happy, calm) emotion faces (See Fig. 1). Participants completed four blocks during which they passively observed the faces, and four during which they actively labeled the emotion of the face. The faces were presented in blocks by valence, such that they completed two blocks of each emotion for each of the two conditions. In the passive condition, participants passively viewed photos of faces expressing emotions. In the active condition, participants were instructed

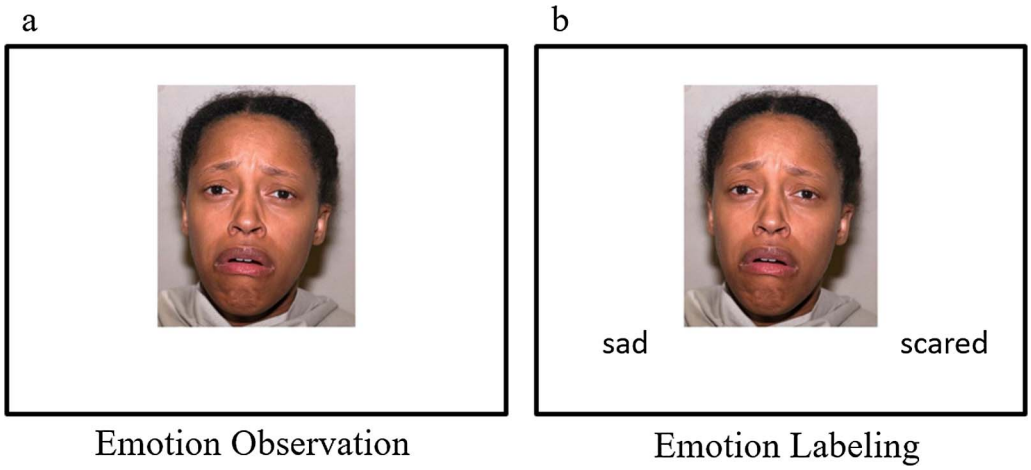


Fig. 1. Example of (a) Observation and (b) Labeling conditions of the emotion regulation task.

to match the expression of the face in the photo to one of two labels (e.g., for negative blocks, sad or scared; angry or fearful; for positive blocks, happy or surprised, etc). The two emotion words were presented below the photo of the face, and participants made a button response to select the correct label. Each block of emotional face photos consisted of six trials, which were presented for 6 s each. Block order was randomized across participants, and each block was separated by a rest period of 10 s. The race of models (half African American, half European American) and emotion types were randomized within the blocks. All photos were of women taken from the NimStim (Tottenham et al., 2009). The duration of the emotion regulation task was 8.07 min.

The active condition of our task is known as affect labeling. Affect labeling is an implicit emotion regulation strategy (Gyurak et al., 2011) that occurs automatically without conscious regulation. This task relies upon implicit distraction, which is an emotion regulation strategy that is an effective counterpart to rumination (Gross, 1998; Nolen-Hoeksema, 1991). The task implicitly distracts participants by focusing attention on the labeling and drawing attention away from the emotional nature of the photos. Indeed, research shows that simply labeling emotions increases regulatory and decreases affective responses at the neural (Lieberman et al., 2007; Lieberman et al., 2011) and behavioral level (Kircanski et al., 2012). Notably, participants show heightened amygdala activation during passive viewing of negative emotional faces, but decreased amygdala activation and increased VLPFC activation when actively labeling emotions (Hariri et al., 2000; Lieberman et al., 2007). Importantly, a recent meta-analysis of 386 studies demonstrated that fMRI tasks that involve emotion words (e.g., as labels) reliably increase VLPFC activation and reduce amygdala activation (Brooks et al., 2016).

2.2.2. Social stress induction

After the emotion regulation task, participants completed Cyberball while still in the scanner. Following other stress-reactive rumination research, which has used *in vivo* stressors to induce stress-reactive rumination (Glynn et al., 2002; Key et al., 2008), all participants played Cyberball to elicit social rejection, a salient social stressor in adolescence (Williams and Jarvis, 2006). Cyberball is a computer-based ball tossing game. During the game, the participant is led to believe that she is playing with two age and gender-matched peers, when, in reality, the performance of the other two players is pre-programmed. Cyberball includes two rounds. In the first round (inclusion), the ball is passed equally among the three players; in the second round (exclusion), the two other players stop passing the participant the ball after 10 throws so that the participant is excluded for the remainder of the game. Thus, the goal of Cyberball was to create an actual social stressor, in the face of which stress-reactive rumination could be measured. Immediately following Cyberball, and while still in the scanner, participants were asked to rate how bad, sad, unfriendly, tense, and angry they felt. Although Cyberball was completed in the scanner, only neural data from the emotion regulation task are discussed here. The neural data from the Cyberball task were previously analyzed and published in Rudolph et al. (2016).

2.2.3. In vivo stress-reactive rumination

Following the scan, participants completed a self-report measure of stress-reactive rumination, which contained 7 items, 3 of which were distractors. This measure was based on the involuntary engagement subscale of the Responses to Stress Questionnaire (RSQ; Compas et al., 1997). Prior work recommends modifying the scale to ask about responses to a specific stressor (Connor-Smith et al., 2000). Thus, our measure of stress-reactive rumination asked specifically about ruminative responses to the stressor, Cyberball (e.g., "I kept thinking I hate this game," "I kept thinking how unfair this game was"). Adolescents rated each item on a 5-point scale (1 = *Not at All* to 5 = *Very Much*). Scores were calculated as the mean of the 4 items, with higher scores indicating greater stress-reactive rumination ($\alpha = 0.80$).

2.2.4. Depressive symptoms

The Short Mood and Feelings Questionnaire (Angold et al., 1995) was used to assess depressive symptoms within the past two weeks (13 items; e.g., "I felt unhappy or miserable."). Adolescents rated each item on a 4-point scale (1 = *Not at All* to 4 = *Very Much*). Scores were calculated as the mean of the items ($\alpha = 0.96$). Validity has been established through moderately high correlations with the Children's Depression Inventory and the Diagnostic Interview Schedule for Children (Angold et al., 1995). This measure also distinguishes depression from other psychiatric disorders (Thapar and McGuffin, 1998).

2.3. fMRI data acquisition and analysis

2.3.1. fMRI data acquisition

Imaging data were collected during the emotion regulation task using a 3 T Siemens Trio MRI scanner. The task included 242 T2*-weighted echoplanar images (EPI) [slice thickness = 3 mm; 38 slices; TR = 2 s; TE = 25 msec; matrix = 92 × 92; FOV = 230 mm; voxel size 2.5 × 2.5 × 3 mm^3]. Structural scans consisted of a T2*weighted, matched-bandwidth (MBW), high-resolution, anatomical scan (TR = 4 s; TE = 64msec; matrix = 192 × 192; FOV = 230; slice thickness = 3 mm; 38 slices) and a T1* magnetization-prepared rapid-acquisition gradient echo (MPRAGE; TR = 1.9 s; TE = 2.3msec; matrix = 256 × 256; FOV = 230; sagittal plane; slice thickness = 1 mm; 192 slices). The orientation for the MBW and EPI scans was oblique axial to maximize brain coverage.

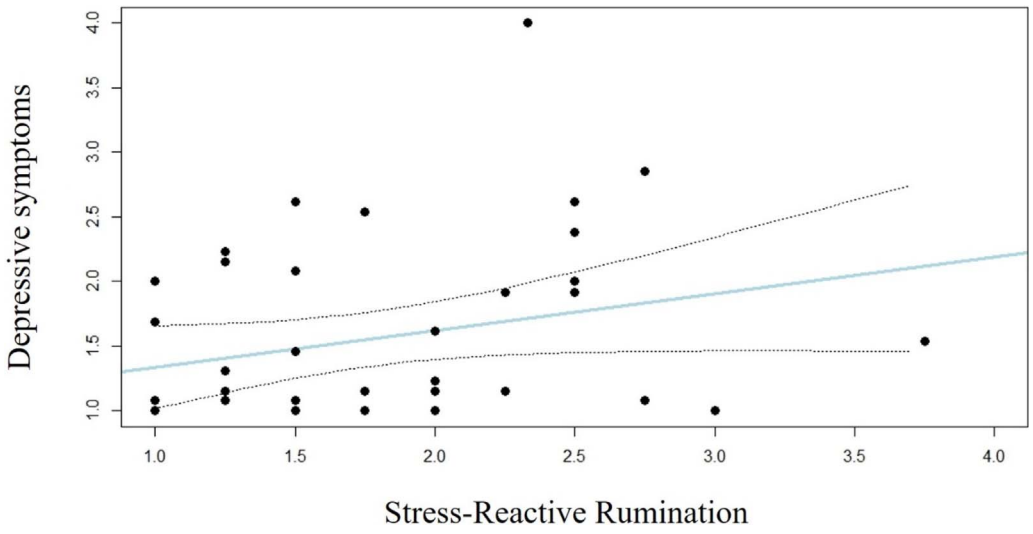


Fig. 2. Correlation between stress-reactive rumination and depressive symptoms. Blue line represents best fit. Dotted lines represent 95% confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3.2. fMRI data preprocessing and analysis

Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) was used to preprocess data. To correct for head motion, images were spatially realigned. No participant exceeded 2.5 mm of maximum image-to-image motion in any direction. Realigned functional data were coregistered to the MPRAGE, which was then segmented into cerebrospinal fluid, grey matter, and white matter. Functional and T2 structural images were then normalized, transforming them into a standardized stereotactic space according to the Montreal Neurological Institute and the International Consortium for Brain Mapping. Functional data were smoothed with an 8 mm Gaussian kernel, full-width-at-half maximum, to increase the signal-to-noise ratio. Statistical analyses were performed using the general linear model in SPM8. Each trial was convolved with the canonical hemodynamic response function. High-pass temporal filtering with a cutoff of 128 s was applied to remove low-frequency drift in the time series. A restricted maximum likelihood algorithm was used to estimate serial autocorrelations with an autoregressive model order of 1.

In each participant's fixed-effects analysis, a general linear model (GLM) was created with the regressors of interest: affect labeling and passive viewing during the emotion regulation task for positive and negative emotion faces. The jittered inter-trial intervals (M = 1.5 s) between each trial and 10 s rest between each block were treated as null events that were not explicitly modeled and therefore constituted an implicit baseline. Individual level contrasts were created for each individual.

The individual subject contrasts were then submitted to group-level analyses. We contrasted neural activation when labeling (Label) emotion faces compared to passively observing (Observe) emotion faces. Labeling versus passive observation (Label > Observe) was used as the contrast of interest because labeling an emotion, or putting it into words, helps regulate emotional reactivity, whereas passively observing an emotion elicits heightened affective arousal in the amygdala (Lieberman et al., 2007). These Label > Observe contrasts were created separately for positive and negative emotions in order to examine brain activity distinctly for the regulation of positive and negative emotion.

To examine neural connectivity, we conducted whole brain psychophysiological interaction (PPI) analyses with the bilateral amygdala as the seed region. The amygdala was defined by combining the left and right amygdala in the AAL atlas in the WFU PickAtlas (Maldjian et al., 2003; Maldjian et al., 2004; Tzourio-Mazoyer et al., 2002). Specifically, the automated gPPI toolbox in SPM (gPPI; McLaren et al., 2012) was used to (1) extract the deconvolved times series from the bilateral amygdala ROI for each participant to create the physiological variables; (2) convolve each trial type with the canonical HRF, creating the psychological regressor; and (3) multiply the time series from the psychological regressors with the physiological variable to create the PPI interaction.

To examine how neural activation and connectivity varied with stress-reactive rumination and depressive symptoms, we conducted whole-brain regression analyses in which we entered each of these separately as regressors. To correct for multiple comparisons, the spatial autocorrelation function (acf) option was used in AFNI's 3dFWHMx to estimate intrinsic smoothness and 3dClustSim to estimate probability of false positives using the corrected approach recommended by Eklund et al. (2016). Cluster size corrections for multiple comparisons at $\alpha < 0.05$ over the whole-brain were achieved with voxel-wise $p < 0.005$.

3. Results

3.1. Behavioral results

First, we examined bivariate correlations among the variables of interest using bootstrapping at 5000 iterations. Greater stress-reactive rumination was significantly associated with higher levels of depressive symptoms (r = 0.281, 95% CI = [0.016, 0.527]; see Fig. 2).

3.2. fMRI results

3.2.1. Stress-reactive rumination, depressive symptoms, and neural connectivity during negative emotion regulation

In order to examine neural connectivity with the bilateral amygdala seed as it varied with depressive symptoms and stress-reactive rumination respectively, we conducted a series of whole brain PPI regression analyses. First, we regressed stress-reactive rumination onto amygdala connectivity during negative emotion regulation trials (NegLabel > NegObserve). We found that greater stress-reactive rumination was related to increased connectivity with the bilateral amygdala seed in the right VLPFC (Table 1 and Fig. 3). Next, we regressed depressive symptoms onto amygdala connectivity during negative emotion regulation. We found that greater depressive symptoms were related to increased amygdala connectivity with the bilateral VLPFC (Table 1 and Fig. 4). Notably, the right VLPFC cluster found for both regressions was the same location.

Table 1
Whole-brain regression with stress-reactive rumination and depressive symptoms for the NegLabel > NegObserve contrast in the PPI with the amygdala as seed region.

Region	x	y	z	k	t
Stress-Reactive Rumination					
R VLPFC	48	32	13	90	4.87
L pSTS	−54	−40	−2	70	5.09
L STS	−54	−1	−20	91	4.37
R MTG	66	−37	4	71	3.34
Depressive Symptoms					
R VLPFC	54	32	7	162	4.37
L VLPFC	−45	23	16	111	4.31

Note. L and R refer to left and right hemispheres; k refers to the number of voxels in each significant cluster; t refers to peak activation level in each cluster; x, y, and z refer to MNI coordinates. VLPFC = ventrolateral prefrontal cortex; pSTS = posterior superior temporal sulcus; STS = superior temporal sulcus; MTG = middle temporal gyrus. Corrected cluster size: 66 contiguous voxels.

3.2.2. Indirect effect of stress-reactive rumination on depressive symptoms via positive amygdala-VLPFC connectivity

Next, we examined whether amygdala-VLPFC connectivity mediates the association between stress-reactive rumination and depressive symptoms. Using the MarsBar toolbox extension in SPM (Brett et al., 2002), cluster overlap was determined by creating masks of the VLPFC clusters related to stress-reactive rumination and depressive symptoms separately, and then combining them into a new mask, which only contained regions of overlap present in both original clusters. This overlap region represents the right VLPFC voxels active in both the depressive symptoms and stress-reactive rumination PPI analyses during the negative emotion regulation trials. We extracted parameter estimates of signal intensity from this mask. We then conducted mediation analyses using Process (Hayes, 2013) to test the indirect effect of stress-reactive rumination on depressive symptoms through positive functional connectivity between the amygdala and rVLPFC during negative emotion regulation. This pathway was tested using a bootstrap estimation approach with 5000 samples. Providing support for the proposed pathway, analyses revealed that the indirect effect of stress-reactive rumination on depressive symptoms via positive functional connectivity was significant (B = 0.3158, SE = 0.1488, 95% CI = [0.1008, 0.7116]). Further, the relationship between stress-reactive rumination and depressive symptoms was no longer significant when amygdala-rVLPFC connectivity was included in the model (B = −0.0319, SE = 0.1646, 95% CI = [−0.3652, 0.3013]).

3.2.3. Stress-reactive rumination, depressive symptoms, and neural connectivity during positive emotion regulation

In order to examine whether our effects were unique to negative emotion regulation as hypothesized, we also conducted separate whole brain PPI regression analyses for positive emotion regulation trials (PosLabel > PosObserve). Greater stress-reactive rumination and depressive symptoms were not associated with amygdala connectivity in any regions of interest (see Table 2). Unlike the negative emotion regulation condition, neither stress-reactive rumination nor depressive symptoms were associated with increased amygdala-VLPFC connectivity.

3.2.4. Stress-reactive rumination, depressive symptoms, and neural activation

Finally, to demonstrate the unique role of amygdala-VLPFC functional connectivity, we also examined how whole brain activation varied with stress-reactive rumination and depressive symptoms during both positive and negative emotion regulation trials. To this end, we ran two separate whole brain analyses, in which we regressed stress-reactive rumination and depressive symptoms onto brain activation during the main effects of negative emotion regulation trials (NegLabel > NegObserve). No regions correlated positively with stress-reactive rumination or depressive symptoms. Finally, stress-reactive rumination and depressive symptoms were regressed onto activation during positive emotion regulation. Neither of these regressions demonstrated statistically significant clusters of activation. These effects underscore the unique role of amygdala-VLPFC connectivity during negative emotion regulation in adolescents' stress-reactive rumination and depressive symptoms.

4. Discussion

Adolescence is a key developmental stage in the onset of depressive symptoms. Although previous research has linked stress-reactive rumination and depressive symptoms in adolescents (Robinson and Alloy, 2003; Rood et al., 2012; Skitch and Abela, 2008), the neural mechanisms underlying this association are not understood. To our knowledge, this study is the first to identify how stress-reactive rumination is associated with neural responses during emotion regulation; it is also the first to demonstrate a specific neural mechanism connecting stress-reactive rumination and depressive symptoms. In our study, participants engaged in the well-validated emotion regulation task of affect labeling. Then, we used novel techniques to induce stress-reactive rumination *in vivo*. During an fMRI scan, participants played Cyberball—a game that creates the salient social stressor of social rejection. Our findings provide new evidence linking stress-reactive rumination to depression via positive functional connectivity between the amygdala and VLPFC during the regulation of negative emotion.

Stress-reactive rumination was significantly correlated with positive functional connectivity between the amygdala and rVLPFC during the negative emotion condition of the emotion regulation task. That is, adolescent girls who engaged in stress-reactive rumination following

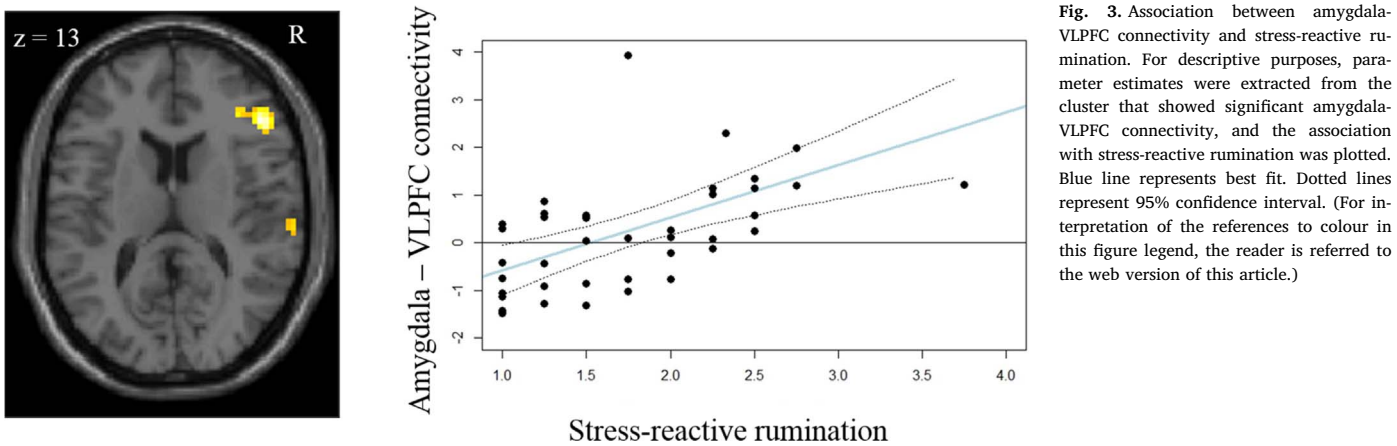
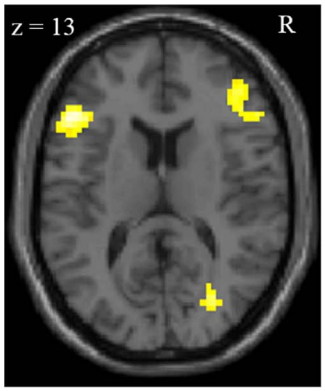


Fig. 3. Association between amygdala-VLPFC connectivity and stress-reactive rumination. For descriptive purposes, parameter estimates were extracted from the cluster that showed significant amygdala-VLPFC connectivity, and the association with stress-reactive rumination was plotted. Blue line represents best fit. Dotted lines represent 95% confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



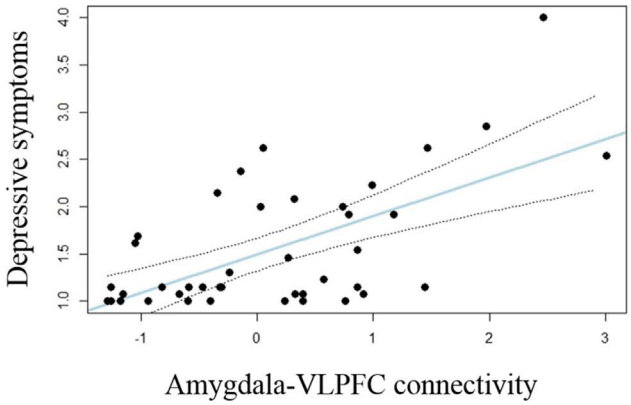


Fig. 4. Association between depressive symptoms and amygdala-VLPFC connectivity. For descriptive purposes, parameter estimates were extracted from the cluster that showed significant amygdala-VLPFC connectivity and the association with depressive symptoms was plotted. Blue line represents best fit. Dotted lines represent 95% confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Whole-brain regression with stress-reactive rumination for the PosLabel > PosObserve contrast in the PPI with the amygdala as a seed region.

Region	x	y	z	k	t
R MCC	6	−34	37	135	4.36
R Calcarine gyrus	6	−67	22	159	3.61

Note. R refers to right hemisphere; k refers to the number of voxels in each significant cluster; t refers to peak activation level in each cluster; x, y, and z refer to MNI coordinates. MCC = medial cingulate cortex. Corrected cluster size: 71 contiguous voxels.

Cyberball also showed disrupted regulatory activation when prompted to regulate negative emotion. This finding is consistent with prior research suggesting that negative functional connectivity between the amygdala and VLPFC is key for effective regulation of negative emotion (Ochsner et al., 2012), whereby the VLPFC down-regulates the amygdala's affective stress response. Our findings can also be interpreted in the context of research showing specific developmental trajectories in amygdala-PFC connectivity. More negative connectivity between the amygdala and PFC is phenotypically mature and beneficial for regulation in adolescence, whereas positive connectivity between these regions reflects a more immature pattern (Gee et al., 2013) and is an indicator of poorer self-control (Lee and Telzer, 2016), a component of emotion regulation. The tendency to perseverate on a stressful, negative event (i.e., engage in stress-reactive rumination) may prevent the development and expression of effective emotion regulation, resulting in greater positive functional connectivity between affective and frontal regions.

Consistent with prior behavioral work that links ineffective emotion regulation with depression (Aldao et al., 2010), we found that poor emotion regulation at the neural level—as evidenced by positive functional connectivity between the amygdala and bilateral VLPFC during the regulation of negative emotion—was associated with greater depressive symptoms. Perhaps this connectivity pattern is associated with greater depressive symptoms because negative emotional stimuli are more salient and threatening when the VLPFC does not down-regulate the amygdala. Further, this interpretation falls in line with symptoms of depression, such as depressed individuals' attentional bias to negative information (Gotlib, 1983) and depressive realism (Moore and Fresco, 2012). Over time, an overactive stress response is a factor that contributes to depression onset (Hammen, 2005), which may help explain the correlation between positive functional connectivity and depressive symptoms.

Because greater stress-reactive rumination and depressive symptoms were both significantly correlated with amygdala connectivity in nearly identical clusters in the right VLPFC, we extracted parameter estimates of signal intensity from this region of overlap. Then, we examined whether the association between stress-reactive rumination and depressive symptoms would be explained (i.e., mediated) by positive functional connectivity between the amygdala and the right VLPFC. Indeed, the indirect effect of stress-reactive rumination on depressive symptoms through positive functional connectivity between the amygdala and rVLPFC was significant. That is, positive functional connectivity between the amygdala and rVLPFC mediated the relationship between stress-reactive rumination and depressive symptoms. In addition, the whole brain regression analysis examining reactivity revealed no significant clusters of activation that correlated positively with stress-reactive rumination or depressive symptoms, respectively. This finding suggests that it is connectivity between the amygdala and rVLPFC, rather than independent activation of each region, that is important for explaining the association between stress-reactive rumination and depressive symptoms. Finally, we should underscore that all our neural effects were specific to negative and not positive emotions. Individuals generally ruminate when processing negative emotions (Nolen-Hoeksema, 1991; Papageorgiou and Wells, 2003). To our knowledge, there is no literature to date suggesting that stress-reactive rumination is a common regulatory strategy for up or down-regulating positive emotion. Thus, it follows that individuals higher in stress-reactive rumination would display disrupted connectivity during negative, but not positive, conditions of our emotion regulation task.

4.1. Contributions and limitations

By inducing social stress, and measuring *in vivo* stress-reactive rumination, our study uncovered the neural processes linking stress-reactive rumination to depression in adolescence. Although a few studies have examined the neural underpinnings of depressive, emotion-focused rumination (e.g., Berman et al., 2014, 2011; Cooney et al., 2010; Piguet et al., 2014), this study is the first to our knowledge to identify how stress-reactive rumination is associated with neural responses during emotion regulation. Nonetheless, our design does not rule out the possibility of reciprocal effects over time. For example, depressive symptoms may undermine emotion regulation at the neural level, which may foster stress-reactive rumination. Future research will need to use longitudinal designs that assess each construct during multiple developmental periods to better understand how social stress, stress-reactive rumination, and neural processing are causally associated with risk for depression during adolescence.

In addition, while we hypothesize that positive functional connectivity represents a failure of the prefrontal cortex to regulate the hyperactive affective system (Gee et al., 2013; Lee and Telzer, 2016), it is important to note that we cannot assess directionality in our functional connectivity analyses. There is some debate, for example, surrounding the function of the VLPFC, with some work suggesting that the area is responsible for attention to relevant cues rather than for response inhibition (Hampshire et al., 2010)—an important component

of emotion regulation. Using this interpretation, it is possible that the VLPFC is not failing to down-regulate the amygdala, but rather the VLPFC and amygdala could be working together to draw attention to negative stimuli. Research using different methodologies is needed to determine with more certainty whether PFC-amygdala connectivity represents top-down regulation.

Finally, we chose to study the regulation of negative emotion using a task that relies on implicit, rather than explicit, emotion regulation. According to one taxonomy of emotion regulation (Webb et al., 2012), our affect labeling task is a "passive neutral distraction" type of emotion regulation task. That is, participants were distracted implicitly by the labeling of the emotional photos, despite the fact that they were not given any explicit instructions to try to distract themselves from the photos. While this is an important aspect of emotion regulation, future studies should examine these effects using explicit emotion regulation tasks. For example, many studies have relied on emotion regulation strategies such as cognitive reappraisal (e.g., Ochsner et al., 2002) or explicit distraction (e.g., McRae et al., 2010). Nonetheless, passive neutral distraction strategies do have a reliable effect size in influencing emotion regulation (Webb et al., 2012). Our findings should be interpreted in this context. Future work should examine if the type of emotion regulation task employed influences how emotion regulation at the neural level connects stress-reactive rumination and depressive symptoms.

4.2. Conclusions

This research begins to unpack the neural processes that link stress-reactive rumination to depressive symptoms in adolescence. Individual differences in adolescents' functional connectivity during an emotion regulation task were associated with heightened depressive symptoms. Engaging in stress-reactive rumination may be one reason why some adolescents maintain the developmentally immature pattern of increased positive functional connectivity between the amygdala and VLPFC. If this neural pattern persists past a developmentally appropriate period, it may be a biomarker of psychopathology. Future interventions might focus on reducing stress-reactive rumination. Dampening maladaptive cognitive responses to social stress and enhancing more adaptive forms of emotion regulation, such as problem solving, might have downstream effects on neural responses during emotion regulation, leading to more developmentally mature negative functional connectivity between the amygdala and VLPFC. Further, intervening to change stress responses and the accompanying patterns of neural connectivity during adolescence may reduce the onset of depressive symptoms in girls during this stage of heightened risk.

Author contributions

E.H.T. and K.D.R. designed research. M.E.M., E.H.T. and K.D.R. performed research. M.E.M. and C.H.F. conducted data analysis. C.H.F., M.E.M., E.H.T. and K.D.R. composed the manuscript.

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