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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

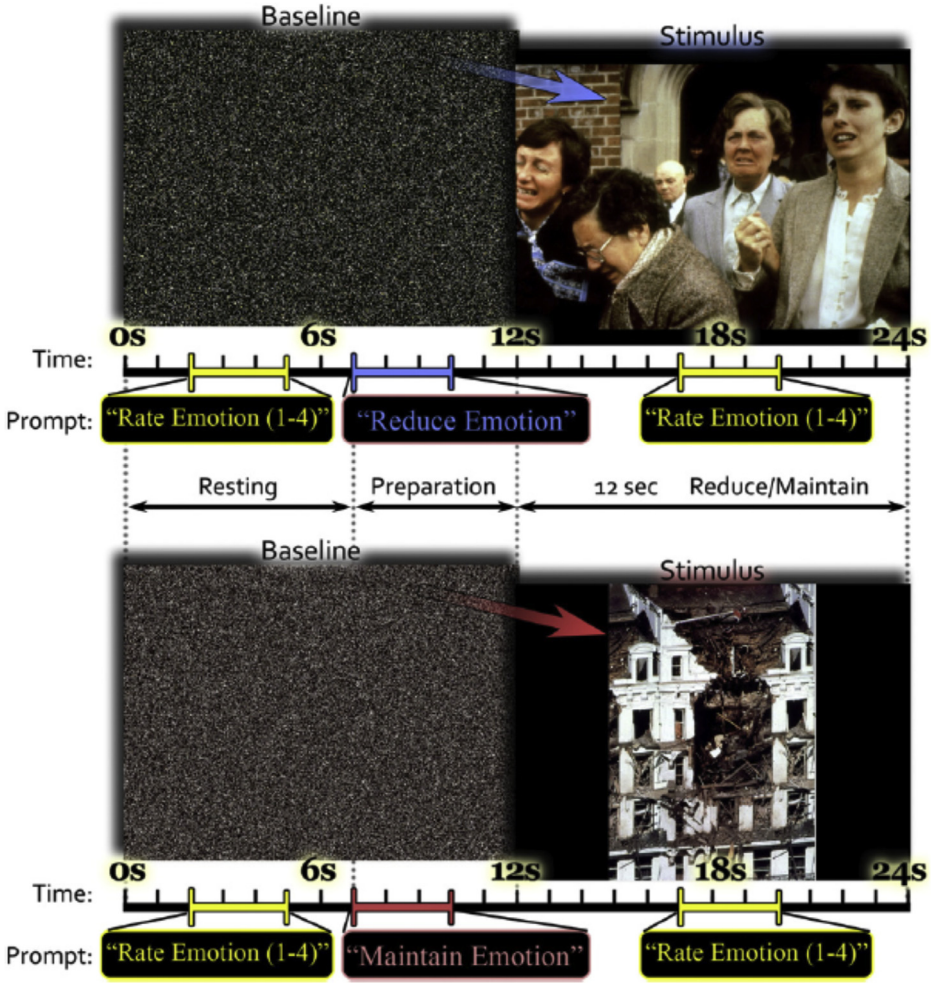

Fig. 1. Graphical representation of the Reduce and Maintain conditions during the cognitive reappraisal task. Our primary contrast of interest was between the Pre-Reduce (between the onset of Reduce stimulus and the "Rate Emotion" prompt) and Pre-Maintain (between the onset of Maintain stimulus and "Rate Emotion" prompt) task periods.

determined by a board certified child and adolescent psychiatrist (TTY). All depressed participants met full criteria for a primary diagnosis of MDD and were excluded if they had a secondary comorbid diagnosis of psychosis, bipolar disorder or substance abuse; however, individuals who also had an anxiety disorder were included given the high rates of comorbidity of depression and anxiety (Merikangas et al., 2010). Healthy adolescents were excluded from the study if they had any family history of mood or psychotic disorders in first- or second-degree relatives (Maxwell, 1992), or an axis I psychiatric disorder, which was determined using the computerized Diagnostic Interview Schedule for Children version 4.0 (Shaffer et al., 2000) and the Diagnostic Predictive Scale (Lucas et al., 2001).

The primary measure of depressive symptoms in this study was the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski and Freeman, 1985), a clinician-administered rating scale. We also included self-report measures of depressive symptoms (e.g., the Reynolds Adolescent Depression Scale (RADS-2) (Reynolds, 2004). CDRS-R scores were used to further characterize study groups; healthy controls with scores higher than 54 and MDD participants with scores lower than 55 were excluded. We assessed psychosocial functioning using the Children's Global Assessment Scale (CGAS) (Green et al., 1994), and anxiety symptoms (Seligman and Ollendick, 1998) with the Multidimensional Anxiety Scale for Children (MASC) (March et al., 1997). Additional exclusion criteria for all participants included: a performance score of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) of less than 70, inability to fully understand and cooperate with study procedures, contraindications for MRI (e.g., metallic implants, claustrophobia, pregnancy or the possibility thereof), left-handedness, prepubertal status (Tanner stage 1 or 2), substance abuse, history of neurological disorders (e.g., head trauma, seizures), misuse of prescription drugs or more than two alcohol drinks per week, and the use of medications with a central nervous system effect within 2 weeks prior to scanning. Socioeconomic status was measured using the Hollingshead two factor index of social position (Hollingshead, 1957), and participants self-reported their ethnicity (Hispanic or Non-Hispanic).

2.3. Clinical scales and demographic measures analysis

All statistical analyses were conducted in R Development Core Team (2012). Between-group differences were assessed using independent *t*-tests for continuous, normally distributed variables (age, IQ, CDRS-R, MASC, CGAS, and RADS-2), Wilcoxon rank-sum test for non-normally distributed continuous variables (socioeconomic status and Tanner stage), and chi-squared tests for categorical variables (sex, race/ethnicity). All depression scales were standardized.

2.4. MR data acquisition and analysis

2.4.1. Experimental stimuli and paradigm

We utilized a previously validated cognitive reappraisal task, which has been described elsewhere (see Campbell-Sills et al., 2011; Perlman

et al., 2012) and has been shown to elicit functional activation in the amygdala and prefrontal cortex in adolescents (Perlman et al., 2012). None of the subjects in the Perlman et al. (2012) pilot study overlapped with the present study. The task involved two conditions. In the first condition, participants were instructed to reduce their affective responses to negative images using cognitive reappraisal ("Reduce"). In the second condition, participants were instructed to maintain their reactions to negative images ("Maintain"). Each trial lasted 24 s and began with a 12 s baseline period during which a scrambled image was presented to give participants time to recover in between trials. After between 1 and 3 seconds of the baseline presentation, a prompt to "Rate Emotion (1–4)" appeared in yellow beneath the scrambled image and lasted for 3 s. Between 1 and 3 s after the "Rate Emotion" prompt, a visual cue displayed that the coming trial was either a "Reduce Emotion" or "Maintain Emotion" trial and lasted for 3 s. The scrambled image remained for another 1–3 s until the 12 s baseline period was over. Next, participants viewed the target image for 12 s (while either reducing or maintaining emotion), with a prompt to "Rate Emotion (1–4)" for 3 s in the middle. After the rating period, the target image remained on the screen for 3–5 s and the trial ended when the target image disappeared (Fig. 1). The Maintain and Reduce conditions were separated into pre-rating and post-rating phases to allow for the analysis of distinct task conditions (Campbell-Sills et al., 2011). In our analysis, we focus on the pre-rating phases of "Pre-Reduce" and "Pre-Maintain" to: (1) isolate cognitive reappraisal independent of assessing one's own emotional state, and (2) to increase the likelihood that the rating of the affective state validly reflects the results of cognitive reappraisal. The task included 12 Reduce trials and 12 Maintain trials and lasted 9.6 min. All subjects included in this analysis completed all 24 task trials.

During the "Rate Emotion (1–4)" prompts, participants rated their distress on a 1–4 scale (1 = no distress to 4 = severe distress) using a response box placed in their right hand. The magnitudes and reaction times for each rating were collected as behavioral data. In our analyses, we focused on the difference in distress ratings in the Reduce and Maintain conditions ("Maintain-Reduce") and henceforth refer to this as "Reappraisal Success," consistent with prior research (Greening et al., 2014; McRae et al., 2012; Wager et al., 2008). Positive scores indicate a reduction in distress rating during the reappraisal condition as compared to the maintain condition. Negative scores indicate greater distress during the reappraisal condition as compared to the maintain condition.

Prior to fMRI scanning, participants were trained on the task for 30 min, which included 10 practice trials (see Campbell-Sills et al., 2011 for more details). Participants were instructed that during "Reduce" trials they were to interpret the image in such a way as to minimize their emotional response. During "Maintain" trials, they were instructed to "notice what they are feeling without trying to change it" and to "maintain emotional reactions." Following the training, participants were asked to describe their cognitive strategies in order to ensure understanding of the task.

2.4.2. Image acquisition

All scanning was carried out on a General Electric 3T MR750 System (General Electric Healthcare, Milwaukee, WI) with Twin Speed gradients and a GE 8-channel head coil at the Center of Functional MRI at the University of California, San Diego. Each session consisted of a three-plane scout scan (10 s), a high-resolution anatomical scan, a series of T2*-weighted echo-planar imaging (EPI) scans to measure the BOLD response. A fast-spoiled gradient recalled sequence was used to collect T1-weighted images for anatomical reference: TR = 8.1 ms, TE = 3.17 ms, TI = 450, flip angle = 12°, 256 × 256 matrix, FOV = 250 × 250 mm, 168 sagittal slices 1 mm thick with an in-plane resolution of 0.98 × 0.98 mm for anatomical reference. For the cognitive reappraisal task, functional scans covering the brain were acquired parallel to the anterior and posterior commissure. EPI were acquired using the following pulse sequence: TR = 2000 ms, TE = 30 ms, flip angle = 90°, 64 × 64 matrix, FOV = 192 × 192 mm, 490 repetitions, 40 contiguous axial slices at 3 × 3 × 3 mm resolution.

2.5. Image processing and analysis

All image processing and analyses were conducted with Analysis of Functional NeuroImages (Cox, 1996) and FSL (Smith et al., 2004). The T1-weighted images were skull-stripped and transformed to MNI152 (Montreal Neurological Institute, Montreal, Quebec, Canada) with an affine transform (Jenkinson and Smith, 2001) followed by nonlinear refinement (Andersson et al., 2007). Echo planar imaging data were slice time and motion corrected and aligned to the T1-weighted images using a localized Pearson correlation function (Saad et al., 2009). Next, the echo planar imaging data were convolved with a 4.2 mm full width at half maximum (FWHM) isotropic Gaussian filter and grand mean scaled before being transformed to MNI152 space at 3 × 3 × 3 mm resolution.

A generalized least squares regression model that estimates the serial correlation of noise with an autoregressive moving average (ARMA) method was used to fit each voxel's time series. The rating, as well as the "Reduce" stimulus (divided into pre and post rating) and "Maintain" stimulus (also divided into pre and post rating) served as five orthogonal regressors of interest. Demeaned motion parameters (three rotational and three translational) and a second-order Legrendre polynomial were included as a nuisance regressors (i.e., baseline, linear, and quadratic trends). Volumes where the Euclidean norm of the motion derivatives were >0.2 or where >10% of voxels exceeded the median absolute deviation of the detrended time series were censored. Subjects in whom >20% of their volumes were censored were removed from the final analysis. For each subject, we calculated a general linear test between the "Pre-Reduce" (prior to affect rating) and "Pre-Maintain" (prior to affect rating) time series, which served as our primary contrast for all analyses. Brain activation was operationally defined as percentage signal change relative to baseline.

2.6. Between group whole brain task analysis

We performed a voxelwise ANCOVA using AFNI's 3dMVM to estimate all models; we used F-tests to identify significant clusters associated with continuous variables, and *t*-tests to examine whole brain group differences (Chen et al., 2014). For voxelwise, between group comparisons, we used a threshold of $p < 0.01$. We addressed possible false-positive cluster detection by thresholding significant cluster volumes to >1755 muL (65 voxels) and $p < 0.05$ using the AFNI 3dClustSim program (version 16.3.03 from October 13, 2016), corrected for smoothing of FWHM = 4.2 mm. We also conducted an analysis of the amygdala as an a priori region of interest (ROI) using a mask based on standardized atlas locations (Talairach and Tournoux, 1988), and a small volume correction for multiple comparisons ($p < 0.05$; threshold cluster volume >270 muL or 10 connected voxels). To test associations consistent with prior work (Erk et al., 2010; Johnstone et al., 2007; Perlman et al., 2012), we report group differences in activation between the depressed and matched control group during reappraisal using an independent *t*-test in a whole brain analysis and for the amygdala ROI. To test whether cognitive control regions necessary for reappraisal would be less effective at reducing negative affect among depressed adolescents when compared with matched healthy controls, we also examined a group-by-reappraisal success interaction to identify activation in clusters that is differentially associated with the reduction of affect during reappraisal by group. For this exploratory interaction, we used a voxelwise threshold of $p < 0.05$ as interactions require more power to be detected (Selvin, 2004). We used the same cluster volume threshold for this analysis (>1755 muL or 65 voxels) and $p < 0.05$ for the group-by-reappraisal success interaction. All models were adjusted for Tanner stage, age, socioeconomic status, sex,

and full-scale IQ. For visualization of between group comparisons, we plotted the marginal means and standard errors calculated from fully adjusted models where extracted percent signal change was predicted by group and adjusted for covariates.

2.7. Functional connectivity analysis (PPI)

Functional connectivity (FC) analyses were conducted in a manner consistent with prior studies of FC in adolescents (Blom et al., 2015; Ho et al., 2015; Vizueta et al., 2012). Specifically, we employed the psychophysiologic interaction (PPI) (Friston et al., 1997) method developed for AFNI using two functionally defined seed regions that were differentially associated with reappraisal success between the two groups (i.e., significant clusters from the group-by-reappraisal success interaction). The mean preprocessed time-series for each seed region was extracted for each participant, detrended, and then deconvolved before being multiplied with the condition regressor ("Pre-Reduce"–"Pre-Maintain") to yield the interaction time-series. The interaction time-series, along with task condition, baseline regressors, and motion regressors, were entered into a generalized least squares regression model that estimated the serial correlation of noise with an ARMA method, with correlation coefficients and corresponding beta-weights as outputs of this model. The resulting correlation coefficients from the regression model were converted to Fisher's z-transformations and extracted for each subject for the purposes of group-level analysis.

2.8. Between-Group functional connectivity analysis

Using the converted *z*-scores representing functional connectivity for each of the two seed regions identified in the group-by-reappraisal interaction as our primary outcome, we estimated the same ANCOVA model described above and implemented the same approach to control for multiple comparisons. We examined the main effect of depression (i.e., group differences) to elucidate general functional connectivity differences associated with adolescent depression. For visualization of between group comparisons, we graphed the marginal means and standard errors of functional connectivity z-scores calculated from fully adjusted models.

3. Results

3.1. Demographics, psychiatric scales, and behavior

After subjects were excluded for missing behavior (N = 6) or imaging data (N = 4), or excessive motion (N = 16), 75 adolescents (41 depressed, 34 healthy controls) were analyzed in this study. The depressed and healthy controls groups did not significantly differ in the number of subjects excluded due to motion or missing data ($p > 0.1$). Compared to healthy controls, depressed adolescents in our sample were not significantly different in age, socioeconomic status, sex or pubertal stage; however, depressed adolescents had significantly lower Full Scale IQs compared to controls, and significantly higher scores on self-rated symptoms of depression and anxiety and lower scores on clinician rated global functioning (Table 1). Notably, there was no significant between-group difference in reappraisal success (i.e., distress ratings during "Maintain" trials minus distress ratings during "Reduce" trials) (Table 1).

3.2. Between-group whole brain task results

We found no evidence of significant differences between healthy controls and depressed adolescents in either whole brain or amygdala ROI analyses in the "Reduce-Maintain" contrast. Two clusters, in the left dmPFC (Fig. 2a) and left dlPFC (Fig. 2b), demonstrated a significant group-by-reappraisal success interaction (Table 2). Specifically, increased activation in dmPFC and dlPFC during the "Reduce-Maintain" contrast was associated with greater reduction in distress rating scores among controls, but activation in these cognitive control regions was not associated with a reduction in distress ratings among depressed adolescents (Fig. 2).

3.3. Between-Group functional connectivity results

We seeded both the left dmPFC (Fig. 2a) and left dlPFC (Fig. 2b) cluster identified in the group-by-reappraisal interaction and examined differences in functional connectivity by group during reappraisal. We found that the left dmPFC was less functionally connected to a cluster in the anterior insula extending into the inferior frontal gyrus (AI/IFG) bilaterally (Fig. 3, Table 3) in depressed adolescents compared to healthy controls. Similarly, the left dlPFC cluster was less functionally connected to left AI/IFG (Fig. 4, Table 4) in depressed adolescents compared to controls.

4. Discussion

We examined differences in the neural circuitry engaged during the cognitive reappraisal of aversive images in a large study of unmedicated, currently depressed adolescents and healthy, well-matched controls. We did not find evidence of significant group differences in the whole brain or amygdala ROI analyses during reappraisal. However, in our exploratory analysis of reappraisal success, we found that increased activation in two regions highly important for cognitive control, the dmPFC and dlPFC, was associated with reduced negative affect in healthy controls but not in depressed adolescents, potentially suggesting less efficient activation among the depressed participants. We also found significantly lower functional connectivity in depressed adolescents between these regions and the AI/IFG but no differences in connectivity with the amygdala. Overall, we found support for the notion that, similar to adult depression, adolescent depression is characterized by less efficient engagement of cognitive control regions during reappraisal (Erk et al., 2010; Johnstone et al., 2007).

Our finding that increased activation in the left dlPFC is associated with a reduction in negative affect during reappraisal in healthy controls, but not in depressed adolescents, is consistent with findings from a recent study in adults (Greening et al., 2014). In this study, left dlPFC activation was positively associated with reductions in negative affect during reappraisal among controls, but no association was observed in depressed adults. Both the dlPFC and dmPFC are consistently engaged during cognitive reappraisal in healthy adults (Buhle et al., 2014). The dlPFC plays an important role in working memory and, during cognitive reappraisal, is hypothesized to support holding new reappraisals in mind (Buhle et al., 2014). The dmPFC has been identified as one of the key regions active during self-referential processing (Buhle et al., 2014; Walter et al., 2009), and is consistently engaged during cognitive reappraisal in healthy adults to monitor and reflect on changing emotional states in cognitive reappraisal (Buhle et al., 2014; Ochsner and Gross, 2005). Both of these regions have been implicated in several studies of adult (Downar et al., 2014; Bora et al., 2012; Koenigs et al., 2008) and adolescent depression (Kerestes et al., 2016; Miller et al., 2015). However, in adolescent and adult depression studies that employ a cognitive reappraisal task, differences in dmPFC and dlPFC functionality are not frequently observed in group comparisons of the reappraisal and non-reappraisal (e.g., "look negative" or maintain) conditions (see Erk, 2010 for an exception) (Dillon and Pizzagalli, 2013; Erk et al., 2010; Johnstone et al., 2007; Perlman et al., 2012; Stephanou et al., 2017). Only the Greening, 2014 study examined regions of the brain associated with changes in subjective affect rating during the reappraisal task, which we also did by adding a group-by-reappraisal success interaction to our fully adjusted model. This approach may be necessary for capturing meaningful associations between activation in cognitive control regions and affect regulation, especially during adolescence when the use and effectiveness of cognitively mediated

Table 1
Demographic and clinical characteristics of analytic sample. MDD = Major depressive disorder; NCL = healthy controls.

Characteristic	MDD	NCL	Statistic	*p*-value
Number of participants in final analysis (n)	41	34	$\chi^2(1.00) = 0.48$	0.49
Gender (M / F)	13 / 28	12 / 22	$\chi^2(1.00) = 0.01$	0.99
Age at time of scan (years)	16.1 ± 1.4	16 ± 1.5	$t(67.63) = 0.41$	0.68
Hollingshead Socioeconomic Score†	40 ± 33	34.5 ± 34.2	$W = 798$	0.28
Tanner Score†	4 ± 0.5	4 ± 0.5	$W = 907$	0.63
Wechsler Abbreviated Scale of Intelligence (Full)	99.6 ± 11.7	107.3 ± 14.3	$t(63.49) = -2.51$	< 0.05
Children's Global Assessment Scale	64 ± 11.5	90.1 ± 7.5	$t(69.46) = -11.75$	< 0.001
Children's Depression Rating Scale (Standardized)	73.3 ± 8.5	34.1 ± 5.8	$t(70.50) = 23.70$	< 0.001
Reynolds Adolescent Depression Scale Total (Standardized)	66.5 ± 7.1	40.3 ± 6.4	$t(72.40) = 16.77$	< 0.001
Reappraisal Success	0.29 ± 0.75	0.50 ± 0.66	$t(73) = -1.27$	0.20

Median ± IQR (min-max) if indicated by †; *W* = Wilcoxson signed rank test.

regulation strategies are increasing.

We found no group differences in amygdala activation or evidence of differences in functional connectivity between the amygdala and the dmPFC or dlPFC. This finding is in contrast to the Greening, 2014 study of depressed adults, which found that dlPFC activation was associated with reductions in amygdala activation only among controls, and other studies of emotion processing tasks in depressed adults which identify group differences in amygdala activity and connectivity (Hamilton

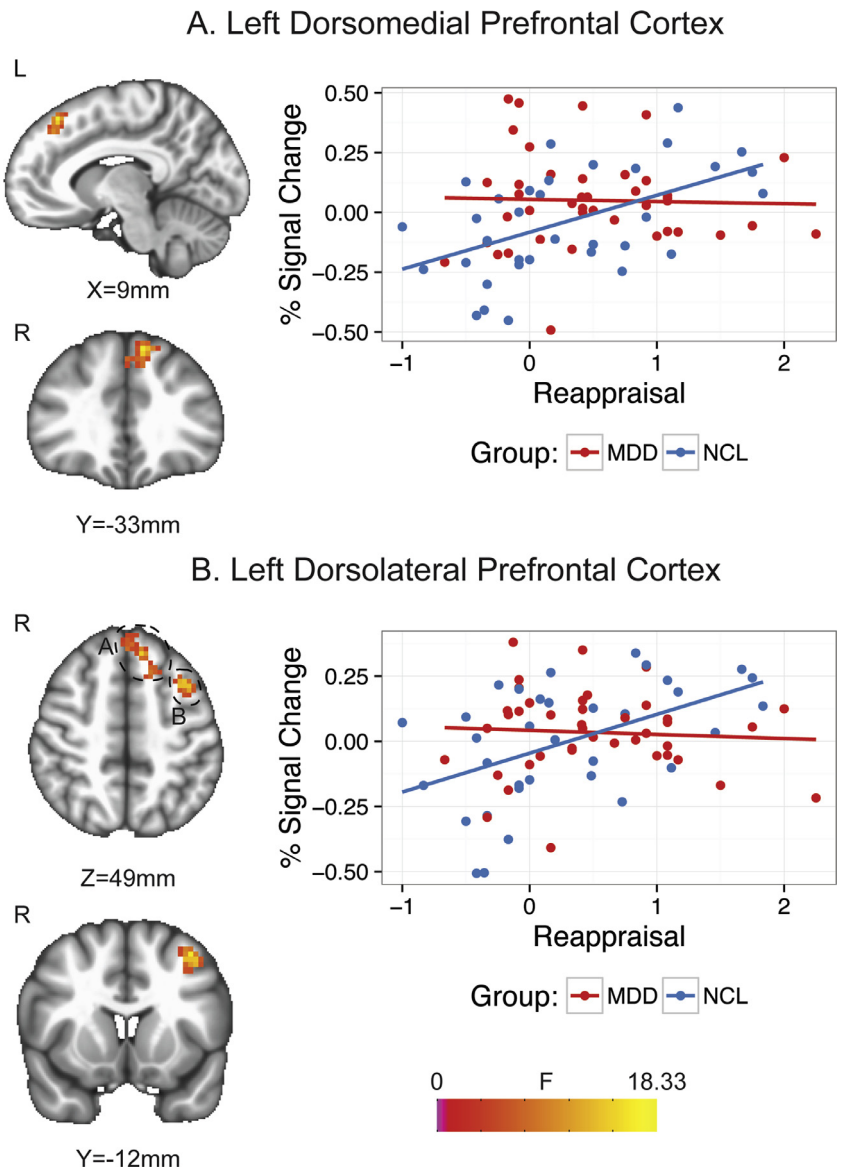

Fig. 2. Regions showing significant group by reappraisal interaction during reappraisal. Both areas survived correction for multiple comparisons at a cluster-wise threshold of $p < 0.05$. Mean percentage signal change for each region was extracted and graphed in relation to reappraisal success ("Reappraisal") for the purposes of visualizing the interaction within the depressed (MDD) and healthy control (NCL) group. Locations are reported in Montreal Neurological Institute (MNI) coordinates (radiologic convention). NCL, healthy control; MDD, major depressive disorder.

Table 2
Significant clusters from the group by reappraisal interaction whole-brain analysis.

Region	Hemisphere	Volume (uL)	Statistic ($F_{1,61}$)	Center of mass		
Superior Frontal Gyrus	L	2619	6.39	−9	33	49
Middle Frontal Gyrus	L	1728	7.72	−37	12	49

Table 3
Significant clusters in the functional connectivity analysis using dmPFC as a seed region. The results reported here are from a two-tailed *t*-test (MDD versus NCL).

Region	Hemisphere	Volume (uL)	Statistic (t_{61})	Center of Mass		
Inferior Frontal Gyrus	R	2160	−2.43	47	23	2
Inferior Frontal Gyrus	L	2052	−2.57	−43	30	0
Fusiform Gyrus	R	1944	−2.52	46	−23	−16

et al., 2012; Price and Drevets, 2010). Modulation of amygdala activation is the one of the most consistent neural signatures of cognitive reappraisal in healthy adults (Buhle et al., 2014), and several studies have demonstrated deficits in modulating amygdala activity in depression (Erk et al., 2010; Johnstone et al., 2007). The absence of differences in amygdala modulation by cortical regions in our study of depressed adolescents is consistent with prior research (Belden et al., 2015; Perlman et al., 2012) and with a growing understanding of the developmental trajectory of the cognitive control of amygdala activation during adolescence (Silvers et al., 2012; Stephanou et al., 2016). Collectively, these studies show that the transition from adolescence to young adulthood is associated with more effective downregulation of amygdala activation in response to reappraisal (Silvers et al., 2012; Stephanou et al., 2016), and that this increase in amygdala modulation with age is not observed in depressed adolescents and young adults (Stephanou et al., 2017). Our findings are consistent with evidence in healthy adolescents that more effective engagement of cognitive control regions during reappraisal is a stronger predictor of negative affect reduction compared to modulation of amygdala reactivity (McRae et al., 2012). Collectively, the implication of this work is that, at least with respect to cognitive reappraisal in depressed adolescents, the focus on amygdala modulation may be less fruitful and that more work should be focused on the functionality of cognitive control regions.

Our exploratory functional connectivity analyses revealed reduced connectivity between the left dmPFC and left AI/IFG, and between the left dlPFC and left AI/IFG among depressed adolescents. Though these results are preliminary and require replication, these findings support a growing body of research highlighting the AI/IFG in cognitive reappraisal and in the neurobiology of depression. Activation of the IFG may signal the successful development of cognitive reappraisal strategies, since during reappraisal, this region is consistently active in adults (Buhle et al., 2014; Johnstone et al., 2007) and increases in activation between childhood and adolescence in healthy individuals (McRae et al., 2012). The IFG has been shown to modulate the selection of goal appropriate responses and goal inappropriate responses (Thompson-Schill et al., 2005), and the selection of new appraisals for a given stimulus (Badre and Wagner, 2007). In a study of adolescents and young adults who were previously depressed, lower left AI/IFG activation was observed during reappraisal among those ever depressed compared to healthy controls (Belden et al., 2015). Together, the dlPFC, dmPFC and IFG play a critical role in higher order cognitive control processes. The increased activation of the dlPFC and dmPFC combined with reduced connectivity with the left AI/IFG observed in our depressed group provide additional support for the notion that, like adult depression (Price and Drevets, 2010), adolescent depression is associated with less effective activation of cognitive control circuity.

These initial exploratory findings suggest innovative directions for future research into the neural correlates of the effectiveness of cognitive behavioral therapies for adolescent depression. Because these treatments, in part, rely on the cognitive control of emotional responses, it follows that the evaluation of both the success of these treatments as well as of predictors of treatment response would benefit from the inclusion of paradigms that activate cognitive control regions. However, only two prior studies have examined the neural correlates of response to cognitive behavior therapy in adolescent depression and neither suggest that dmPFC or dlPFC activation are predictors of treatment effectiveness; however, neither study used a cognitive reappraisal task (Chuang et al., 2016; Straub et al., 2015), and one study employed a region-of-interest analysis that did not include the dmPFC or dlPFC (Straub et al., 2015). Several studies of adult depression have found associations between dmPFC (Thompson et al., 2015; Yoshimura et al., 2014) and dlPFC (Thompson et al., 2015) activation at baseline

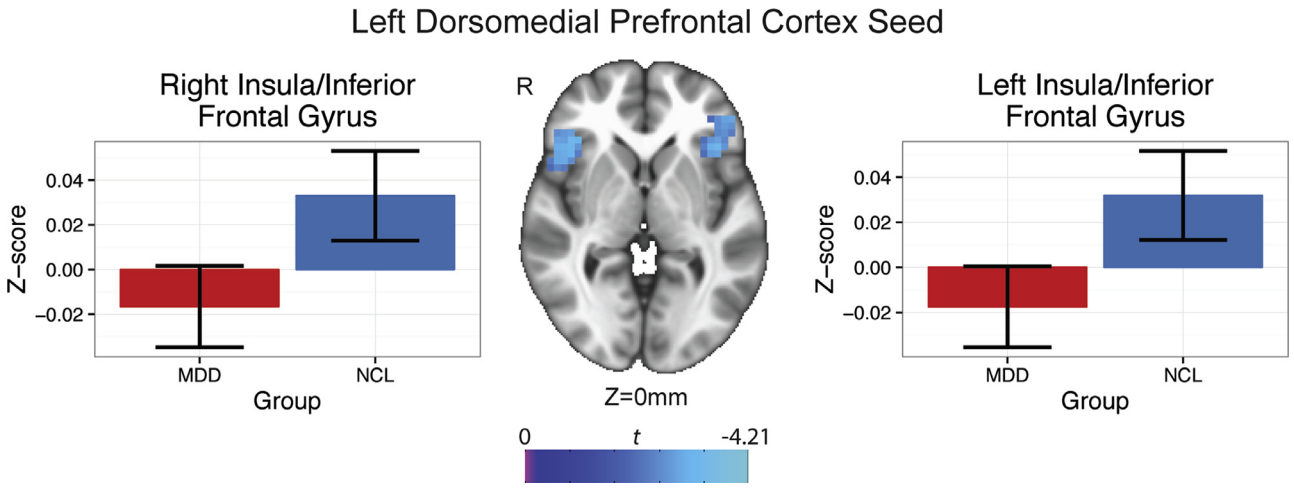

Fig. 3. Regions showing significant between-group differences in functional connectivity with the dmPFC seed (Fig. 2a). Both areas survived correction for multiple comparisons at a cluster-wise threshold of $p < 0.05$. Mean functional connectivity (FC) values are reported as Fisher's z-scores, which were extracted for the purposes of visualization. Histograms show least squared means from fully adjusted models in FC z-scores with right and left insula/inferior frontal gyrus (see"Methods and Materials" for more details). Locations are reported in MNI coordinates (radiologic convention). NCL, healthy control; MDD, major depressive disorder.

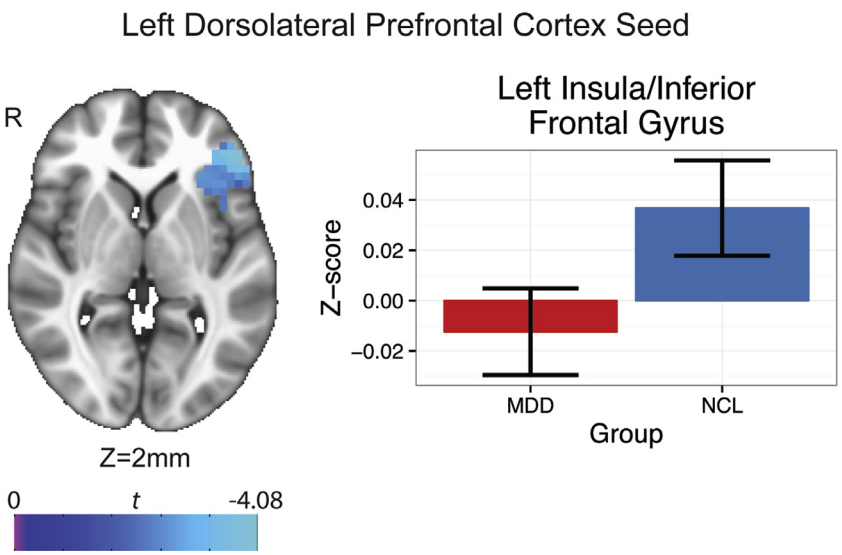

Fig. 4. Regions showing significant between-group differences in functional connectivity with the dlPFC seed (Fig. 2b). This region survived correction for multiple comparisons at a cluster-wise threshold of $p < 0.05$. Mean functional connectivity (FC) values are reported as Fisher's z-scores, which were extracted for the purposes of visualization. Histograms show least squared means from fully adjusted models in FC z-scores with left insula/inferior frontal gyrus (see "Methods and Materials" for more details). Locations are reported in MNI coordinates (radiologic convention). NCL, healthy control; MDD, major depressive disorder.

Table 4
Significant clusters in the functional connectivity analysis using dlPFC as a seed region. The results reported here are from a two-tailed *t*-test (MDD versus NCL).

Region	Hemisphere	Volume (uL)	Statistic ($t_{1,61}$)	Center of mass		
Inferior Frontal Gyrus	L	3186	−2.68	−44	31	2
Middle Temporal Gyrus	R	2592	−2.44	50	−26	−14

and response to CBT treatment. However, given the rapid development of these regions during adolescence, it is unclear whether predictors of treatment response would be similar for adolescents. Our findings suggest that future studies of the underlying neural circuitry that predicts effectiveness of cognitive therapies for adolescent depression may benefit from including tasks that better reflect the cognitive strategies relied upon in treatments like CBT and engage prefrontal cognitive control regions.

While we present the results from the largest study to date of the neural circuitry underlying cognitive reappraisal in adolescent depression, our study should be interpreted in light of its limitations. First, we used a less conservative statistical threshold to identify significant clusters in our reported group-by-reappraisal interaction given reductions in power associated with testing interactions; these results would not survive formal cluster correction and should therefore be considered exploratory (Eklund et al., 2016). However, we suggest that our interaction results are appropriate for the purposes of hypothesis generation given the very limited number of studies that have investigated correlates of reappraisal success in depressed adolescents. Future studies should be powered to examine both adolescent and young adult emotion regulation so that we can better understand differences specific to adolescence. Second, while we adjusted for confounding by sex in our regression models, we were underpowered to test sex specific results. Given substantial evidence of sex differences both in the etiology and course of depression (Kendler and Gardner, 2014; Wade et al., 2002), as well as in the neural circuitry underlying reappraisal in adolescents (McRae et al., 2008), future studies should include samples that provide adequate power to detect sex differences. Second, our study is cross-sectional, so we are unable to make inferences about whether baseline brain states predict clinical course or treatment responsiveness. Finally, while our reappraisal task is a more ecologically valid tool to engage the processes relied upon in cognitive behavioral therapies for depression (Berking et al., 2013; Gotlib and Joormann, 2010) than, for example, a face-matching task, a reappraisal task is still only an approximation of the skills that might be relied upon in these therapies, limiting our ability to make direct inferences to treatment responsiveness or efficacy.

In conclusion, we present several findings that build on prior work and also provide novel directions for future research. Our exploratory analysis suggests that differences in activation of the dmPFC and dlPFC during cognitive reappraisal, and reduced connectivity between these regions and the AI/IFG may be additional biomarkers of early onset depression. Collectively, our results support the notion that adolescent MDD, like adult MDD, is not characterized by failure to recruit cognitive control regions of the brain in response to reappraisal, but rather that greater recruitment is necessary to modulate self-reported affect (Greening et al., 2014). This suggests that depressed adolescents may need to "work harder" to achieve the same degree of emotion regulation as healthy controls (Farb et al., 2010). Unlike adult MDD, we did not find evidence of group differences in either amygdala activation or connectivity. However, even in non-depressed adolescents, there is limited evidence of amygdala modulation in response to cognitive reappraisal (McRae et al., 2012; Silvers et al., 2015; Stephanou et al., 2016). Together, this work suggests that, due to the developmental time course of amygdala reactivity and regulation, the search for differences in amygdala modulation during reappraisal tasks may be less fruitful in the context of adolescent depression. Our findings highlight the utility of tasks that engage cognitive control neural circuitry, such as our cognitive reappraisal task, in revealing important differences in how depressed adolescents engage regions of the prefrontal cortex. Relatedly, future investigations of brain-based biomarkers of treatment responsiveness should consider these more ecologically valid tasks to better understand how individual depressed adolescents may respond to treatment modalities that rely heavily on the complex cognitive processes necessary to actively modulate emotional responses.

Contributors

Kaja Z. LeWinn Sc.D. developed the study questions and analytic plan, conducted the data analysis, interpreted the results and developed the manuscript.

Irina A. Strigo Ph.D. helped develop the analytic plan, supervised the data analysis, and contributed to data interpretation and manuscript development.

Colm G. Connolly Ph.D. contributed to the study design, supported the data analysis, generated figures for and edited the manuscript.

Tiffany C. Ho Ph.D. contributed to the analytic plan, reviewed results and edited the manuscript.

Olga Tymofiyeva Ph.D. contributed to the analytic plan, reviewed results and edited the manuscript.

Matthew D. Sacchet, Ph.D., contributed to the analytic plan, reviewed results and edited the manuscript.

Helen Y. Weng, Ph.D., contributed to the analytic plan, reviewed results and edited the manuscript.

Eva Henje Blom MD, Ph.D contributed to the analytic plan, reviewed results and edited the manuscript.

Alan N. Simmons Ph.D. contributed to the analytic plan, provided specific feedback on the data analysis, reviewed results and edited the manuscript.

Tony T. Yang M.D., Ph.D. is the PI of the study that generated this data; he developed the study design and edited the manuscript.

Conflict of interest

The authors have no conflicts of interest to report.

Role of the funding source

The funders of this study played no role in the study design, collection, analysis, and interpretation of data; in writing this manuscript; or in the decision to submit the article for publication.

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