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Amygdala Response and Functional Connectivity During Emotion Regulation: A Study of 14 Depressed Adolescents

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Abstract

Background—Ineffective emotion regulation and abnormal amygdala activation have each been found in adolescent-onset major depressive disorder. However, amygdala activation during emotion regulation has not been studied in adolescent-onset major depressive disorder.

Method—Fourteen unmedicated adolescents diagnosed with current depression without comorbid psychiatric disorders and fourteen well-matched controls ages 13 to 17 years underwent an emotional regulation task during functional magnetic resonance imaging. During this task, participants viewed negatively-valence images and were asked to notice how they were feeling without trying to change it and maintain their emotional reaction (“Maintain”) or to interpret the image in such a way as minimize their emotional response (“Reduce”).

Results—Imaging analyses demonstrated that adolescents with depression showed: (1) greater right amygdala activation during the maintain condition relative to controls, (2) less connectivity during the maintain condition between the amygdala and both the insula and medial prefrontal

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Contributors

Dr. Tony Yang and Dr. Alan Simmons designed the study and study protocol. Dr. Alan Simmons wrote the computerized task, based upon a previously published task authored by Dr. Alan Simmons and Dr. Laura Campbell-Sills. Dr. Alan Simmons, Mr. Jing Wu, and Mr. Kevin Hahn ran the data analyses and statistical analyses. Dr. Greg Perlman, Mr. Jing Wu, Mr. Kevin Hahn, and Dr. Tony Yang managed the literature searches, and wrote the first draft of the manuscript. All authors contributed to and have reviewed and approved the final manuscript.

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cortex than controls, and (3) a significant positive correlation between amygdala-seeded connectivity during maintenance of emotion and psychosocial functioning.

Limitations—The current study is cross-sectional comparison and longitudinal investigations with larger sample sizes are needed to examine the association between amygdala reactivity and emotion regulation over time in adolescent MDD.

Conclusions—During the maintain condition, adolescents with depression showed a heightened amygdala response and less reciprocal activation in brain regions that may modulate the amygdala. A poorly modulated, overreactive amygdala may contribute to poor emotion regulation.

Keywords

Major Depression; Functional MRI; Insula; Reappraisal; Prefrontal Cortex

INTRODUCTION

Adolescent-onset major depressive disorder (aMDD) is a prevalent psychiatric condition (Lewinsohn et al., 1998) and associated with a range of deleterious outcomes (Fergusson and Woodward, 2002). The point prevalence in adolescents for aMDD ranges from 0.4%–8.3%, and the lifetime prevalence is approximately 10–28% (Lewinsohn et al., 1998). aMDD is associated with early pregnancy, poor school performance, and diminished social, family, and work functioning (Fergusson and Woodward, 2002).

Evidence suggests that aMDD may be associated with ineffective emotion regulation (Sheeber et al., 2001, Cicchetti and Toth, 1998), the collection of strategies to alter the psychological, physiological, or cognitive aspects of emotional experience (Gross, 2002). Surveys of adolescents have shown that symptoms of MDD correlate positively with less use of effective emotion regulation strategies (Garnefski and Kraaij, 2006). In addition, adolescents who report more symptoms of MDD, compared to adolescents who report fewer symptoms of MDD, report less relief from the use of emotion regulation strategies (Silk et al., 2003). Because emotion regulation may play a key role in reducing affective reactivity to aversive cues and disengaging from protracted negative mood states (Gross, 1998), ineffective emotion regulation may lead adolescents with MDD to experience heightened reactivity to aversive stimuli or protracted negative mood states (Pine et al., 2001).

Ineffective emotion regulation in aMDD may be associated with aberrant functioning of the amygdala, a brain region involved in evaluating the salience of affective cues. Consistent with this hypothesis, amygdala activation has been found to differ between adolescents with MDD and healthy controls in several neuroimaging studies (Beesdo et al., 2009, Roberson-Nay et al., 2006, Yang et al., 2010). Although there have not been any published studies of amygdala activation during an emotion regulation task in aMDD, several neuroimaging studies in both healthy adults (Ochsner et al., 2002, Goldin et al., 2008, Phan et al., 2005) and depressed adults (Erk et al., 2010) have utilized an emotion regulation task to study amygdala reactivity. These studies have found that engaging in an emotion regulation task modulates amygdala reactivity to affective stimuli. In particular, one finding from this literature is that engaging in an emotion regulation strategy to reduce the averseness of an aversive cue is associated with decreased amygdala reactivity relative to viewing the aversive image (Ochsner et al., 2002). A similar pattern of amygdala activation during emotion regulation has been reported in younger populations (Pitskel et al., 2011).

Aberrant amygdala reactivity and ineffective emotion regulation in aMDD may also be associated with dysfunction in a network of brain regions involving regions of the prefrontal, insular, and anterior cingulate cortices that help modulate amygdala reactivity to

affective cues (Drevets, 2001, Banks et al., 2007). Activation in regions of this network have been shown to correlate with amygdala activation during emotion regulation in studies of healthy adults (Banks et al., 2007) and healthy youth (Pitskel et al., 2011). Adults with MDD relative to controls have been found to demonstrate an abnormal pattern of coactivation between the amygdala and these modulatory regions during an emotion regulation task (Johnstone et al., 2007). Furthermore, adults with MDD relative to controls have shown decreased coactivation between the amygdala and modulatory brain regions using a variety of task paradigms (Veer et al., 2010, Matthews et al., 2008, Simmons et al., 2008). Furthermore, specific brain regions in this network appear to be dysfunctional in adolescents with MDD (Yang et al., 2009) and in adults with MDD (Drevets, 2001). One method to study patterns of correlated functional activation among brain regions that comprise a coherent network is functional connectivity analysis, a functional magnetic resonance imaging (fMRI) technique (Friston et al., 1997). Thus, connectivity analysis is ideally suited to study the patterns of functional activation between the amygdala and modulatory brain regions during an emotion regulation task in aMDD. However, to date, there have been no connectivity studies of aMDD using an emotion regulation task to study the correlations among amygdala reactivity with regions of this modulatory network.

To address this significant gap in our current knowledge, a group of unmedicated adolescents with MDD without a comorbid psychiatric disorder and a group of well-matched healthy controls performed an emotion regulation task while undergoing blood-oxygenated level dependent (BOLD) fMRI at 3-Tesla. Based upon prior research with adolescents with MDD (Yang et al., 2010), we hypothesized that there would be greater amygdala activation in response to an emotion regulation task among adolescents with MDD relative to matched controls. Furthermore, based upon research in depressed adults (Veer et al., 2010, Matthews et al., 2008, Simmons et al., 2008), we hypothesized that adolescents with MDD would demonstrate less connectivity between the amygdala and other key modulatory brain regions relative to healthy adolescents.

METHODS

Subjects

This research was approved by both the Rady Children's Hospital and University of California at San Diego (UCSD) Institutional Review Boards. All parents/legal guardians gave written informed consent, and all adolescents gave written assent to participate in this study. All participants received financial remuneration for their time and effort. Adolescents with MDD ages 13–17 years from all ethnicities and both genders were recruited from mental health and primary care outpatient clinics in San Diego. Exclusionary criteria for the adolescents with MDD included: (1) having a full IQ score of less than 80 on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999); (2) being color blind or having less than 20/40 correctable vision as determined by the Ishihara color plates (8 plate, 2005 edition) and standard Snellen eye chart; (3) any contraindication to MRI imaging (ferromagnetic implants, braces, claustrophobia); (4) any history of neurological disorder (e.g., meningitis, migraine, HIV), head trauma with loss of consciousness >2 minutes, learning disability, serious medical health problem, or a complicated or premature birth <33 weeks of gestation (exclusionary due to potentially abnormal neurodevelopment); (5) being pregnant or suspect being pregnant; (6) any evidence of illicit drug use, misuse of prescription drugs, or more than 2 alcohol drinks per week either currently or within the past month as determined by the Customary Drinking and Drug Use Record (Brown et al., 1998); (7) left-handedness, as determined by the Edinburgh handedness scale (Oldfield, 1971); (8) prepubertal status (Tanner stages 1 or 2; Tanner, 1962); (9) inability to fully understand and cooperate with the study procedures; (10) a psychiatric diagnosis other than MDD; (11) use of medication with central nervous system effects within the past 2 weeks prior to scanning;

and (12) Children's Depression Rating Scale-Revised (CDRS-R) T-score less than 55, which would indicate low probability of MDD (Poznanski, 1996; Poznanski et al., 1979). Healthy control (CTL) adolescents were recruited from San Diego through e-mail, internet, and flyers. CTLs were excluded from the study if they were assessed on the Family Interview for Genetics Studies (Maxwell, 1992) to have a family history of mood or psychotic disorders in first- or second-degree relatives, a CDRS-R T-score over 45, or if they met any of first 11 exclusion criteria listed above for the adolescents with MDD.

Fourteen adolescents (mean $\pm$ SD, 15.7 $\pm$ 1.5 years; range, 13.33–17.75 years; eight males) suffering from an active major depressive episode with a current DSM-IV diagnosis of MDD, and fourteen carefully-matched CTL adolescents (mean $\pm$ SD, 15.1 $\pm$ 1.6 years; range, 12.67–17.42 years; eight males) participated in this study. An experienced child and adolescent psychiatrist administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Kaufman et al., 2000) to both the parents and adolescents to substantiate the current diagnosis of MDD. None of the adolescents with MDD had a comorbid psychiatric disorder. All adolescents with MDD were symptomatic and medication-free at the time of their fMRI scan. Healthy adolescents were interviewed using the Diagnostic Interview Schedule for Children Version IV (DISC-IV; Shaffer et al., 2000) and the DISC-IV predictive scales (Lucas et al., 1997) to screen for the presence of any Axis I diagnoses.

The MDD and CTL adolescents did not significantly differ on WASI IQ ($t_{26}=-0.75$, $p=0.46$), socioeconomic status ($\chi^2_{7[n=28]}=8.95$, $p=0.26$), pubertal developmental stage (Tanner Stage, $\chi^2_{5[n=28]}=1.87$, $p=0.87$), age ($t_{26}=1.03$, $p=0.31$), or ethnicity ($\chi^2_{4[n=28]}=2.89$, $p=0.58$). In addition, all adolescents were administered the Children's Global Assessment Scale (CGAS; Shaffer et al., 1983) Multidimensional Anxiety Scale for Children (MASC; March et al., 1997) and the CDRS-R. On the MASC, the MDD adolescents endorsed significantly greater levels of anxiety than CTL adolescents ($t_{26}=3.04$, $p<0.01$; MDD=mean $\pm$ SD, 60.07 $\pm$ 10.16; CTL=49.79 $\pm$ 7.81). On the CGAS, a measure of psychosocial functioning, the MDD adolescents scored significantly lower than the CTL adolescents ($t_{26}=10.88$, $p<0.01$; mean $\pm$ SD, MDD=52.36 $\pm$ 13.88; CTL=94.14 $\pm$ 3.73). On the CDRS-R, the MDD adolescents demonstrated significantly greater mean T-score than CTL adolescents ($t_{26}=13.64$, $p=0.01$; MDD=mean $\pm$ SD, 74.61 $\pm$ 11.29; CTL=31.21 $\pm$ 3.77).

Experimental Task

Task Structure and Stimuli—We utilized an emotion regulation task that has been shown to elicit functional activation in the amygdala and the prefrontal cortex in adults (Campbell-Sills et al., 2011). The task involved two conditions. In the first condition, participants were instructed to reduce their emotions using cognitive reappraisal ("Reduce"). In the second condition, participants were instructed to maintain their reactions to negative images ("Maintain"). The task was comprised of 12 Reduce trials and 12 Maintain trials and lasted 9.6 minutes.

34 images were selected from the International Affective Picture System (IAPS; Lang et al., 1999) because these stimuli had been shown to reliably elicit moderate levels of negative affect. IAPS images have been rated by valence (1 to 9; extremely negative to extremely positive) and arousal (1 to 9; no arousal to extreme arousal). We selected age-appropriate images that were rated between 2 to 3.5 on valence and 5 to 7 on arousal. 24 IAPS images were randomly assigned into either the Reduce or Maintain condition and 10 images were used for practice trials.

Each trial lasted 24 s and began with a 12 s baseline period to give participants time to recover in between trials. During the 12 s baseline, a scrambled image was presented. Each

scrambled image was derived from that trial's IAPS image by a pixel-wise randomization routine, which served to match the scrambled image and IAPS image for luminance and color. After between 1–3 s, a prompt to “Rate Emotion (1–4)” appeared in yellow beneath the scrambled image and lasted for 3 s. After between 1–3 s, a visual cue displayed that the trial was “Reduce Emotion” or “Maintain Emotion” 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 seconds (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 seconds. The trial was over when the target image disappears, allowing for 4–6 seconds of preparatory time and 12 seconds of total Reduce or Maintain cognitive engagement (Figure 1). The Maintain and Reduce conditions were separated into Pre-rating and Post-rating phases to allow for separate analysis for functional imaging, in order to match the analysis found in prior literature (Campbell-Sills, Simmons et al., 2011).

The condition order used for all participants was created pseudorandomly and was restricted such that there were no more than 3 consecutive trials of the same condition. Reduce images and Maintain images were not found to differ significantly on valence, arousal, or content (e.g., people, animals, and objects). 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.

Procedure

Prior to fMRI scanning, participants underwent a 30-minute training session on the fMRI task by an experienced member of the research team. Details of the training procedure are described elsewhere (Campbell-Sills et al., 2011). Briefly, participants were taught the task instructions and were given 10 practice trials. More specifically, participants were instructed that during “Reduce” trials they were to interpret the image in such a way as minimize their emotional response. Participants were instructed that during “Maintain” trials they were to “notice what you are feeling without trying to change it” and to “maintain your emotional reaction until the picture disappears.” After completing the practice trials and before beginning the task, participants were asked to describe their cognitive strategies in order to ensure understanding of the task.

Image Acquisition

Images were acquired on a 3.0 T GE scanner (General Electric, Milwaukee, WI) with Twin Speed gradients using a GE 8-channel head coil. Each session consisted of a three-plane scout scan (10s), a high-resolution anatomical scan, a series of T2*-weighted echo-planar imaging (EPI) scans to measure the BOLD response, and EPI-based field maps to correct for susceptibility induced geometric distortions. Functional scans covering the entire brain were acquired parallel to the anterior and posterior commissure (T2*-weighted EPI, TR=2000ms, TE=32ms, flip angle=90°, FOV=23cm², 64×64 matrix, thirty 2.6mm oblique slices with a 1.4mm gap, 290 repetitions). During the same experimental session, a high resolution T1-weighted image (FSPGR, TI=450ms, TR=8.0ms, TE=4ms, flip angle=12°, FOV=25cm², 256×256 matrix, 0.98×0.98×1.0 mm voxels, 172 sagittally-acquired slices) was collected for anatomical reference.

Processing of Imaging Data

All functional and structural image processing and analyses were conducted with the Analysis of Functional NeuroImages (AFNI; Cox, 1996). Additional details of the following neuroimaging analysis pathway have been published elsewhere (Yang et al., 2007). Data

were time-corrected for slice acquisition order (3dTshift). To minimize motion artifact, an AFNI 3D-coregistration algorithm (3dvolreg) was used to realign all echo-planar images, and the time series data for each individual were analyzed using a multiple regression model (3dDeconvolve). Time points of excessive head motion from total outlier voxel count for each EPI acquisition (3dToutcount) was censored from multiple regression. The rating, Reduce (pre/post rating) and Maintain (pre/post rating), served as five orthogonal regressors of interest (Campbell-Sills et al., 2011). Three motion parameters (roll, pitch, yaw) were used as nuisance regressors to account for motion artifacts. In addition, the total outlier voxel count was used to account for variance in data quality within the time series. A modified gamma variate function was convolved with these regressors to account for the dispersion brain response and delay of the BOLD-fMRI signal due to hemodynamics (Cohen, 1997, Friston et al., 1995). Two additional regressors modeled residual motion in the baseline and linear trends. To account for individual variations in the anatomical landmarks, a Gaussian filter with a full-width-half-maximum of 4 mm was applied to the voxel-wise percent signal change data.

After smoothing, imaging data for each adolescent were normalized to stereotaxic Talairach coordinates (Talairach and Tournoux, 1988). The voxel-wise percent signal change data were entered into a paired *t*-test for the task effect analysis (Reduce versus Maintain) separately for the MDD and CTL groups. Further, an independent samples *t*-test (MDD versus CTL) was conducted for the Reduce versus Maintain contrast. The whole brain analysis was protected against false-positive cluster detection at cluster-wise $p < .05$ and cluster volume $> 704 \mu\text{L}$, as determined by the AFNI function AlphaSim. This was followed by 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), resulting in a corrected cluster-wise activation probability of 0.05 using a minimum volume of $192 \mu\text{L}$ (3 connected voxels). Only activations within the area of interest that survived the volume and voxel connection criteria were extracted and used for further analysis.

Functional Connectivity Analysis

Functional connectivity analysis was performed on both MDD and CTL adolescents. The connectivity results are calculated for Reduce and Maintain conditions separately. We used functional connectivity method based on the psychophysiological interaction method (Friston et al., 1997) and adapted for AFNI (<http://afni.nimh.nih.gov/sscc/gangc/CD-CorrAna.html>). Additional details of the functional connectivity analysis have been published elsewhere (Simmons et al., 2010). Before conducting the functional connectivity analysis, the individual raw signal datasets underwent time- and motion-correction, as described above in “Processing of Imaging Data.” Individual time courses in these processed raw signal datasets were extracted for the seed ROI (i.e., right amygdala). Data points were censored if they differed by more than two standard deviations from the average EPI signal for the seed ROI. We then used AFNI function “3dTfitter” to remove hemodynamic delay from these right amygdala time courses. The resultant signal in right amygdala was then multiplied by the condition regressor (Reduce and Maintain) thereby creating two interaction time courses, which were then each convolved with a hemodynamic covariate function. Two regression models were run thereafter to examine connectivity of right amygdala during reduce and maintain stimulus conditions. Interaction time courses were used as regressors of interest. Twelve nuisance regressors controlling for baseline differences, linear drift, head movement (roll, pitch, and yaw), seed activation across the time series, five task regressors (see Processing of Imaging Data), and fluctuations in white matter signal were added to each regression model. The resulting correlation coefficient for each time course of interest was calculated for each voxel. This provided correlation maps for the time course in the seeded ROIs and the time

course from all other brain voxels as a function of task condition (Reduce or Maintain). The Fisher Z transforms of these correlation maps were then warped to conform to the Talairach atlas (Lancaster et al., 2000), and a Gaussian blur of 4 mm FWHM was applied to allow for group comparisons of the Fisher Z transforms in the right amygdala during Reduce and Maintain conditions using independent two-sample t-tests. The resulting voxel-based data was cluster thresholded as described in the primary analysis and the mean Fisher Z transformations of the interaction terms were extracted for further analysis.

Correlational Analysis of Imaging data

We also conducted correlational analyses to examine the relationship of behavioral measures (i.e. subjective distress ratings), and clinical measures (i.e. CDRS-R, CGAS), to activation in functionally defined ROIs in the task and connectivity analysis. Analyses involving behavioral data were conducted with SPSS/PASW 18.0 (Norusis, 1990).

RESULTS

Group Differences in Task-Related Behavioral Measures

An analysis of variance (ANOVA) examined the effects of trial type (Baseline, Reduce, or Maintain) and group (MDD or CTL) on the magnitude of distress ratings. There was an effect of trial type ($F_{2, 23}=23.11$, $p<.001$) such that baseline periods were associated with the lowest levels of distress, followed by Reduce trials, and then by Maintain trials in the combined groups (MDD plus CTL). No group effect was observed ($F_{1,24}=2.49$, $p=0.13$).

Task Effects on BOLD Activity

The percent signal change during Maintain and Reduce conditions were contrasted in both the MDD and the CTL groups. The CTL adolescents demonstrated greater activation in the left anterior insula, bilateral middle frontal gyrus, inferior frontal gyrus, and left anterior cingulate during the Maintain condition relative to the Reduce condition, and greater activation in the bilateral temporal and medial frontal gyri during the Reduce condition relative to the Maintain condition (Table 1).

In contrast, the MDD adolescents demonstrated greater activation in the anterior cingulate, right insula, left parahippocampus, left middle occipital gyrus, and bilateral lingual gyrus in the Maintain condition relative to the Reduce condition (Table 1). No regions demonstrated greater activation in the Reduce condition relative to the Maintain condition in the MDD group.

Group Differences in BOLD Activity on the Maintain vs. Reduce Contrast

A whole-brain analysis of the percent signal change for the Maintain vs. Reduce contrast found greater activation in the MDD adolescents compared to the CTL adolescents in the right middle occipital and left lingual gyri. The CTL adolescents compared to the MDD adolescents showed greater activation in the left inferior frontal gyrus. An ROI analysis showed a significant cluster of activation in the right amygdala, wherein the MDD adolescents demonstrated greater difference in Maintain vs. Reduce condition than the CTL adolescents (Figure 2, Table 2).

Group Contrast in Functional Connectivity

The Maintain and Reduce conditions were examined in a functional connectivity analysis seeded from the right amygdala (Figure 3, Table 3). During the maintain condition, MDD adolescents relative to the CTL adolescents demonstrated lower connectivity between the amygdala and several cortical regions (bilateral insula; bilateral ventral medial frontal, right

superior frontal, left superior temporal, right inferior frontal, middle temporal gyri). During the Reduce condition, the MDD adolescents relative to the CTL adolescents showed greater connectivity in the left medial frontal gyrus and subgenual anterior cingulate cortex.

Relationship between Clinical Measures and fMRI Activity

The Children's Global Assessment Scale (CGAS) showed significant correlations with functional connectivity findings in the left anterior insula (Spearman's $\rho=0.56$, $p=0.04$) and the medial prefrontal cortex (Spearman's $\rho=0.59$, $p=0.03$) in adolescents with MDD. No additional significant correlations were found with functional connectivity. No significant correlations were found with BOLD activations.

DISCUSSION

The current study is the first to use an fMRI task to examine differences in emotion regulation between adolescents with MDD and a group of well-matched controls. This is also the first fMRI study to identify differences in functional connectivity between adolescents with MDD and controls during an active task. This study yielded three main results. First, an ROI analysis showed that adolescents with MDD relative to controls had greater activation in the right amygdala during the Maintain versus Reduce condition. Second, during the Maintain condition adolescents with MDD relative to controls showed decreased amygdala-mPFC connectivity and decreased amygdala-insula connectivity. Third, this connectivity was significantly associated with psychosocial functioning for adolescents with MDD.

This is the first investigation to find increased amygdala activation among adolescents with MDD relative to controls using an emotion regulation task. As shown in Figure 2, this effect was driven by more amygdala reactivity during the Maintain condition and less amygdala reactivity in the Reduce condition among adolescents with MDD relative to controls. Increased amygdala activation among adolescents with MDD relative to controls has been reported in other studies (Beesdo et al., 2009, Roberson-Nay et al., 2006, Yang et al., 2010), as well as increased amygdala activation among adults with MDD relative to controls (Fales et al., 2008, Matthews et al., 2008). Together, these findings suggest that relative to controls, adolescents with MDD may be prone to greater emotional reactivity to aversive cues (LeDoux, 1996, Drevets, 2001), and that this may be accentuated when adolescents are not actively engaging in an emotion regulation strategy.

During the maintain condition, adolescents with MDD relative to controls showed less amygdala-mPFC connectivity. This is the first fMRI study to show altered amygdala-mPFC connectivity during emotion regulation in adolescents with MDD. This finding is consistent with studies of amygdala-mPFC connectivity in adults with MDD. For example, less amygdala-PFC connectivity has been found in adults with MDD relative to controls using an emotion regulation task (Erk et al., 2010), as well as other tasks (Chen et al., 2008, Pezawas et al., 2005, Matthews et al., 2008). Because the mPFC is thought to be important in the cognitive regulation of emotion (Phillips et al., 2008), our findings may help to shed light on the neural correlates of ineffective emotion regulation in aMDD. For instance, intact amygdala-mPFC connectivity may facilitate top-down regulation of the amygdala by the mPFC (Banks et al., 2007, Erk et al., 2010). In support of this idea, in healthy adults the strength of amygdala-mPFC connectivity has been shown to positively correlate with the magnitude of reduced negative affect following reappraisal of aversive stimuli (Banks et al., 2007). Thus, our finding of decreased amygdala-mPFC connectivity in adolescents with MDD suggests that poor top-down regulation of the amygdala by the mPFC may hinder effective emotion regulation in aMDD.

During the maintain condition adolescents with MDD relative to controls showed less amygdala-insula connectivity. This is the first investigation to show altered amygdala-insula connectivity during emotion regulation in adolescents with MDD. This finding is consistent with a study that found less amygdala-insula connectivity in unmedicated adults with MDD without comorbid disorders relative to healthy adults (Veer et al., 2010). This finding may also help to understand the neural correlates of emotion dysregulation in aMDD. For instance, one model theorizes that the insula integrates emotional information provided by the amygdala in order to substantiate interoception, or the moment-to-moment conscious awareness of emotional state (Craig, 2009, Craig, 2010). According to this model, intact amygdala-insula connectivity may facilitate self-awareness of emotional state and accurate identification of emotionally-evocative cues (Craig, 2009, Craig, 2010). Thus, our finding of decreased amygdala-insula connectivity may suggest that in adolescents with MDD, emotions generated by the amygdala are poorly integrated into conscious awareness by the insula (i.e., poorly identified or mis-attributed feelings).

Finally, poorer psychosocial functioning was significantly associated with less amygdala-insula connectivity and amygdala-mPFC connectivity during the maintain condition among adolescents with MDD. To our knowledge, this is the first fMRI study of aMDD to report a significant correlation between connectivity and an indicator of psychosocial functioning. That brain activation found in aMDD is associated with an index of real-world functioning provides important convergent validation of our fMRI findings. Prior fMRI studies of adults with MDD have reported significant correlations between brain activation and severity of clinical impairment (Steele et al., 2004), between MDD symptom severity and decreased ability to down-regulate response to aversive stimuli (Erk et al., 2010), and between FC in the amygdala and ACC with severity of depressive symptoms (Matthews et al., 2008).

Several clinical implications for treatment of adolescents with MDD stem from our results. First, our findings suggest that adolescents with MDD may benefit from treatments that help normalize amygdala activation. Among adults, some of the most common successful treatments for MDD (e.g., CBT, SSRIs) have been found to normalize amygdala reactivity (Fu et al., 2004, Sheline et al., 2001, Fu et al., 2008). In contrast, although these treatments are empirically supported treatment standards for aMDD (Ma et al., 2005), there have been no longitudinal studies to date that examine whether conventional treatments for aMDD normalize amygdala activation. Second, our connectivity findings may also help to refine therapeutic strategies aimed at improving emotion regulation in adolescents with MDD. Less amygdala-PFC connectivity may indicate that adolescents with MDD struggle to use cognitive strategies to regulate their mood. This could be improved by therapies that teach skills in emotion regulation. For example, cognitive therapy exercises that teach how to challenge negative thoughts might help adolescents with MDD to develop better top-down modulation of the amygdala by the PFC. In addition, less amygdala-insula connectivity may indicate that adolescents with MDD may be less consciously aware of their current emotional state. This deficit might be improved through therapy exercises focused on teaching self-awareness of internal sensations and emotion, such as mindfulness and progressive muscle relaxation. Mindfulness-based treatments have been shown to be effective in reducing mood symptoms among adolescents in outpatient therapy settings (Biegel et al., 2009, Goldin and Gross, 2010).

The present study's results are tempered by several limitations. The number of adolescents with MDD in this study is preliminary for an fMRI study of pediatric depression, and future studies with larger sample sizes are needed. Additionally, similar to prior fMRI pediatric depression studies (Roberson-Nay et al., 2006, Yang et al., 2010), the current study is a cross-sectional comparison of brain activation in adolescents with MDD and controls.

Longitudinal studies are needed to examine the effects of different pharmacological and behavioral treatments on amygdala reactivity over time in adolescent MDD.

In summary, our findings significantly contribute to the field of aMDD by demonstrating that adolescents with MDD have greater amygdala response relative to matched healthy controls during the maintain condition of an emotion regulation task. Compared to controls, adolescents with MDD were also found to show less amygdala-mPFC and amygdala-insula connectivity during the maintain condition relative to the reduce condition. Finally, less amygdala-mPFC connectivity and less amygdala-insula connectivity was associated with lower scores on a clinical measure of psychosocial functioning. Our results suggest that the association between poor emotion regulation and adolescent MDD may be due to an over-reactive amygdala that is insufficiently modulated by the mPFC and poorly integrated by the insula. These findings suggest that adolescents with MDD may benefit from treatments that aim to normalize amygdala reactivity, teach skills in emotion regulation by increasing top-down control of the amygdala by the mPFC, and improve self-awareness of emotional states by integrating information from the amygdala into the insula.

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Fig 1. Graphical representations of the Reduce and Maintain conditions during the experimental task. Periods of "Reduce Emotion" and "Maintain Emotion" were presented alternately, each containing 12 s of a baseline and 12 s of a target image.

Fig 2.
BOLD activity in the amygdala for the interaction between group (MDD, CTL) and task (Maintain, Reduce).

Fig 3. Right amygdala-seeded functional connectivity analysis demonstrated group differences in the bilateral anterior insula and medial prefrontal cortex (mPFC).

Table 1

Significant clusters for the maintain versus reduce contrast for depressed and control adolescence

Brain region	t value	Cluster size (mm ³)	X	Y	Z
Whole Brain Analysis: 14 Control Subjects					
Reduce > Maintain					
Right Middle Temporal Gyrus (BA 39)	2.69	2752	41	-66	15
Right Middle Frontal Gyrus (BA 8)	2.88	2624	30	16	36
Left Inferior Temporal Gyrus (BA 19)	2.88	768	-45	-57	-4
Right Medial Frontal Gyrus (BA 6)	3.07	704	12	-1	59
Maintain > Reduce					
Left Inferior Frontal Gyrus (BA 10)	2.67	1152	-39	46	0
Left Inferior Frontal Gyrus (BA 45)	2.81	1088	-44	19	10
Left Anterior Cingulate (BA 32)	2.89	768	-24	36	5
Right Inferior Frontal Gyrus (BA 47)	2.94	704	28	31	-6
Whole Brain Analysis: 14 MDD Subjects					
Maintain > Reduce					
Left Lingual Gyrus (BA 19)	2.76	7744	-24	-61	-6
Right Anterior Cingulate (BA 24)	2.63	4864	13	27	11
Left Dentate	2.66	1664	-16	-46	-27
Right Lingual Gyrus (BA 18)	2.72	1472	18	-79	-5
Left Parahippocampal Gyrus (BA 34)	2.85	1088	-17	-11	-14
Left Lingual Gyrus (BA 18)	2.57	896	-5	-65	2
Left Precuneus (BA 31)	2.72	832	-25	-71	18
Right Parahippocampal Gyrus (BA 38)	3.08	704	33	-4	-14

Note. Coordinates correspond to the Talairach-Tournoux atlas, and *t* statistics are reported for the voxel within each cluster with the average BOLD response. BA = Brodmann area; R = right; L = left; R/L = bilateral; MDD = major depressive disorder.

Table 2

Significant clusters for the group contrast for the maintain versus reduce contrast

Brain region	t value	Cluster size (mm ³)	X	Y	Z
Whole Brain Analysis: MDD > Control					
L Lingual gyrus (BA 18)	2.38	1856	-3	-66	4
L Lingual gyrus (BA 19)	2.56	1344	-25	-72	-5
L Lingual gyrus (BA 18)	2.66	1024	-21	-54	1
R Middle occipital gyrus (BA 18)	2.53	896	27	-82	3
Whole Brain Analysis: Control > MDD					
L Inferior frontal gyrus (BA 10)	2.81	1088	-39	52	0
Region of Interest Analysis: MDD > Control					
R Amygdala	2.41	192	18	-4	-23

Table 3
Significant clusters for the group contrast for amygdala seed connectivity during Maintain and Reduce conditions

Brain region	t value	Cluster size (mm ³)	X	Y	Z
Whole Brain Analysis: Maintain condition: Control > MDD					
L Insula (BA 13)	3.17	10624	-35	12	-6
R Medial Frontal Gyrus (BA 10)	3.20	7744	3	49	8
R Insula (BA 13)	3.09	2816	33	20	9
L Middle Occipital Gyrus (BA 37)	3.16	1536	-40	-60	-6
R Inferior Frontal Gyrus (BA 47)	3.52	1152	35	22	-7
L Middle Occipital gyrus (BA 39)	3.17	1088	-34	-76	14
R Superior Temporal Gyrus (BA 38)	3.15	768	48	8	-9
R Superior Frontal Gyrus (BA 6)	3.57	768	2	23	57
Whole Brain Analysis: Reduce condition: MDD > Control					
R Brodmann area 30 (BA 30)	3.53	4928	26	-51	11
Hippocampus (EC)	4.05	2368	-3	-10	-21
L Paracentral Lobule (BA 6)	3.53	2176	-12	-29	57
L Middle Frontal Gyrus (BA 8)	3.41	768	-47	11	44