2016

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Developmental Cognitive Neuroscience 18 (2016) 89–100

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: http://www.elsevier.com/locate/dcn

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

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ARTICLE INFO

Article history:
Received 17 April 2015
Received in revised form 16 October 2015
Accepted 13 November 2015
Available online 28 November 2015

Keywords:
Functional connectivity
Rumination
Cognitive reappraisal
Amygdala
Subgenual cingulate

ABSTRACT

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

1. Background

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

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

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http://dx.doi.org/10.1016/j.dcn.2015.11.003

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

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

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

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

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

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

cognitive tasks. Excessive sACC activity has been associated with symptom severity in MDD (Matthews et al., 2009), while deep brain stimulation inhibiting sACC activity in treatment-resistant MDD can lead to remission of depression (Mayberg et al., 2005). Thus, the association of increased DLPFC and sACC activation with rumination in MDD suggests that trait measures of rumination may be particularly closely associated with altered regulation of emotion in MDD.

While brooding rumination may be associated with atypical emotion regulation in MDD, It has been suggested that rumination may take a more adaptive form in healthy non-depressed individuals. In particular "reflective pondering" – a type of rumination with an emphasis on problem solving and addressing or alleviating negative emotions – is more prevalent than brooding rumination in healthy individuals (Joormann et al., 2006). Further, unlike brooding rumination, it is not associated with depressive measures in healthy individuals (Joormann et al., 2006). In contrast, in MDD brooding rumination is more prevalent than reflective pondering (Joormann et al., 2006) and both types of rumination are associated with increased depression (Raichle et al., 2001; Mazoyer et al., 2001), though reflective pondering is associated with decreases in depressive symptoms at follow-up (Treynor et al., 2003). If reflective pondering is indeed adaptive in healthy subjects, it is possible that greater use of this form of rumination in the absence of brooding rumination may be associated with more effective emotion regulation in healthy subjects. As the use of brooding rumination appears to decrease following peak use in late childhood and early adolescence (Hampel and Petermann, 2005; Hankin, 2008; Rood et al., 2009), it is possible that healthy development in this period involves decreasing ruminative thought and/or shifting to a more adaptive reflective style of rumination. In this context, the continued use of brooding rumination may contribute to MDD risk.

It is important to note that prefrontal activity has regularly been associated with *both* effective emotion regulation as well as rumination, both of which involve reflecting upon and interpreting emotional content. As such, simply measuring activity of prefrontal regions during a reappraisal task may provide incomplete evidence as to whether that activity represents effective emotional regulation. Rather, a stronger indicator of effective regulation is whether such increased prefrontal activity is associated with decreased activity of regions associated with reactivity to emotional stimuli. PPI is an ideal method to evaluate this question, as it measures changes in the strength and direction of functional connectivity across task states, indicating, for example, whether reappraisal leads to stronger negative connectivity between prefrontal cortex and amygdala than is seen during passive viewing of negative stimuli. The current study used PPI functional connectivity analyses to specifically evaluate how FC of the amygdala and of the sACC change between passively viewing and reappraising sad images, and how differences in rumination influences those changes in children with a history of MDD (MDD-ever) and healthy control (HC) children. If rumination is indicative of ineffective emotion regulation in MDD-ever, individuals with greater tendency to ruminate should show less moderation of amygdala activity during reappraisal. As rumination is also associated with increased activation of prefrontal regions, it may also be associated with increased FC between amygdala and frontal regions in MDD-ever, indicating inefficient or ineffective control by those regions. We further hypothesized that rumination would be associated with increased FC of the sACC during reappraisal in MDD-ever, as ineffective regulation of the sACC could lead to increased attention to the effort to reappraise, including self-referential attention to one's emotional response (Cooney et al., 2010). For control subjects, we hypothesized that to the extent that this group endorsed rumination, these measures might index reflective pondering, and would thus be associated with greater FC anti-correlations between amygdala and prefrontal control regions during reappraisal, as indicative of effective regulation.

2. Methods

2.1. Participants

Forty-six children between 8 and 15 years old participated in the current imaging study after providing consent according to the guidelines of the Washington University School of Medicine Institutional Review Board. Child participants and their primary caregivers were a sub-sample of participants enrolled in a larger longitudinal study examining the course of preschool-onset depression and brain development. Subjects in the current study were a subset of a larger group that participated in the reappraisal fMRI study (Belden et al., 2015) that met strict motion criteria necessary for functional connectivity analysis. There were nineteen children with a history of clinically diagnosed Major Depressive Disorder diagnosis (MDD-ever), as well as recent significant levels of depression, defined as either MDD diagnosis or Children's Depression Inventory (CDI) score that met a clinical threshold for depression (total score ≥ 65) within 24 months of the scan (10 male; mean age: 12.27 (1.14)). Twenty-seven psychiatrically healthy children (13 male; mean age: 11.33 (1.95)) were also included in the current analyses. Table 1 summarizes demographic and clinical data for healthy and MDD groups. An additional 36 children were scanned, but were excluded from the current analysis for one or more of the following: excessive movement during fMRI ($n = 3$), errors in data collection or processing ($n = 8$), child unwilling to start or finish the fMRI protocol ($n = 4$), child fell asleep during the fMRI ($n = 3$), child did not meet MDD threshold within 24 months of scan but met criteria at an earlier time in development ($n = 8$), child had other psychiatric diagnosis but not MDD ($n = 9$), extreme outlier values of FC data ($n = 1$). Non-included subjects did not differ significantly ($p < 0.05$) from children with useable fMRI data in relation to their age at scan, IQ, gender, ethnicity, or MDD history (healthy vs MDD ever).

2.2. Materials

The Cognitive Emotion Regulation Questionnaire (CERQ) is a parent-report and child self-report measure that assesses the child's cognitive emotion regulation strategies typically used after a negative event (Garnefski et al., 2007). Only the self-report of the child version (CERQ-k) was examined here. Subjects indicate the frequency with which they use a given reappraisal strategy on a 5 point Likert scale [1: (almost) never; 5: (almost) always]. The questionnaire divides regulation strategies into nine factors, with four questions contributing to each factor. The current study focused on the Rumination subscale, given hypotheses about the relationship

Table 1
Demographic and clinical characteristics of participants.

	HC		MDD	
	Mean	SD	Mean	SD
Age	11.33	1.94	12.27	1.14
Sex (%female)	51.80%		47.37%	
IQ	109.56	13.47	99.67	16.78
CDI-P (*t*-scores)	53.84	9.04	67.82	5.09
CERQ rumination	10.44	3.15	10.52	2.36
Age of MDD onset			5.60	2.54
Number of past episodes			3.47	1.92

Notes: Age of MDD onset reflects age of first diagnosis as clinically assessed in the course of the longitudinal study. Number of past episodes reflects number of annual assessment waves in which child met clinical criteria for MDD diagnosis, up to and including the date of the current scan.

between rumination and alterations in connectivity outlined above (Koster et al., 2011; Cooney et al., 2010).

2.3. Task design

Using a previously validated task (Belden et al., 2014), children were instructed to decrease their experience of negative emotions in response to viewing sad images using positive cognitive reappraisal strategies. The trial structure was similar to investigations of cognitive reappraisal conducted with older children and adults (Ochsner et al., 2004; Perlman et al., 2012; Perlman and Pelphrey, 2011; Pitskel et al., 2011; Wager et al., 2008), modified for use with school-age children. As shown in Supplemental Fig. 1, at the start of each trial, a neutral or sad photo was presented for a 4-s interval. Next an instruction appeared below the photo, 'VIEW' appeared to indicate non-regulation trials, 'MAKE-POSITIVE' appeared to indicate regulation trials (regulation trials only occurred for sad photos). The instruction and photo remained on the screen together for 4 s, after which the photo disappeared while the instruction remained onscreen for an additional 4 s. Following each picture, children were prompted to answer the question 'How do you feel?'. Children had 4 s to rate their negative affect, on a scale from 1 to 4. Responses were made on a 4-button box. The continuation of reappraisal instructions following the presentation of the image allows for modeling of reappraisal both during and after the experience of a social stimulus – a key aspect of the design, as rumination is characterized by impaired disengagement from thoughts about negative stimuli even after the experience has ended. This extended period of reappraisal and self-evaluation of emotional state increases the likelihood of uncovering associations between reappraisal and rumination. After the affect rating period, the word 'RELAX' appeared on the screen for 4–8 s (pseudo-randomly determined). The combinations of neutral and sad photos with non-regulate or regulate instructions resulted in 3 conditions: View Neutral (non-emotional), View Sad (sadness inducing but no reappraisal), and Reappraise (instructed to engage in reappraisal while viewing sad photo).

Stimuli were taken from the International Affective Picture System (Bradley et al., 2001), supplemented with an in-house set of images selected to be appropriate for viewing by children (e.g., photos of other children crying). IAPS stimuli have been rated for valence (1–9; extremely negative to extremely positive) and arousal (1–9; no arousal to extreme arousal). The images used had valence scores less than 4 and arousal scores greater than 4. We used 20 neutral and 40 sad pictures during the fMRI task.

Each run presented 12 trials divided equally among view neutral (4 per run), view sad (4 per run), and reappraise sad (4 per run). Trial orders were pseudo-randomized to allow for estimates of BOLD responses to each trial type. Stimuli used for the "View Sad" versus "Reappraise" conditions were counterbalanced so that stimuli were not confounded with condition. In its entirety, the reappraisal task included 5 runs of 12 trials each (60 trials total, 20 in each condition). Each trial lasted 16 s (followed by a 4–8 s jitter) and each run lasted approximately 4 min and 40 s.

2.4. Procedure

A comprehensive pre-scan training procedure was used to assure that children understood the fMRI reappraisal task. Reappraisal training details are identical to those in Belden et al. (2014), and are provided in the Supplementary Material.

2.5. Behavioral data analysis

To evaluate whether groups differed in whether rumination scores were associated with brooding or reflective pondering (as the CERQ rumination scale does not differentiate these measures), rumination scores for each group were correlated with CERQ subscores associated with reappraisal, including Positive Reappraisal, Positive Refocusing, Refocusing on Planning, and Putting Into Perspective. Further, a multiple regression was run to determine whether CDI scores predicted rumination, and whether prediction differed by group. To evaluate reappraisal success during the fMRI task, behavioral reports of emotional state during View Sad and Reappraise conditions were compared between groups using a repeated measures analysis of variance (ANOVA) to test for diagnostic group differences. Correlations between rumination scores and emotional state ratings as well as age were also assessed across and within diagnostic group.

2.6. fMRI data acquisition and preprocessing

Functional images were collected with a 12-channel head coil in runs using an asymmetric spin-echo echo-planar sequence sensitive to BOLD contrast (T2*) (TR = 2000 ms, TE = 27 ms, FOV = 256 mm, flip = 90°). During each functional run, sets of 32 contiguous axial images with isotropic voxels (3 mm × 3 mm × 3 mm) were acquired parallel to the anterior-posterior commissure plane. Further details on structural image acquisition parameters can be found in Supplemental Material.

fMRI data was reconstructed into images and normalized across runs by scaling whole-brain signal intensity to a fixed value and removing the linear slope on a voxel-by-voxel basis to counteract effects of drift. The MR data was aligned to correct for head motion using rigid-body rotation and translation correction algorithms. These algorithms provided estimated movement parameters that allowed us to quantitatively evaluate movement differences across children. We also quantitatively compared signal-to-noise ratios (SNR = mean/variance). All MR data (structural and functional) was registered to a common space optimized for children's heads (Talairach Space) using 12 parameter linear (affine) transformations of the participant's average MP-RAGE structural images to a target image in Talairach atlas space. Previous research has shown that this procedure can be validly applied to the brains of children in this age range (e.g. Burgund et al., 2002) and our average image in Talairach space was optimized for this age range. Frames with excessive movement were identified and excluded from further analysis, particularly those where the sum frame-wise displacement across all 6 rigid body movement correction parameters exceeded 0.9 mm, following a modified procedure suggested by (Siegel et al., 2014). Subjects with more than 20% of frames removed by this procedure were not included in current analyses ($N = 3$).

2.7. PPI construction and statistical analysis

To assess the relationship between rumination and functional connectivity of reappraisal, PPI analyses were performed. In this method, correlations of activity in an a priori region of interest and voxels in the rest of the brain are compared between psychological task states to assess task-related changes in functional connectivity. The magnitude of a PPI value therefore indicates the difference in functional connectivity between a given voxel and the seed region in the two task states.

Seed regions for PPI analysis were created for left and right amygdala, and subgenual anterior cingulate. To create each seed region, automated parcellations of each region of interest (from cortical parcellations using the Destrieux atlas (Destrieux et al., 2010) for sACC and the FreeSurfer subcortical parcellations for amygdala) were created from structural T1 images of 116 subjects from a larger subject pool using FreeSurfer v4.5.0 software. These parcellated regions were then summed across the 116 subjects and thresholded

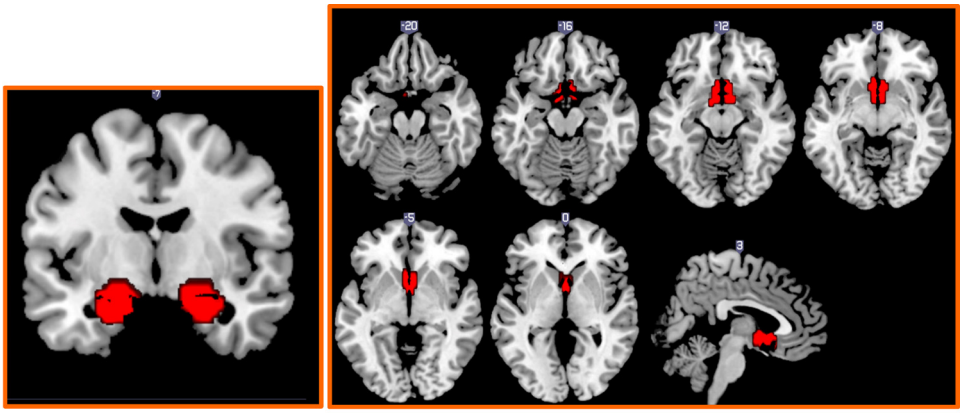

Fig. 1. Seed regions for amygdala (A) and sACC (B) PPI analyses.

to only include voxels within the individual parcellations of 25 or more subjects at a cluster threshold of at least 10 voxels (Fig. 1).

For each subject, the first eigenvariate time series of activity was extracted for all of the voxels in each seed region, concatenated across all runs that met motion criteria. A General Linear Model (GLM), in which each event type (View Neutral, View Sad, Reappraise; jittered between-task rest periods were not explicitly modeled) was modeled as a 12 second task block, with onsets corresponding to the appearance of the specific task instructions (View or Make Positive) following the initial 4 s of passive viewing (see supplemental Fig. 1). This GLM was then convolved with a canonical HRF function (SPM canonical model). A design matrix was then created in which three regressors represented the seed region timecourse, the HRF-convolved task model, and an interaction term between the first two regressors: the PPI regressor. The PPI regressor was then used as a template to interrogate patterns of similar task-related activity across the brain.

Whole-brain multiple regression analyses were run with CERQ rumination scores, diagnostic group, and their interaction as predictors of voxel-wise PPI with each seed, using a PPI contrast of Reappraise > View Sad. All regression analyses were thresholded at $z > 2.5$, 35 contiguous voxels, yielding a significance level of $p < 0.05$, corrected for multiple comparisons based on a Monte Carlo simulation of random noise distribution. To determine whether subject age influenced regression results, regression analyses were run with and without subject age included as a covariate of no interest. Regions showing a significant group × rumination interaction were transformed to ROIs. Reappraise > View Sad PPI values for each interaction ROI were then separately correlated with rumination scores within each diagnostic group, To further illustrate which conditions drove the interaction, separate PPIs for Reappraise > baseline and View Sad > baseline were correlated with rumination scores separately by group. Regions showing a main effect of rumination were transformed to ROIs and tested for correlation with rumination scores within each diagnostic group separately. Regions showing a main effect of group were transformed to ROIs and average PPI values for Reappraise vs baseline and View Sad vs baseline contrasts were compared between groups to determine whether a single condition was driving group differences in the Reappraise > View Sad contrast. To aid interpretation of main effects, regions showing a group × rumination interaction were masked out of main effects maps, ensuring that significant regions would only show main effects.

3. Results

3.1. Group differences in rumination measures

CERQ Rumination scores were correlated with CERQ subscores for Positive Reappraisal, Positive Refocusing, Refocusing on Planning, and Putting into Perspective separately by group. Neither group showed significant correlations between rumination and positive reappraisal, positive refocusing, or putting into perspective. However, healthy controls showed a significant positive correlation between rumination and refocusing on planning scores ($r = 0.412$, $p = 0.033$), which was not seen in the MDD-ever group ($r = 0.055$, $p = 0.824$). A group comparison of correlation strengths using a Fisher r-to-z transform found that the z values did not fall outside the 95% confidence interval (z-obs = 1.19, $p = 0.117$) indicating that the group difference for this correlation did not reach significance in this sample. A multiple regression evaluating whether CDI scores, diagnostic group, or a group × CDI interaction predicted rumination scores found that rumination scores were not significantly predicted by CDI ($B = 0.293$, $p = 0.298$), diagnostic group ($B = -3.204$, $p = 0.087$), or by a group × CDI interaction ($B = 3.130$, $p = 0.075$), though the trend-level interaction was driven by a marginal positive correlation between CDI and rumination in MDD-ever ($r = -0.461$, $p = 0.054$), but not in healthy controls ($r = -0.171$, $p = 0.485$). While neither of these tests directly indicate that rumination is qualitatively different between the healthy and MDD-ever subjects, the strong correlation with focusing on planning in controls and with CDI scores in MDD-ever subjects gives some support to the hypothesis that rumination may indeed be more closely associated with "reflective pondering" in controls and with "brooding" in MDD-ever children.

3.2. Self-report of negative affect

Emotional state ratings measured in the scanner after each trial showed no significant main effect of condition between View Sad and Reappraise trials, $F(1,42) = 1.77$, $p = 0.191$. No diagnostic group differences were seen in behavioral ratings, $F(1,42) = 0.49$, $p = 0.486$, and no group × condition interaction was seen $F(1,42) = 2.14$, $p = 0.151$. However, in paired t-tests of View Sad and Reappraise ratings separated by group, HC children showed a trend toward more positive ratings for Reappraise than View Sad trials, $t(25) = 1.95$, $p = 0.062$, while MDD-ever children showed no difference in ratings by trial type, $t(17) = 0.11$, $p = 0.914$. To confirm that sad images did influence emotional state ratings

Table 2
Regions showing a main effect of rumination.

Seed	Hemi	Region	*X*	*Y*	*Z*	BA	HC *r*	HC *p*	MDD-ever *r*	MDD-ever *p*
L Amyg	Left	Superior temporal gyrus	−46	−35	0	22	0.325	**0.049**	0.671	**0.001**
	Right	Middle temporal gyrus	59	−38	−2	21	0.361	**0.032**	0.605	**0.003**

Note: Coordinates and region labels represent cluster centers of mass. Pearson *r* values and significance levels are shown for both groups for the correlation between rumination scores and values for the Reappraise > View Sad PPI. *p* values at or below 0.05 are in bold.

in both groups, a group × condition (View Neutral, View Sad) ANOVA was performed, which showed a main effect of condition, $F(1,42) = 82.09$, $p < 0.001$, but no main effect of group ($p = 0.686$) or group × condition interaction ($p = 0.588$). No significant correlation was seen between rumination scores and emotional state ratings for either condition, which was true within the full group (View Sad: $R = -0.218$, $p = 0.155$; Reappraise: $R = -0.164$, $p = 0.286$), as well as for groups separated by diagnosis ([MDD-ever View Sad: $R = -0.016$, $p = 0.949$; Reappraise: $R = 0.091$, $p = 0.720$] [HC View Sad: $R = -0.288$, $p = 0.153$; Reappraise: $R = -0.202$, $p = 0.323$]). Age was not correlated with rumination measures or reappraisal affect difference scores (Reappraise – View Sad affect ratings) in either group ([MDD-ever rumination: $R = -0.003$, $p = 0.991$; reappraisal: $R = -0.053$,$p = 0.834$] [HC rumination: $R = 0.098$, $p = 0.627$; reappraisal: $R = 0.233$, $p = 0.251$]). As behavioral measures showed no association with variables of interest, they were not used in subsequent fMRI analyses.

3.3. fMRI data

A whole-brain mask was used to assess group × rumination interactions for each seed region. For main effects, regions that showed significant group × rumination interactions for the respective seed regions were masked out of whole-brain masks. All regression analyses were run both with and without age included as a covariate of no interest. No difference was seen between models that did and did not control for age for any seed for main effects of rumination, group × rumination interactions, or main effects of group.

3.4. Main effect of rumination

Left Amygdala: A main effect of rumination on left amygdala connectivity was seen in left superior temporal gyrus and in right middle temporal gyrus. For both regions, PPI values were positively correlated with rumination scores (Table 2, Supplemental Fig. 2), meaning that greater rumination was associated with stronger amygdala FC during Reappraise than View Sad trials. No main effects of rumination were seen for the right amygdala or sACC seeds.

3.5. Group × rumination Interactions

Left amygdala: The map of left amygdala connectivity showed group × rumination interactions in a distributed network of frontal, temporal, occipital and subcortical regions, including the caudate and thalamus (Table 3; Fig. 2a). Of the 11 regions showing an interaction, only the left postcentral gyrus showed significant correlations between PPI values and rumination scores for both groups, with HC children showing a negative correlation and MDD-ever children showing a positive correlation. In nine regions, the interaction was driven by significant positive correlations in the MDD-ever group but no significant correlations in the control group. Positive correlations between PPI values and rumination scores in MDD-ever were seen in left inferior frontal gyrus, left thalamus, left superior temporal gyrus, bilateral cuneus, right middle temporal gyrus, right middle occipital gyrus, right middle temporal gyrus, and right middle frontal gyrus. One region, the right fusiform gyrus, showed an interaction despite no significant correlation between PPI values and rumination scores in either group.

Right amygdala: The map of right amygdala connectivity showed group × rumination interactions in eleven regions (Table 3; Fig. 2b). All regions showed significant correlations between PPI values and rumination scores in both HC and MDD-ever children, with HC showing negative correlations, and MDD-ever showing positive correlations. Those regions included left superior temporal gyrus, left cuneus, left postcentral gyrus, left middle temporal gyrus, left inferior frontal gyrus, left insula, bilateral thalamus, right middle temporal gyrus, right insula, right medial frontal gyrus, and right paracentral lobule.

Subgenual cingulate: Maps of subgenual cingulate connectivity showed group × rumination interactions in a narrowly defined network of prefrontal and parietal regions. All clusters, which included two regions in the right precuneus and one in the right middle frontal gyrus showed significant positive correlation between PPI values and rumination scores in MDD-ever children and negative correlation in HC children (Table 3; Fig. 2c).

Overlap across seed regions: Regions showing group × rumination interactions with multiple seed ROIs are described in the supplementary materials.

3.6. Main effect of group

Left amygdala: A main effect of group on left amygdala connectivity was seen in nine clusters, including the left anterior cingulate, left thalamus, left middle cingulate, right superior temporal gyrus, right insula, right precuneus, right postcentral gyrus, right precentral gyrus, and right superior frontal gyrus. All regions showed more positive PPI values for HC than MDD-ever children (Table 4, Fig. 3).

Right amygdala: A main effect of group on right amygdala connectivity was seen in bilateral temporal and occipito-parietal regions, with clusters in left middle temporal gyrus, left inferior parietal lobule, right superior temporal gyrus, and right precuneus. All regions showed more positive PPI values for HC than MDD-ever children (Table 4; Fig. 3).

Subgenual cingulate: A main effect of group was seen in bilateral fronto-parietal regions, including bilateral inferior parietal lobule, left superior parietal lobule, left superior frontal gyrus, right medial frontal gyrus, and right posterior cingulate gyrus. All regions showed more positive PPI values for HC than MDD-ever children (Table 4; Fig. 3).

All regions showing a main effect of group showed greater PPI values for HC than MDD-ever for the contrast of Reappraise > View Sad. This was an opposite pattern to that seen when evaluating group × rumination interactions, in which PPI values were greater in MDD-ever. To determine what might account for this shift, FC values for the Reappraise and View Sad conditions were compared separately against baseline for each region showing a main effect of group, to determine whether these PPI differences were driven by a particular group or condition. Between-group *t*-tests showed that no regions showed significant group differences in FC values for the Reappraise condition for any seed region (all *p* values > 0.13) but as shown in Table 4, a number of regions showed significant

Table 3
Regions showing a group × rumination interaction in PPI values.

Seed	Hemi	Region	*X*	*Y*	*Z*	BA	Reappraisal > View Sad PPI				Reappraise > Baseline PPI				View Sad > Baseline PPI			
							HC *r*	HC *p*	MDD-ever *r*	MDD-ever *p*	HC *r*	HC *p*	MDD-ever *r*	MDD-ever *p*	HC *r*	HC *p*	MDD-ever *r*	MDD-ever *p*
L Amyg	Left	Postcentral gyrus	−63	−18	29	1	−0.406	**0.018**	0.595	**0.004**	−0.492	**0.005**	0.137	0.289	0.164	0.207	−0.700	**0.000**
	Left	Inferior frontal gyrus	−47	31	−3	47	−0.128	0.262	0.610	**0.003**	−0.422	**0.014**	0.433	**0.032**	−0.342	**0.040**	−0.482	**0.018**
	Left	Thalamus	−7	−28	5	–	−0.224	0.131	0.688	**0.001**	−0.412	**0.016**	0.301	0.106	−0.115	0.284	−0.488	**0.017**
	Left	Cuneus	−21	−87	22	18	−0.320	0.052	0.711	**0.000**	−0.267	0.089	0.216	0.188	0.173	0.194	−0.693	**0.001**
	Right	Middle temporal gyrus	55	−29	−1	21	−0.197	0.162	0.656	**0.001**	−0.257	0.098	0.306	0.102	−0.002	0.495	−0.477	**0.020**
	Right	Middle occipital gyrus	41	−83	3	19	−0.127	0.264	0.496	**0.015**	−0.026	0.448	0.081	0.371	0.118	0.278	−0.388	**0.050**
	Right	Middle Temporal Gyrus	43	−55	25	39	−0.251	0.103	0.725	**0.000**	−0.403	**0.019**	0.510	**0.013**	−0.074	0.356	−0.630	**0.002**
	Right	Middle frontal gyrus	39	16	27	9	−0.230	0.124	0.575	**0.005**	−0.367	**0.030**	0.779	**0.000**	−0.105	0.300	0.042	0.433
	Right	Cuneus	31	−82	31	19	−0.237	0.118	0.734	**0.000**	−0.245	0.109	0.360	0.065	0.112	0.289	−0.516	**0.012**
	Left	Superior temporal gyrus	−36	−31	5	41	0.083	0.340	0.443	**0.029**	−0.147	0.232	0.026	0.458	−0.217	0.138	−0.605	**0.003**
	Right	Fusiform gyrus	33	−73	−9	19	−0.140	0.243	0.068	0.391	−0.034	0.433	−0.028	0.455	0.137	0.247	−0.100	0.342
R Amyg	Left	Postcentral gyrus	−59	−21	29	2	−0.466	**0.007**	0.624	**0.002**	−0.489	**0.005**	0.189	0.219	0.060	0.384	−0.624	**0.002**
	Left	Superior temporal gyrus	−39	−49	20	22	−0.401	**0.019**	0.710	**0.000**	−0.549	**0.001**	0.357	0.067	−0.202	0.156	−0.627	**0.002**
	Left	Cuneus	−20	−83	28	18	−0.413	**0.016**	0.737	**0.000**	−0.413	**0.016**	0.270	0.132	0.158	0.216	−0.678	**0.001**
	Bilat	Thalamus	0	−30	8	–	−0.460	**0.008**	0.738	**0.000**	−0.495	**0.004**	0.388	**0.050**	0.044	0.415	−0.513	**0.012**
	Right	Middle temporal gyrus	34	−53	22	39	−0.429	**0.013**	0.782	**0.000**	−0.490	**0.005**	0.535	**0.009**	−0.003	0.495	−0.653	**0.001**
	Right	Insula	41	12	16	13	−0.381	**0.025**	0.711	**0.000**	−0.400	**0.019**	0.717	**0.000**	0.069	0.366	−0.497	**0.015**
	Right	Medial frontal gyrus	2	52	20	9	−0.531	**0.002**	0.607	**0.003**	−0.459	**0.008**	0.652	**0.001**	0.018	0.464	−0.320	0.091
	Right	Paracentral lobule	3	−37	55	5	−0.425	**0.014**	0.698	**0.000**	−0.473	**0.006**	0.092	0.354	−0.009	0.483	−0.534	**0.009**
	Left	Middle temporal gyrus	−52	−19	−3	21	−0.373	**0.028**	0.706	**0.000**	−0.448	**0.010**	−0.086	0.364	−0.171	0.196	−0.563	**0.006**
	Left	Inferior frontal gyrus	−48	29	2	45	−0.369	**0.029**	0.656	**0.001**	−0.434	**0.012**	0.525	**0.011**	−0.025	0.452	−0.486	**0.017**
	Left	Insula	−42	−3	11	13	−0.379	**0.026**	0.719	**0.000**	−0.379	**0.026**	0.306	0.101	0.028	0.445	−0.550	**0.007**
sACC	Right	Precuneus	6	−58	46	7	−0.548	**0.002**	0.608	**0.003**	−0.456	**0.008**	0.187	0.221	−0.102	0.307	−0.603	**0.003**
	Right	Middle frontal gyrus	30	16	49	6	−0.584	**0.001**	0.601	**0.003**	−0.579	**0.001**	0.459	**0.024**	−0.107	0.298	−0.426	**0.035**
	Right	Precuneus	39	−62	32	39	−0.379	**0.026**	0.590	**0.004**	−0.433	**0.012**	0.184	0.226	−0.154	0.221	−0.651	**0.001**

Note: Coordinates and region labels represent cluster centers of mass. PPI correlations by group are shown for regions showing a group × rumination interaction for the Reappraise > View Sad PPI. For illustrative purposes, correlations are shown for each condition > baseline in the same regions to illuminate the source of the interaction. HC *r* and MDD *r* columns indicate the Pearson *r* correlation between PPI values and rumination scores for each group, HC *p* and MDD *p* columns indicate the significance of each within-group correlation. *p* values at or below 0.05 are in bold.

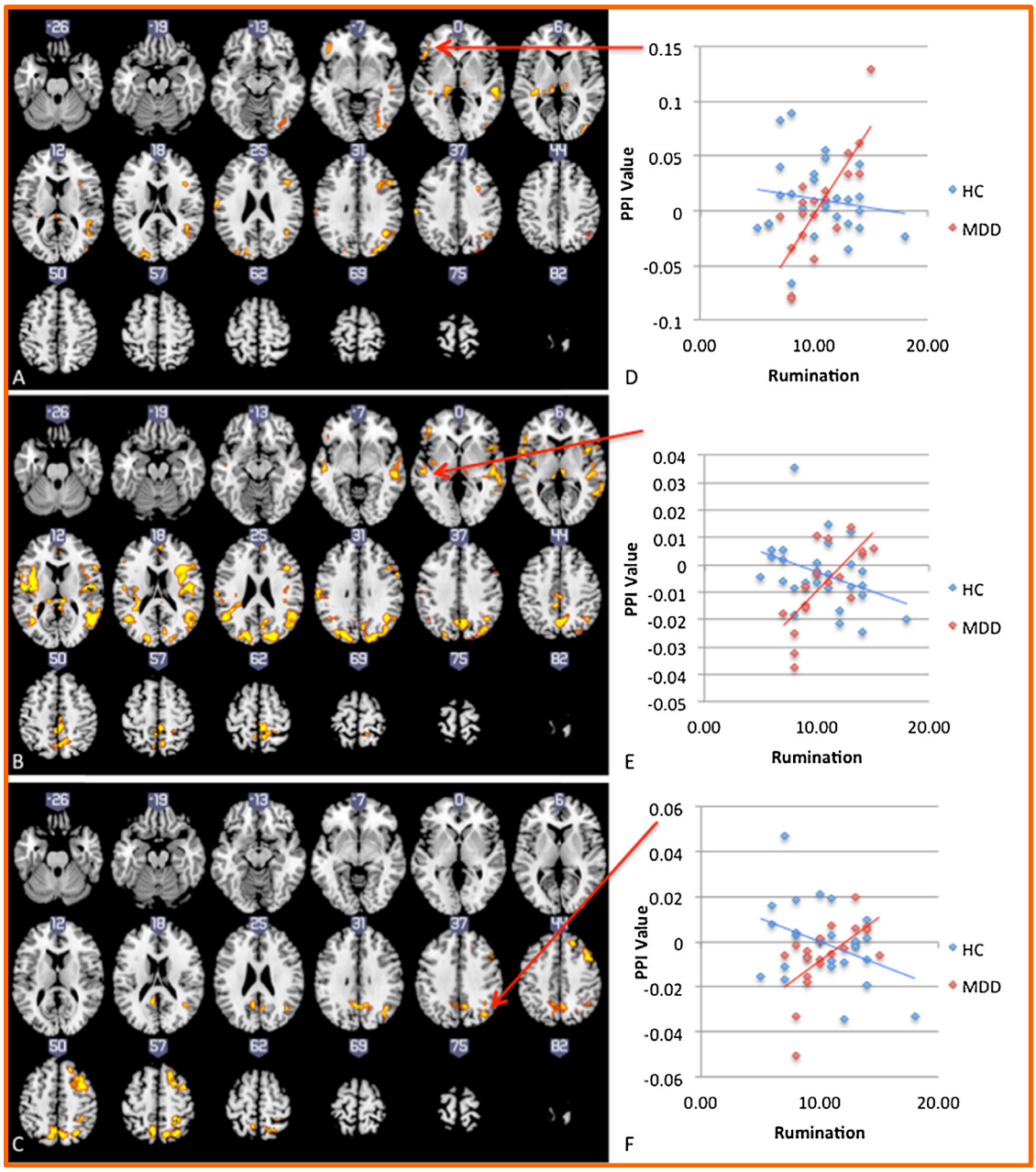

Fig. 2. Regions showing group × rumination interactions in Reappraise > View Sad PPI values with the left amygdala seed (A), right amygdala seed (B), and sACC seed (C). All regions show greater PPI values as rumination increases in MDD-ever, and lower PPI values as rumination increases in HC. Scatterplots (D–F) illustrate a representative relationship between group and rumination scores from a single cluster in each interaction.

between-group differences in the View Sad condition. For each region showing significant differences, MDD-ever showed stronger positive FC than controls in the View Sad condition. As PPI values are based on Reappraise > View Sad FC differences, a more positive FC value in the View Sad condition in MDD subjects would decrease the value of the difference in the PPI, resulting in lower PPI values for MDD-ever than control subjects. Further, within-group paired *t*-tests showed no FC differences between View Sad and Reappraise trials in HC children (all p values > 0.089), while MDD-ever children showed significant condition differences in seven sACC-seed clusters, two right amygdala-seed clusters, and one left amygdala seed cluster – all of which showed greater FC in View Sad than Reappraise trials (Table 4). Thus, main effects of group appear to have been driven largely by greater FC in MDD-ever children in the View Sad condition, rather than group differences in the Reappraise condition.

4. Discussion

The goal of the current study was to examine the relationship between individual differences in rumination and functional connectivity observed during cognitive reappraisal of emotions in children with a history of MDD relative to healthy controls. Overall, findings indicated a relationship between rumination and functional connectivity of the amygdala and subgenual cingulate that was greater in MDD-ever children than healthy children during emotion regulation (cognitive reappraisal). In regions where a group by rumination interaction was found, children with a history of MDD showed greater Reappraise > View Sad differences in connectivity with amygdala and sACC as rumination increased. As effective reappraisal would be expected to decrease connectivity with those regions, this finding suggests that rumination is associated with inefficient regulation of affect-processing regions in

Table 4
Regions showing a main effect of diagnostic group.

Seed	Hemi	Region	*X*	*Y*	*Z*	BA	View Sad	Reappraise	HC Cond Diff	MDD-ever Cond Diff
L Amyg	Left	Anterior cingulate	−8	40	1	32	0.720	0.429	0.180	0.943
	Left	Thalamus	−16	−31	9	–	**0.013**	0.386	0.089	**0.034**
	Left	Cingulate gyrus	−7	−28	41	31	0.059	0.936	0.261	0.477
	Right	Superior temporal gyrus	44	−54	15	22	**0.009**	0.351	0.117	0.072
	Right	Insula	43	−12	18	13	0.612	0.137	0.958	0.076
	Right	Precuneus	4	−57	49	7	**0.028**	0.395	0.181	0.106
	Right	Postcentral gyrus	50	−20	37	3	0.239	0.767	0.66	0.660
	Right	Precentral gyrus	35	−8	47	6	0.291	0.613	0.385	0.424
	Right	Superior frontal gyrus	1	20	52	8	**0.033**	0.892	0.096	0.712
R Amyg	Left	Middle temporal gyrus	−44	−62	9	37	0.205	0.255	0.221	0.082
	Left	Inferior parietal lobule	−37	−55	46	40	0.147	0.868	0.775	0.210
	Right	Superior temporal gyrus	59	−26	5	22	**0.013**	0.885	0.462	**0.039**
	Right	Precuneus	18	−62	21	31	**0.005**	0.534	0.136	**0.032**
sACC	Left	Cerebellum	−23	−62	−58	–	**0.044**	0.269	0.756	**0.029**
	Left	Superior parietal lobule	−30	−57	40	7	0.085	0.414	0.401	0.110
	Left	Superior frontal gyrus	−16	30	45	8	**0.006**	0.989	0.425	**0.014**
	Left	Inferior parietal lobule	−44	−43	42	40	**0.040**	0.543	0.433	**0.030**
	Right	Medial frontal gyrus	3	47	23	9	**0.009**	0.578	0.313	**0.020**
	Right	Inferior parietal lobule	45	−54	36	40	**0.017**	0.901	0.911	**0.011**
	Right	Medial frontal gyrus	12	32	45	8	**0.001**	0.346	0.593	**0.006**
	Right	Cingulate gyrus	5	−39	36	31	**0.036**	0.639	0.672	**0.026**

Note: Coordinates and region labels represent cluster centers of mass. View Sad and Reappraise columns show the *p* values of group differences in PPI values for the View Sad > Baseline PPI and the Reappraise > Baseline PPI respectively. HC Cond Diff and MDD-ever Cond Diff shows within-group differences between Reappraise > Baseline and View Sad > Baseline PPI differences.

MDD-ever children, but not in healthy controls. This may reflect group differences in rumination styles, with rumination in MDD-ever children more closely fitting a maladaptive "brooding" pattern than in healthy controls. Main effects of rumination were only seen in a few focal areas, in which connectivity in HC and MDD-ever children were similarly associated with rumination scores. Additionally, main effects of group were seen in several regions that did not show an association with rumination, which were driven by FC differences between MDD-ever and healthy children in passive viewing of sad stimuli.

Behaviorally, self-reports of negative affect following View-Sad and Reappraise trials did not show significant reduction in negative affect by reappraisal. However, a trend level effect was seen in control children, similar to that seen in a smaller and younger sample of healthy children in a previous study (Belden et al., 2014), There was no such trend in MDD-ever children, but the differences between the groups in the level of negative affect change was not significant. Thus, this pattern hints at the MDD children showing less reappraisal, but is not sufficient to make any strong conclusions. Given that the self-reports in reappraisal tasks are likely strongly influenced by demand characteristics (i.e., children know you want them to reduce their negative affect), self-reports may not be a particularly sensitive indicator of reappraisal efficacy.

A large constellation of regions showed group by rumination interactions in FC related to viewing and reappraising sad images. For both left and right amygdala seeds, regions showing a group by rumination interaction had positive correlations between rumination and PPI values for reappraisal in children with a history of MDD and negative correlations between rumination and PPI

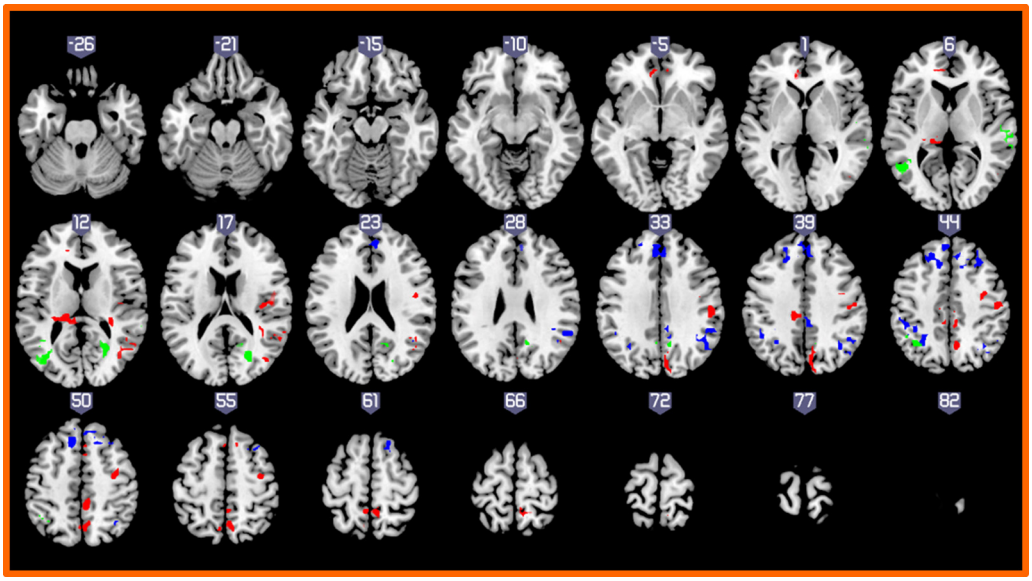

Fig. 3. Regions showing a main effect of group in the Reappraise > View Sad PPI contrast. All regions show greater PPI values for HC than MDD-ever children. Main effects from the left amygdala seed are shown in red, from the right amygdala seed are shown in green, and the sACC are shown in blue.

values for reappraisal in control children. Regions showing this pattern included prefrontal, temporal, parietal and occipital cortical areas, as well as bilateral thalamus (Table 3). A number of these regions, particularly frontal and lateral temporal regions, have been associated with emotion regulation (Buhle et al., 2013; Wager et al., 2008; Kohn et al., 2014). As the typical influence of these control regions is to modulate amygdala activity during reappraisal (Belden et al., 2014), increased FC between these regions and amygdala in MDD-ever children may indicate that rumination is associated with inefficiency in the abilities to modulate affect-processing regions. Increased amygdala connectivity with areas associated with emotion and affect processing, including thalamus, insula, and right middle and superior temporal gyri, further suggests that rumination may be associated with less modulation of these regions during emotional reappraisal in MDD-ever children. Increased connectivity was also seen with bilateral cuneus, a region that has been associated with selective attention to stimulus attributes, including emotional content (Sander et al., 2005), as well as emotional reappraisal (Goldin et al., 2008). This suggests that MDD-ever ruminators exert increased effort with less effect in regulating their attention to the negative emotional aspects of the stimuli that they are attempting to reappraise. These findings are in line with findings in adult MDD, in which rumination is associated with patterns of neural activity suggesting inefficient regulation (Vanderhasselt et al., 2011; Cooney et al., 2010). In addition, many of these regions showed a negative correlation between rumination and PPI values for the View Sad condition in MDD-ever children, but none showed a significant correlation in controls. These findings are consistent with previous work examining the influence of worry during the processing of negative emotional stimuli. Worry is strongly associated with rumination in MDD (McEvoy et al., 2013), and acts as a cognitive avoidance technique that has been shown to reduce autonomic arousal to negative images (Borkovec et al., 2004) and both inhibits amygdala activity and increases negative connectivity between amygdala and prefrontal regions (Hoehn-Saric et al., 2005). While worry was not measured in the current sample, a speculative interpretation of these results may be that either rumination itself or a closely related manifestation of repetitive negative thinking, such as worry, may influence amygdala connectivity during passive viewing of negative images in the absence of explicit reappraisal effort in children with a history of MDD. Overall, these findings suggest that in children with a history of MDD, rumination is associated with increased connectivity between affect and emotion processing regions during attempts to reappraise emotional content, suggesting inefficient modulation of affect and emotion processing in regions associated with cognitive reappraisal, as well as decreased connectivity in these regions in the absence of conscious effort to reappraise.

A similar pattern was seen in sACC connectivity. Children with a history of MDD showed a positive correlation between rumination and Reappraise PPI values with right middle frontal gyrus and bilateral precuneus, while HC children showed negative correlations in these regions. The sACC is frequently implicated in self-referential processing (Gusnard et al., 2001), and shows increased activity (Matthews et al., 2009) and resting functional connectivity (Greicius et al., 2007) in MDD, as well as correlation with depressive symptoms (Matthews et al., 2009). Thus, it has been hypothesized that increased activity of the sACC in MDD may be associated with inability to inhibit self-referential thoughts related to negative emotions (Matthews et al., 2009). The increased correlation of rumination with sACC connectivity during reappraisal in MDD is consistent with the hypothesis that, in evaluating whether the act of reappraisal is improving one's emotional state, individuals with MDD may become more focused on negative emotions with an inability to effectively regulate them. This is consistent with previous findings of increased sACC activity in MDD during specifically directed rumination (Cooney et al., 2010).

It is important to note that the pattern of connectivity seen in healthy children, in whom rumination scores are negatively correlated with reappraisal PPI values, at first appears counterintuitive when rumination is ostensibly associated with maladaptive emotional regulation. This is because a negative correlation between amygdala or sACC and prefrontal regions is more consistent with a pattern of effective inhibition of amygdala and sACC activity during reappraisal. As such, this finding suggests that in healthy individuals, as rumination increases, individuals are more able to inhibit self-relevant processing during reappraisal relative to viewing negative stimuli. This may be evidence that the reasons for endorsement of rumination in healthy children are qualitatively different than those in MDD-ever children. In particular, "reflective pondering" is thought to be an adaptive form of rumination with an emphasis on problem solving and addressing or alleviating negative emotions, as opposed to depressive "brooding" rumination in which the focus is anxious or critical thoughts of one's negative mood or circumstances (Treynor et al., 2003). It is possible that the rumination endorsed by healthy controls in the current study is more closely aligned with adaptive self-referential thought than the brooding rumination frequently associated with MDD. This hypothesis is supported by the finding that rumination scores in control children, but not MDD-ever children, were correlated with a measure of refocusing on planning – a process of "thinking about what steps to take and how to handle the negative event" (Garnefski et al., 2007). However, this interpretation is wholly speculative as the rumination measure collected did not distinguish between brooding and reflective pondering styles of rumination, and such a hypothesis would need direct testing in future studies using a more granular assessment of rumination style.

Only a few regions showed main effects of rumination across MDD-ever and control children. The left amygdala seed region showed main effects of rumination on connectivity, and this was seen only with left superior temporal and right middle temporal gyri. PPI values for both regions increased with rumination. The lateral temporal lobes have been implicated in emotional reappraisal (Buhle et al., 2013), as regions that underlie the reconstruction of semantic and perceptual representations of emotional stimuli – a key aspect of reappraisal (Ochsner and Gross, 2005; Gross, 2009). This may indicate that both adaptive and maladaptive types of rumination are associated with increased representation of meaningful content of emotional stimuli.

Main effects of group were seen for connectivity with each of the seed regions. For all regions showing main effects of group, HC children showed greater PPI values than MDD children – a result largely driven by greater FC during the View Sad than Reappraise condition in MDD. As main effects analyses excluded regions showing interactions with rumination, these regions represent group differences that are not associated with rumination. Of note is the fact that, when rumination is controlled for, there are no group differences in the Reappraise > Baseline PPI, indicating that group differences not associated with rumination are driven by differences in passive viewing of sad images. Further, while rumination is correlated with decreased amygdala and sACC connectivity during the View Sad condition, controlling for rumination highlights brain regions that show greater connectivity with amygdala and sACC during View Sad in MDD-ever than controls. Regions showing group differences in amygdala connectivity included areas implicated in the orienting of visual attention, including the right precentral and postcentral gyri, right precuneus, and medial superior frontal gyrus (supplementary motor area) (Cavanna and Trimble, 2006; Corbetta et al., 2008), as well as areas associated with processing affect and emotion, including left thalamus, right insula, rostral anterior cingulate, and right superior temporal gyrus.

Regions showing group differences in sACC connectivity included bilateral dorsal and medial frontal regions, as well as bilateral parietal and posterior cingulate regions. Many of the regions showing group connectivity differences in right amygdala and sACC are associated with the Task Positive Network (TPN) that is engaged in many cognitive processes, while the posterior cingulate is a key node of the default mode network that is engaged during both rest and self-referential processing (Fox et al., 2005). Recent findings have suggested that abnormal resting-state connectivity of DMN regions relative to TPN regions in MDD is associated with depressive rumination (Hamilton et al., 2011). While these findings are main effects of group rather than related to rumination scores, they also suggest that these networks may both exhibit abnormal connectivity during negative emotion processing in children with MDD. As none of these regions showed significant FC differences by condition in HC children, but did show reduced FC during reappraisal in MDD, it is possible that these regions are automatically regulated in HC children even in the absence of conscious desire to regulate emotions (Mauss et al., 2007), while MDD children are able to regulate them only when exerting conscious effort to do so, though this speculative hypothesis requires further investigation.

5. Limitations

One limitation of the current study is that the measure of rumination used did not differentiate between brooding and reflective rumination styles that may differently correspond to adaptive or maladaptive behavior. However, findings of significant interactions between group and rumination in terms of task-based differences in connectivity indicate that rumination was differently associated with FC in the two groups. A positive correlation between rumination and a measure of adaptive refocusing in controls but not MDD-ever children further supports this hypothesis, as does a positive correlation between rumination and CDI in MDD-ever but not controls. Follow-up studies should evaluate the relationship of rumination style on FC differences between the two groups. Additionally, while the current sample size was not large enough to investigate whether age interacted with rumination and reappraisal across groups, this is an important consideration for future studies, as prefrontal development across adolescence may change the relative influence of ruminative fixation and prefrontal regulation abilities. Finally, while preschool-onset MDD shows evidence of homotypic continuity with later childhood and early adolescent MDD (Luby et al., 2014), it is currently unknown whether the neurobiology underlying depressive symptoms in early-onset individuals differs meaningfully from adolescent- or adult-onset MDD. Future research investigating the influence of MDD onset age on the relationship between rumination and reappraisal, as well as the influence of an acute depressive episode relative to a history of depression, may clarify the generalizability of the current findings to a wider MDD population.

6. Conclusion

Rumination is a trait that is associated with maladaptive emotion regulatory processes in MDD. In a task requiring cognitive reappraisal of sad stimuli, rumination was correlated with increased functional connectivity of bilateral amygdala and subgenual anterior cingulate in children with a history of MDD but with decreased functional connectivity in healthy controls, and included areas associated with both emotion regulation and emotional reactivity. This may be indicative of group differences in using adaptive or maladaptive types of rumination. As the amygdala and sACC are associated with processing emotional salience and self-relevance respectively, the increased connectivity seen in MDD-ever high ruminators during reappraisal suggests that rumination is associated with both inefficient engagement of regulatory regions, and poor inhibition of emotion processing regions. These findings parallel previous behavioral reports of ruminators' attempts to regulate negative emotions resulting in greater attention to those emotions and may be indicative of an inability to inhibit self-reflected attention to sad emotional content in children with a history of MDD. Few regions showed main effects of rumination on FC across MDD-ever and healthy children, suggesting there are likely significant overall differences in rumination between the groups, possibly delineating differences in adaptive and non-adaptive rumination in healthy individuals. Additionally, when controlling for rumination, group differences were driven by differences in the passive viewing of sad images, rather than in emotional reappraisal. These findings suggest that future studies are warranted to focus more closely on the relationship between reappraisal of emotions and rumination in MDD.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dcn.2015.11.003.

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