



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



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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

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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

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