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Functional connectivity of the amygdala and subgenual cingulate during cognitive reappraisal of emotions in children with MDD history is associated with rumination

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ABSTRACT

Major Depressive Disorder (MDD) is characterized by poor emotion regulation. Rumination, a maladaptive strategy for dealing with negative emotions, is common in MDD, and is associated with impaired inhibition and cognitive inflexibility that may contribute to impaired emotion regulation abilities. However, it is unclear whether rumination is differently associated with emotion regulation in individuals with MDD history (MDD-ever) and healthy individuals. In this study, children (8–15 years old) performed a cognitive reappraisal task in which they attempted to decrease their emotional response to sad images during fMRI scanning. Functional connectivity (FC) between both the amygdala and subgenual anterior cingulate (sACC) increased with cortical control regions during reappraisal as rumination increased in MDD-ever, while connectivity between those regions decreased during reappraisal as rumination increased in healthy controls. As the role of cortical control regions is to down-regulate activity of emotion processing regions during reappraisal, this suggests that rumination in MDD-ever, but not controls, is associated with inefficient regulation. This finding suggests that rumination may be particularly associated with poor emotion regulation in MDD-ever, and may also indicate qualitative group differences in whether rumination is maladaptive. These differences in rumination may provide important insight into depressive risk and potential avenues for treatment.

1. Background

A growing body of literature suggests that Major Depressive Disorder (MDD) is associated with impaired cognitive control processes necessary for effective emotion regulation (Diener et al., 2012). These impairments are often coupled with ineffective or maladaptive regulation strategies that may exacerbate reactivity to, and the impact of, negative or distressing emotions (Campbell-Sills and Barlow, 2007). Rumination, or brooding, is one such maladaptive regulation strategy that involves recurring thoughts about self-relevant negative emotional states or situations (Nolen-Hoeksema, Nov 1991). Rumination has been associated with MDD, including the development, severity, and chronicity of depressive episodes (Nolen-Hoeksema, 2000; Nolen-Hoeksema et al., 2008). It has been hypothesized that rumination in MDD stems from deficits in cognitive control functions such as inhibition (De Lissnyder et al., 2011) and disengagement (Koster et al., 2011), leading to excessive processing and preoccupation with self-relevant negative emotion (Joormann and Gotlib, 2010).

The period of late childhood and early adolescence is one in which the incidence of MDD increases (Angold and Costello, 2006), and corresponds with significant development of cognitive emotional regulation strategies, which begin to supplant more rudimentary behavioral strategies (e.g. covering ears) from middle childhood (McRae et al., 2012; Davis and Levine, 2013; Garnefski et al., 2007). This period also marks increased use of cognitive emotion regulation strategies, which increase over a protracted period, with even late adolescents using fewer strategies than adults (Garnefski and Kraaij, 2006), though patterns of cognitive strategy use are similar between late childhood and early

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adolescence (Garnefski et al., 2007). However, use of rumination as a regulation strategy also peaks in early adolescence, with higher rates than in late childhood (Hampel and Petermann, 2005), which then decrease from early- to mid-adolescence (Hankin, 2008). Rumination and depression are more closely associated in adolescents compared to younger children (Rood et al., 2009). It has been suggested that rumination may contribute to psychopathology by interfering with the use of effective self-regulation techniques (Nolen-Hoeksema et al., 2015), though the mechanism by which this occurs is unclear. Thus, it is important to understand the association between maladaptive regulation strategies such as rumination and ineffective use of adaptive regulation strategies in this critical developmental period.

In contrast to rumination, cognitive reappraisal is considered to be an adaptive emotion regulation strategy shown to effectively minimize the excessive experience of negative emotions (Ochsner et al., 2004). Cognitive reappraisal is the reinterpretation of the meaning of affective stimuli or events in a way that may change the magnitude and valence of affective responses. Research has shown that reappraisal modulates the emotional experience of a negative event or stimulus (Ochsner et al., 2004), and that habitual use of reappraisal is associated with improved well being, interpersonal functioning, and overall greater positive emotion (Gross and John, 2003). Neurally, studies have shown that use of cognitive reappraisal is associated with increased activity of prefrontal and parietal cognitive control regions and semantic and perceptual regions of the lateral temporal cortex, as well as with modulation of amygdala activity (Buhle et al., 2013). Importantly, this pattern has been shown in healthy school aged children (Belden et al., 2014) as well as in adults (Goldin et al., 2008; Wager et al., 2008).

The neuroimaging literature on reappraisal indicates less effective modulation of emotion processing regions, such as the amygdala, by prefrontal control regions in adult MDD. One study found greater activation of right amygdala, insula, temporal pole, and dorsal cingulate in MDD adults compared to controls during reappraisal (Beauregard et al., 2006). A study of medication-free MDD adults showed increased activation of right lateral middle frontal gyrus during a "reappraise" condition compared to an "attend" condition while controls showed the opposite pattern (Johnstone et al., 2007). A separate study of MDD adults found a different pattern in which controls showed greater dorsolateral prefrontal cortex (DLPFC) activation and greater down-regulation of amygdala activity than MDD adults during reappraisal (Erk et al., 2010). Additionally, during negative emotion reappraisal, MDD adults fail to reduce activity in a number of regions in the default mode network (DMN), including ventromedial prefrontal cortex and anterior cingulate cortex, that show reduced activity in controls (Sheline et al., 2009). As the DMN is associated with self-referential thought (Fox et al., 2005), this may indicate difficulty in regulating self-referential activity in the context of negative emotions. In children with MDD history (many of whom overlapped with the current sample), deficits in emotion regulation abilities were associated with decreased activity of left inferior frontal gyrus (IFG) and inferior temporal sulcus (ITS) during reappraisal, while increased MDD severity was associated with increased amygdala activation during passive viewing of sad images (Belden et al., 2015). Together, these findings suggest that MDD is characterized by increased activation of emotional reactivity regions during reappraisal of negative emotions, and that this reactivity may be associated with abnormal function of prefrontal control regions (whether hyper- or hypoactive), leading to deficient emotional regulation.

Evidence that further clarifies the deficient regulation of emotional reactivity by prefrontal control regions in MDD comes from studies of task-based functional connectivity (FC). Rather than examining which regions are more active in one task than another, FC examines the correlation of activity between brain regions over time (either during tasks or during rest), with the assumption that strong correlations across time are indicative of communication between those regions in the performance of some function. Task-based FC measures, such as psychophysiological interaction (PPI) analyses (Friston et al., 1997), examine how FC between regions changes across different psychological task states. In the case of emotion regulation, this technique can demonstrate how the functional relationship between response and regulation regions changes between passive and effortful regulation states. If, during regulation, increased prefrontal activation is associated with decreased amygdala activation, this negative correlation may indicate prefrontal regulation of amygdala activity – an interpretation that is directly supported if task-based FC data shows that this pattern is more pronounced during regulation trials than passive viewing trials.

Task-based FC studies of emotion regulation in MDD reveal a pattern of altered regulation of bottom-up processing regions, particularly the amygdala. One study found that during emotional reappraisal, adults with MDD showed a positive correlation between amygdala and VMPFC activity during reappraisal while controls showed the more typical negative correlation (Johnstone et al., 2007). In another study, adolescents with MDD showed more positive connectivity between the right amygdala and left MFG, hippocampus, posterior cingulate, and sACC than controls during emotional reappraisal. However, during maintenance of a negative emotion (no down-regulation necessary), control subjects showed more positive FC between amygdala and bilateral insula and right prefrontal regions than MDD (Perlman et al., 2012). Further, another study found that healthy adults showed strong coupling between the amygdala and right DLPFC during reappraisal, such that increased DLPFC activation was associated with decreased amygdala activation during reappraisal. In contrast, medicated MDD patients showed reduced coupling between those regions, with less DLPFC activation and less of a decrease in amygdala activity during reappraisal (Erk et al., 2010). Together, these task-based FC studies suggest that the negative correlation between prefrontal and amygdala activation that normally accompanies effective emotion regulation is diminished in MDD.

While the above literature suggests the existence of differences between MDD and healthy groups in neural correlates of reappraisal, understanding individual differences in emotion regulation within MDD may further elucidate the factors underlying impaired reappraisal processes in this illness. In other words, although on average individuals with MDD are more likely to use maladaptive emotion regulation strategies such as rumination, there is important variation across individuals with MDD. As described above, brooding rumination is associated with attentional inflexibility (Whitmer and Banich, 2007) and impaired emotional disengagement (Vanderhasselt et al., 2011) – both key aspects of reappraisal. In healthy adults, greater use of brooding rumination has been associated with increased DLPFC activity during emotional disengagement, consistent with the hypothesis that increased attentional control may be required for disengagement in high ruminators (Vanderhasselt et al., 2011). In non-emotional conflict monitoring tasks, rumination in MDD adults has been associated with decreased amplitude of the N2 ERP component associated with recruiting cognitive control (Alderman et al., 2015). Further, induced brooding rumination in MDD adults is associated with greater activation in DLPFC, orbitofrontal cortex, and subgenual anterior cingulate (sACC) than in controls (Cooney et al., 2010), as rumination may make emotion regulation more difficult. The sACC is associated with self-referential thinking (Ochsner and Gross, 2005) and is considered part of the default-mode network. It is more active in the absence of cognitive tasks (Raichle et al., 2001), when individuals are more likely to focus on autobiographical thoughts (Mazoyer et al., 2001), but is down-regulated during