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Research paper

An exploratory examination of reappraisal success in depressed adolescents: Preliminary evidence of functional differences in cognitive control brain regions

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ABSTRACT

Background: Most neuroimaging studies of adolescent depression employ tasks not designed to engage brain regions necessary for the cognitive control of emotion, which is central to many behavioral therapies for depression. Depressed adults demonstrate less effective activation of these regions and greater amygdala activation during cognitive reappraisal; we examined whether depressed adolescents show similar patterns of brain activation.

Methods: We collected functional magnetic resonance imaging (fMRI) data during cognitive reappraisal in 41 adolescents with major depressive disorder (MDD) and 34 matched controls (ages 13–17). We examined group differences in (1) activations associated with reappraisal and reappraisal success (i.e., negative affect reduction during reappraisal) using whole brain and amygdala region-of-interest analyses, and (2) functional connectivity of regions from the group-by-reappraisal success interaction.

Results: We found no significant group differences in whole brain or amygdala analyses during reappraisal. In the group-by-reappraisal success interaction, activations in the left dorsomedial prefrontal cortex (dmPFC) and left dorsolateral PFC (dlPFC) were associated with reappraisal success in healthy controls but not depressed adolescents. Depressed adolescents demonstrated reduced connectivity between the left dmPFC and the anterior insula/inferior frontal gyri bilaterally (AI/IFG) and between left dlPFC and left AI/IFG.

Limitations: Our results should be considered exploratory given our less conservative statistical threshold in the group-by-reappraisal interaction.

Conclusions: We find preliminary evidence that depressed adolescents engage cognitive control regions less efficiently than healthy controls, suggesting delayed maturation of regulatory prefrontal cortex regions; more research is needed to determine whether cognitive therapies improve functioning of these regions in depressed youth.

1. Introduction

Ineffective emotion regulation is one of the hallmarks of clinical depression. Cognitive reappraisal, which involves changing one's interpretation of an affective stimulus to modify its emotional impact, is a frequently targeted emotion regulation skill in treatments for depression like cognitive behavioral therapy (CBT) (Beck, 2005). Adolescence is not only a period of rising incidence of depression

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(Center for Behavioral Health Statistics and Quality, 2015), but is also a period during which the use and effectiveness of cognitive reappraisal strategies are increasing (Garnefski et al., 2002; Gullone et al., 2010; McRae et al., 2012). Thus, functioning of the neural circuitry that supports cognitive reappraisal during this sensitive period may be a determinant of both risk for early onset depression and how well depressed adolescents may be able to engage with cognitive therapies. Despite a need to understand the functioning of neural circuity involved in the cognitive control of emotion, most functional magnetic resonance imaging (fMRI) studies in both adult and adolescent depression rely on task paradigms that trigger emotion-processing circuitry but do not require cognitive reappraisal (e.g., the emotional go-no-go task) (Hare et al., 2008) or engage cognitive control regions reliably (e.g., face matching paradigms) (Hariri et al., 2002).

Many of the brain regions that mediate high level cognitive functions, such as planning and decision making and the supporting executive functions of attention and working memory, are frequently engaged during cognitive reappraisal (Buhle et al., 2014; Otto et al., 2014). The dorsolateral prefrontal cortex (dlPFC) focuses attention on the stimuli that are relevant for reappraisal and keeps reappraisal goals in mind; the ventrolateral prefrontal cortex (vlPFC) supports the selection of a new reappraisal of the initial stimuli; and the dorsomedial prefrontal cortex (dmPFC) monitors emotional states and the effectiveness of reappraisal (Buhle et al., 2014; Otto et al., 2014). While studies in healthy adolescents are limited, similar regions (e.g., vlPFC, dmPFC) appear to be involved in cognitive reappraisal (McRae et al., 2012; Silvers et al., 2015; Vijayakumar et al., 2014). These cognitive control regions are thought to modulate activation of emotion processing regions during reappraisal (Buhle et al., 2014; Menon, 2011). The most widely studied of these regions is the amygdala; however, studies of cognitive reappraisal in adolescents specifically (ages 13–18) less frequently find evidence of amygdala modulation (McRae et al., 2012), likely due to the developmental time course of corticolimbic circuitry and a diminished ability to use cognitive strategies to down regulate emotional responses during adolescence (Silvers et al., 2015; Stephanou et al., 2016).

Depressive disorders in adults are characterized by ineffective activation of cognitive control regions and hyperactivation of emotion processing regions such as the amygdala (Mayberg, 2003). Studies of emotion processing in general suggest that depressed adults show alterations in corticolimbic circuitry and altered function in those cognitive control regions involved in top-down regulation of emotion, such as the dlPFC, as well as in limbic regions like the amygdala and insula which are associated with bottom-up generation of emotional responses (Mayberg, 1997; Siegle et al., 2007; Phillips et al., 2003; Price and Drevets, 2010; Sheline et al., 2009). During cognitive reappraisal, depressed adults show greater activation in cognitive control regions (Johnstone et al., 2007; Beauregard et al., 2006; Greening et al., 2014) that is less effective at reducing negative affect in depressed participants compared to healthy controls (Greening et al., 2014), as well as reduced functional connectivity between cognitive control regions (i.e., the dlPFC) and the amygdala (Erk et al., 2010). Collectively, these findings suggest that depressed individuals may engage cognitive control regions more extensively but less effectively to achieve the same degree of modulation of emotion processing regions (Beauregard et al., 2006; Greening et al., 2014).

Our understanding of how cognitive control regions function during reappraisal among depressed adolescents is limited. One prior study found that, compared to healthy controls, adolescents with MDD demonstrated differences in right amygdala reactivity and connectivity between the amygdala and bilateral insula and medial PFC during the non-reappraisal condition alone (i.e., maintaining one's emotional response to a negative stimulus), but no group differences specifically associated with reappraisal (i.e., a contrast between the reappraisal and non-reappraisal conditions) (Perlman et al., 2012); however, this was a relatively small study (N = 28; 14 depressed and 14 healthy matched controls). A larger, recent study found that depressed adolescents and young adults (ages 15–25; mean age: 19.7; SD: 2.7) showed significantly greater activation of vmPFC during reappraisal compared with healthy controls, and weaker downregulation of right amygdala activation during reappraisal (Stephanou et al., 2017). Downregulation of amygdala activation during reappraisal increased with age among the healthy controls but not among the depressed group, suggesting not only that the development of subcortical regulation may be delayed in depressive disorders (Stephanou et al., 2017), but also that during adolescence, there may be minimal differences in the downregulation of amygdala activation between depressed and healthy controls due to the developmental time course of the regulation of subcortical structures. However, this study only included a limited number of adolescents (i.e. 18 years of age or under), and highlights the need for additional examination of the cognitive control of emotion in a well-powered study of adolescent depression specifically.

We contribute to this literature by examining the neural underpinnings of cognitive reappraisal in a large sample of actively depressed, unmedicated adolescents (ages 13–17) and well-matched healthy controls. Given the rapid developmental changes in corticolimbic neural circuitry during adolescence, combined with epidemiological evidence that adolescence is the period during which the incidence of depression increases most dramatically, we argue that it is especially important to understand the functioning of cognitive control regions in our well-powered study of depressed adolescents. In addition to examining group differences in neural activation during reappraisal, we also conduct an exploratory analysis of brain regions that are differentially associated with reappraisal success (i.e. successful reduction of negative affect during reappraisal) (Greening et al., 2014; March et al., 2004; Wager et al., 2008) in an unrestricted, whole brain analysis, as well as group differences in the functional connectivity of those regions during reappraisal. Because both behavioral (Cox et al., 2012; Gullone et al., 2010; Klein et al., 2007; Silvers et al., 2012) and neuroimaging (Center for Behavioral Health Statistics and Quality, 2015; McRae et al., 2012; Silvers et al., 2015) studies indicate that cognitive reappraisal skills are developing rapidly during adolescence, we propose that focusing on correlates of reappraisal success will provide specific insights into the functioning of cognitive control regions among depressed teens. We hypothesize that, compared to matched healthy controls, depressed adolescents will show greater activation in cognitive control regions but that this activation will be less effective at reducing negative affect.

2. Methods and materials

2.1. Participants

Of 101 participants recruited, 75 post-pubertal adolescents (41 depressed, 34 healthy controls) ranging in age from 13–17 years were included in this study, which was approved by the institutional review boards of University of California (UC), San Diego, UC San Francisco, Rady Children's Hospital, and the County of San Diego. Adolescents with depression were recruited from psychiatric and primary care clinics in San Diego, California; healthy control participants were recruited from the same geographic area via e-mail, internet, or flyers. All participants gave written informed assent and their parent/legal guardians provided written informed consent. Adolescents of all genders and ethnicities were allowed to participate, and all were compensated for their time (details on those excluded from the analytic sample are provided in Results).

2.2. Clinical scales and demographic measures

All potentially depressed adolescents were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS-PL) (Kaufman et al., 1997) and final diagnoses were