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Neural indicators of emotion regulation via acceptance *vs* reappraisal in remitted major depressive disorder

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Mood disorders are characterized by impaired emotion regulation abilities, reflected in alterations in frontolimbic brain functioning during regulation. However, little is known about differences in brain function when comparing regulatory strategies. Reappraisal and emotional acceptance are effective in downregulating negative affect, and are components of effective depression psychotherapies. Investigating neural mechanisms of reappraisal *vs* emotional acceptance in remitted major depressive disorder (rMDD) may yield novel mechanistic insights into depression risk and prevention. Thirty-seven individuals (18 rMDD, 19 controls) were assessed during a functional magnetic resonance imaging task requiring reappraisal, emotional acceptance or no explicit regulation while viewing sad images. Lower negative affect was reported following reappraisal than acceptance, and was lower following acceptance than no explicit regulation. In controls, the acceptance > reappraisal contrast revealed greater activation in left insular cortex and right prefrontal gyrus, and less activation in several other prefrontal regions. Compared with controls, the rMDD group had greater paracingulate and right midfrontal gyrus (BA 8) activation during reappraisal relative to acceptance. Compared with reappraisal, acceptance is associated with activation in regions linked to somatic and emotion awareness, although this activation is associated with less reduction in negative affect. Additionally, a history of MDD moderated these effects.

Keywords: emotion regulation; remitted major depression; acceptance; reappraisal; mindfulness

INTRODUCTION

The ability to navigate one's emotional landscape, and especially the ability to consciously downregulate negative affect that interferes with adaptive functioning, is a critical factor for psychological health. Functional magnetic resonance imaging (fMRI) studies of emotion regulation have focused on a top-down frontolimbic regulatory network (Ochsner *et al.*, 2004). As we have summarized previously (Smoski *et al.*, 2013), prefrontal cortical regions, including dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC) and anterior cingulate cortex (ACC), mediate the modulation of emotion-elicited activation in limbic regions (Ochsner and Gross, 2008). Within this regulatory circuit, activation in prefrontal cognitive control regions is negatively associated with changes in limbic activation while processing negative stimuli (Siegle *et al.*, 2006; Urry *et al.*, 2006).

Emotion regulation is especially critical in the context of major depressive disorder (MDD), in which biological, cognitive and behavioral responses to affective stimuli are dysregulated (Davidson *et al.*, 2002; Ressler and Mayberg, 2007). A recent review (Rive *et al.*, 2013) concluded that during early, automatic emotion regulation processes, individuals with MDD may engage in compensatory recruitment of lateral prefrontal cortex during successful regulation. This compensatory recruitment occurs in the medial prefrontal cortex, including the ACC. However, during conscious regulation occurring later in an emotional experience, recruitment of lateral prefrontal cortex is diminished, with less activation in dlPFC and/or vlPFC in individuals with MDD compared with healthy controls (Rive *et al.*, 2013). Differential prefrontal cortical influence on amygdala activation in MDD has been observed during regulation of both negative and positive emotions (Greening *et al.*, 2014), although not all studies have found evidence of altered frontolimbic indicators of regulation in MDD (Dillon and Pizzagalli, 2013). Altered frontolimbic activation during emotion regulation is also observed in euthymic individuals with a history of MDD (Kanske *et al.*, 2012), and increases in dlPFC and ventral medial prefrontal cortex (vmPFC) activation during emotion regulation are associated with symptom improvement during treatment with antidepressant medications (Heller *et al.*, 2013), further emphasizing the importance of emotion regulation on the trajectory of changes in depressive symptoms.

To date, functional neuroimaging studies of emotion regulation in MDD have focused almost exclusively on reappraisal as a regulation strategy. During reappraisal, the meaning of an emotional stimulus is reinterpreted to change its affective tone. In contrast, acceptance of an emotion is a component of the broader construct of mindfulness that has been defined as the awareness that arises through 'paying attention in a particular way: on purpose, in the present moment, and non-judgmentally' (Kabat-Zinn, 1994, p. 4). Notably, mindfulness may be used to describe a psychological trait (i.e. naturally occurring and consistent across contexts); a mode or state of awareness (i.e. brought about through intention, through eliciting aspects of the context or as a result of experimental induction or training) or a practice of cultivating mindfulness (e.g. mindfulness meditation) (Germer *et al.*, 2005; Keng *et al.*, 2011). There is natural variation in trait mindfulness in the population in the absence of mindfulness training (Brown and Ryan, 2003), and training in mindfulness has been demonstrated to increase trait mindfulness (Brown and Ryan, 2003; Shapiro *et al.*, 2007; Greeson *et al.*, 2011; Robins *et al.*, 2012). Within the concept of mindfulness, acceptance of emotion requires attention and awareness of one's current emotional state, while maintaining a non-judgmental stance toward that state. In individuals who do not have an extensive

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history of mindfulness or meditation practice or training, both trait and state mindfulness are associated with increased prefrontal and decreased limbic activation under affective challenge (Chiesa *et al.*, 2013), with reduced activation in midline cortical structures associated with interoception, including insular cortex, ACC, and medial prefrontal cortex during mindful practice (Ives-Deliperi *et al.*, 2011). Mindfulness is also associated with a detached ability to observe thoughts, emotions and sensations (Feldman *et al.*, 2010), which may be associated with a concurrent reduction in self-referential processes associated with midline cortical structures of the default mode network (DMN) (Chiesa *et al.*, 2013).

Several studies have compared the relative effectiveness of reappraisal and emotional acceptance in downregulating negative affect. Reappraisal and acceptance appear equivalent in promoting flexible physiological regulation among individuals with heightened anxiety (as indexed by heart rate variability; Cristea *et al.*, 2012) and in reducing physiological arousal (Hofmann *et al.*, 2009). However, acceptance may be less effective at regulating anxiety and anger than reappraisal (Hofmann *et al.*, 2009; Szasz *et al.*, 2011). Other studies have found equivalent decreases in subjective distress (Wolgast *et al.*, 2011). With the exception of Cristea *et al.* (2012) who studied individuals who scored high on a self-report measure of social anxiety, these studies all involved non-clinical samples. In adults with mild to moderate symptoms of MDD, both reappraisal and emotional acceptance were similarly effective in downregulating sadness (Keng *et al.*, 2013). No study to date has compared the neural correlates or subjective effectiveness of reappraisal *vs* emotional acceptance among individuals with remitted major depressive disorder (rMDD).

The purpose of this study was to compare the neural mechanisms of acceptance and reappraisal of sad images in unmedicated individuals with and without a history of MDD. As highlighted by Ochsner and Gross (2008), regulation strategies are composed of subcomponents that may differ in their attentional, linguistic and cognitive control demands, and as such may rely on differentiable neural processes. Therefore, one aim of this study was to demonstrate commonalities and differences between reappraisal and acceptance in the never-depressed control group and in the rMDD group. The second aim of this study was to test if the neural effects of acceptance are moderated by a history of MDD. Finally, we evaluated in an exploratory manner whether there were associations between neural correlates of emotion regulation and self-reported affect post-acceptance.

METHODS

Participants

Nineteen affectively healthy right-handed adult control participants (7 male, 15 Caucasian, 27.9 ± 6.3 years old, all right handed) were recruited from the lists of potential participants maintained by the UNC-Duke University Medical Center (DUMC) Brain Imaging and Analysis Center. Nineteen adults with rMDD (4 male, 13 Caucasian, 24.5 ± 5.4 years old, 17 right handed) were recruited via a participant database maintained at the Cognitive Behavioral Research and Treatment Program at DUMC. Data from one rMDD participant were excluded due to an elevated Beck Depression Inventory-II (BDI; Beck *et al.*, 1996) score on the day of the scan (BDI = 30), resulting in a final sample of 18 rMDD participants. Exclusion criteria for both groups included age<19 or >55 years, current Axis I psychopathology assessed with the Structured Clinical Interview for DSM-IV Axis I semi-structured interview (First *et al.*, 1996), psychiatric medication use within the past month, verbal IQ scores (estimated by the North American Adult Reading Test; Uttl, 2002) <80, BDI >8 or MRI contraindications. Inclusion in the rMDD group was contingent on a prior diagnosis of MDD. Control participants were lifetime free of MDD. None of the control participants and 2 rMDD participants were receiving psychotherapy at the time of participation. Five rMDD participants had previously used psychotropic medications. All participants consented to a protocol approved by the local Human Investigations Committees at both University of North California at Chapel Hill and Duke UMCs and were paid $35 for completing the imaging portion of the study. All participants had normal or corrected-to-normal vision and completed a mock scan session prior to imaging. Information about demographics and clinical characteristics are presented in Table 1.

Table 1 Demographic and symptom severity information for control and rMDD participants

	Remitted subjects ($n = 18$) Mean (s.d.)	Control subjects ($n = 19$) Mean (s.d.)	*P* value
Age	24.8 (4.7)	27.9 (6.3)	0.10
Gender: male/female	4/14	7/12	0.33
Race			0.37
African American	6%	16%	
Caucasian	72%	79%	
Asian	11%	5%	
American Indian	6%	0%	
Hispanic ethnicity	22%	6%	0.18
NAART VIQ	110.7 (3.3)	110.2 (5.1)	0.70
BDI	2.9 (5.0)	1.4 (2.4)	0.24
No. of previous depressive episodes	1.6 (0.9)	–	–
No. of months since previous episode	40.4 (46.2)	–	–

Notes: Two-tailed *P* values for between-group *t* tests or chi-square analyses are in the final column. BDI: Beck Depression Inventory, 2nd edition (Beck *et al.*, 1996); NAART VIQ: North American Adult Reading Test (Uttl, 2002).

fMRI task

Each trial began with a fixation cross (6 s) followed by presentation of a sad or neutral picture (Figure 1 depicts the timing and content of each trial). After initial picture display (6–9 s, jittered) without regulation instruction, a visual regulation instruction was superimposed on the bottom of the picture, indicating the regulation strategy to use. Regulation continued for 5 s following image offset. Finally, participants rated their post-trial affect using a visual analog scale (ranging from 1 = most negative to 4 = most positive). The task included three regulation conditions. In the 'view' condition, used with both sad and neutral pictures, participants were instructed not to regulate their emotion response. In the 'accept' condition, used only with sad images, participants were asked to notice what they were thinking and feeling, and to allow those thoughts and feelings to remain, without needing to push them away. In the 'reappraise' condition, used with only sad images, participants were asked to reinterpret the image to reduce its negative impact. Both self-focused and situation-focused reappraisal strategies were permitted (Ochsner *et al.*, 2004). Four runs of 12 trials each were administered (48 trials total; 4'24" per run), and there were 12 trials for each regulation condition.

Immediately prior to the scan, participants learned and practiced the regulation strategies with an experimenter until they could correctly implement them without assistance. Instructions for the reappraise and accept conditions are shown in Table 2. Task images were drawn from two sources: (i) sad images from the International Affective Picture System based on normative sadness ratings (Mikels *et al.*, 2005) and (ii) a normed set of sad and neutral images used in previous MDD imaging studies (Wang *et al.*, 2005, 2008; Dichter *et al.*, 2009, 2010).

Fig. 1 The emotion regulation task. Each trial consisted of a neutral or sad image presented first without a regulation cue for 6–9 s, then the presentation of the regulation cue while the image remained presented for another 3 s, a period of 5 s after picture offset during which regulation continued and then a 5 s query for current affect. ITI were 6 s. ITI = Inter-trial intervals.

Table 2 Training instructions for (A) the accept and (B) reappraise emotion regulation strategies

A. Accept

'To accept, your task is to notice what you are thinking and feeling, and to allow those thoughts and feelings to be there. So rather than try to push the feeling or thought away or try to feel differently, you just acknowledge it, perhaps saying, "That's just how it is right now," "This feeling will come and go," or "I can accept this thought." Note that acceptance doesn't mean that you have to like the feeling, or that you are resigning yourself to the feeling. It is reminding yourself that it's ok to feel what you feel without having to change it'.

B. Reappraise

'To reappraise something means to take a look at it in a different light or from another perspective. For the negative images in this study, that will mean reinterpreting the image in some way. For example, you could remind yourself that you don't know the people in the picture, so no one close to you was affected by the situation. Alternatively, you could continue the story from the picture but give it a happy ending. For example, if you saw a picture of a couple arguing, you could imagine them working out their differences and being happy with one another again'.

Notes: Following the written instructions, participants were presented with sample pictures and practiced the strategies aloud with an experimenter, who provided corrective feedback on strategy use, as necessary.

Imaging methods

Scanning was performed on a General Electric (Waukesha, WI) MR750 3.0 Tesla scanner equipped with high power, high duty cycle 50 mT/m gradients at 200 T/m/s slew rate and a 32-channel head coil for parallel imaging. A high-resolution T1-weighted image with 166 slices was acquired using a three-dimensional FSPGR pulse sequence (Repetition time (TR) = 7.484 ms, Echo time (TE) = 2.984 ms, Field of view (FOV) = 256 mm, image matrix = 256 × 256, voxel size = 1 mm^3) and used for co-registration with the functional data. This structural image was aligned in a near axial plane defined by the anterior and posterior commissures. Whole-brain functional images were acquired using a spiral pulse sequence with SENSE reconstruction sensitive to blood oxygenation level-dependent contrast (TR = 1500 ms, TE = 30 ms, FOV = 256 mm, image matrix = 64 × 64, $\alpha = 60^{\circ}$, voxel size = 4 mm^3, 32 axial slices). Functional images were aligned similarly to the T1-weighted structural image. A semi-automated high-order shimming program ensured global field homogeneity.

Imaging data analysis

Functional data were preprocessed using FSL version 4.1.8 [Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford University, UK]. Preprocessing was applied in the following steps: (i) brain extraction for non-brain removal (Smith *et al.*, 2004), (ii) motion correction using MCFLIRT (Smith, 2002), (iii) spatial smoothing using a Gaussian kernel of FWHM 5 mm, (iv) mean-based intensity normalization of all volumes by the same factor and (v) high-pass filtering (Jenkinson *et al.*, 2002). Functional images of each participant were co-registered to structural images in native space, and structural images were normalized into a standard stereotaxic space (Montreal Neurological Institute) for inter-subject comparison. This transformation included resampling voxel sizes to 2 mm^3. The same transformation matrices used for structural-to-standard transformations were then used for functional-to-standard space transformations of co-registered functional images. All registrations were carried out using an intermodal registration tool (Jenkinson *et al.*, 2002; Smith *et al.*, 2004). Voxel-wise temporal autocorrelation was estimated and corrected using FMRIB's Improved Linear Model (FILM; Jenkinson and Smith, 2001). Onset times of events were used to model a signal response containing a regressor for each strategy, which was convolved with a double-γ function to model the hemodynamic response. Model fitting generated whole-brain images of parameter estimates and variances representing average signal change from baseline. Group-wise activation images were calculated by a mixed-effects higher level analysis using Bayesian estimation techniques, FMRIB Local Analysis of Mixed Effects (FILM; Woolrich *et al.*, 2001; Smith *et al.*, 2004).

An a priori mask was created for small volume correction that included the frontal lobes and bilateral amygdala generated in FSL using the Harvard–Oxford cortical and subcortical structural probabilistic atlases. Masks were thresholded at 25%, binarized and then combined into a single mask using fslmaths. For all analyses, voxels were considered significant if they passed a statistical threshold of $P < 0.005$, uncorrected and were part of a 35-voxel (280 mm^3) cluster of contiguous significant voxels, resulting in a cluster-corrected significance threshold of $P < 0.05$. This cluster size was determined by performing 1000 Monte Carlo simulations using 3dClustSim (Ward, 2000).

Only trials with sad images are analyzed here. Results from the pre-regulation phase and comparisons between the reappraise and view conditions were reported previously (Smoski *et al.*, 2013), and here we focus on only analysis involving the accept condition during the presentation of sad images. General linear models evaluated clusters that showed significant interactions of Group (rMDD, control) with trial type (accept relative to reappraise, accept relative to view). Activation localizations were based on Harvard–Oxford cortical and subcortical structural probabilistic atlases, with Brodmann area identification via the Talairach Daemon, as implemented in FSLView version 3.1.8. Exploratory correlation analyses between brain activation magnitudes and clinical characteristics of the rMDD group were conducted by extracting contrast estimates from each participant and condition within significant clusters identified by the whole-brain general linear models described above.

RESULTS

Emotion regulation self-report

In-scanner self-reported emotion regulation was evaluated via a 2 (Group: rMDD, control) × 3 (Trial Type: view, reappraise, accept) repeated measures analysis of variance conducted on mood rating

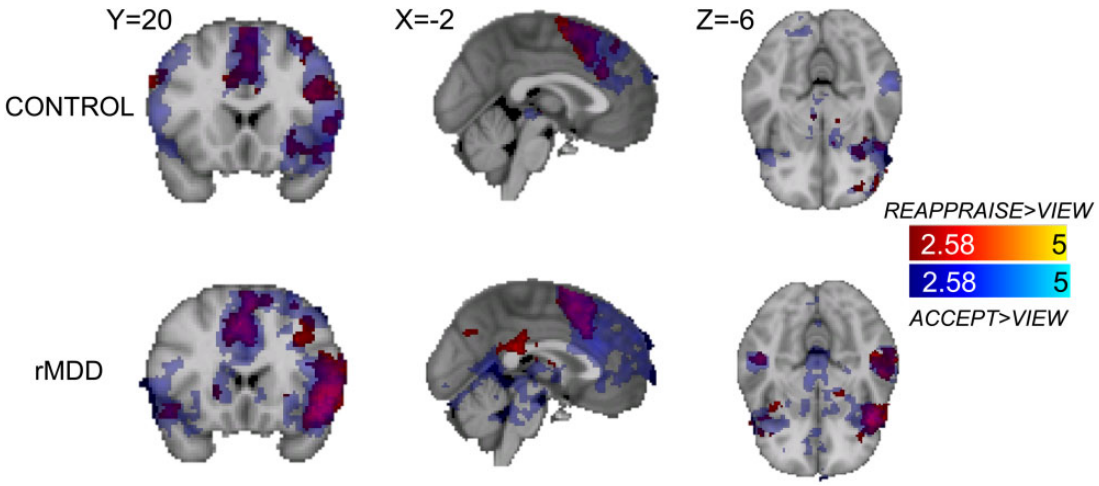

Fig. 2 Activation to accept > view (blue) and reappraise > view (red) and their overlap (green) in the control group (top) and the rMDD group (bottom).

Table 3 Clusters showing within and between-group activation differences to the acceptance of sad images > viewing sad images contrast

	Side	BA	Size (mm^3)	Z max	MNI co-ordinates		
					X	*Y*	*Z*
Control							
Frontal pole	L	9	472	3.17	−14	58	36
Frontal pole	L	47	2152	3.86	−44	44	−16
Frontal pole	L	9	680	3.14	−26	44	30
Frontal pole	R	8	1400	3.22	36	44	38
Frontal pole	R	47	336	6.25	32	24	−14
Anterior cingulate gyrus	R	32	11 088	4.33	4	28	30
Frontal orbital cortex	L	13	784	4.94	−34	26	−6
Precentral gyrus	R	9	536	3.05	60	18	30
rMDD							
Frontal orbital cortex	L	13	25 632	8.15	−38	24	−2
Frontal orbital cortex	R	47	352	3.15	50	30	−6
Frontal pole	R	10	912	3.39	34	54	6
Frontal pole	L	9	456	3.14	−14	66	24
Paracingulate gyrus	L	6	9896	5.05	4	18	44
rMDD < control							
Frontal pole	R	9	280	3.22	44	38	30

L: left; R: right.

Table 4 Clusters showing within- and between-group activation differences to the acceptance of sad images > reappraising sad images contrast

	Side	BA	Size (mm^3)	Z max	MNI co-ordinates		
					X	*Y*	*Z*
Control							
Insular cortex	L	13	784	5.18	−42	−6	8
Precentral gyrus	L	4	360	3.32	−40	−14	52
rMDD < control							
Paracingulate gyrus	R	24	360	3.14	6	40	−6
Middle frontal gyrus	R	8	296	3.00	26	28	38

L: left; R: right.

Table 5 Clusters showing within-group activation differences to the reappraisal of sad images > accepting sad images contrast

	Side	BA	Size (mm^3)	Z max	MNI co-ordinates		
					X	*Y*	*Z*
Control							
Frontal pole	R	8	304	3.24	14	56	42
Medial frontal cortex	R	11	464	3.31	2	44	−22
rMDD							
Inferior frontal gyrus, pars triangularis	R	45	1088	3.49	52	28	−6
Inferior frontal gyrus, pars opercularis	R	44	744	3.31	52	18	12
Frontal operculum	L	13	1776	5.25	−40	12	2
Paracingulate	R	32	29 752	4.94	8	44	12
Superior frontal gyrus	L	8	600	3.39	−24	24	40
Inferior Frontal Gyrus, pars opercularis	R	44	4176	4.67	46	18	16

L: left; R: right.

data. There was a significant main effect of Trial Type ($F(2,70) = 53.78$, $P < 0.0001$). Follow-up paired *t*-tests indicated less intense negative affect following accept trials ($M = 2.19$, s.d. = 0.34) than view trials ($M = 2.05$, s.d. = 0.35; $t(36) = 2.24$, $P = 0.03$), but more negative affect following accept trials than reappraise trials ($M = 2.80$, s.d. = 0.45; $t(36) = 8.03$, $P < 0.001$). There was no main effect of Group ($F(1,35) = 0.27$, $P = 0.60$) or Group × Trial Type interaction ($F(2,70) = 1.63$, $P = 0.20$).

Imaging data: within groups

Within the control group, the accept > view contrast revealed activation in a large dorsal medial PFC with peak activation in anterior midcingulate, extending to left lateral PFC. Activation was also observed in several clusters within the frontal pole, left orbitofrontal cortex (OFC) and right dlPFC (Figure 2 and Table 3). There was one frontal pole cluster with greater activation during view than accept. The accept > reappraise contrast revealed activation in left insular cortex and left precentral gyrus (Table 4). There was greater activation during reappraisal than acceptance in several regions of the right PFC, including frontal pole, medial and inferior frontal gyrus, as well as left frontal operculum (Table 5).

Within the rMDD group, the accept > view contrast revealed activation in a large left lateral PFC cluster with peak activation in the left OFC. Activation was also observed in the right OFC, bilateral frontal pole and anterior midcingulate (Table 3). There were no clusters with significant activation during the view > accept or accept > reappraise

contrasts. The reappraise > accept contrast revealed activation in a large vmPFC cluster with peak activation in the paracingulate. Additional activations were observed in the left superior frontal gyrus and right inferior frontal gyrus.

Note that within-group analyses of the reappraisal > view contrast were reported previously (Smoski *et al.*, 2013).

Imaging data: group differences

The accept > view contrast revealed less activation in the right frontal pole in the rMDD relative to the control group, and no regions with relatively greater activation in the rMDD group than control group view (Figure 3 and Table 3). The accept > reappraise contrast revealed less activation in the rMDD group relative to the control group in the right paracingulate gyrus and the right middle frontal gyrus, and no regions with relatively greater activation in the rMDD group than the control group (Table 4).

Correlations between brain activation and self-reported affect post-acceptance

To test for relations between brain activation magnitudes and self-reported affect during acceptance, correlations between in-scanner reports of post-acceptance affect and activation magnitudes of within-groups clusters are reported in Tables 3–5. As these analyses were exploratory, they were not corrected for multiple comparisons. Within the control group, there was a significant correlation between self-reported negative affect post-acceptance and activation in left insular cortex during the accept > reappraise contrast ($r(18) = -0.61$, $P = 0.005$) (Figure 4). No other correlations were significant in the control group. Within the rMDD group, no clusters correlated significantly with self-reported affect post-acceptance.

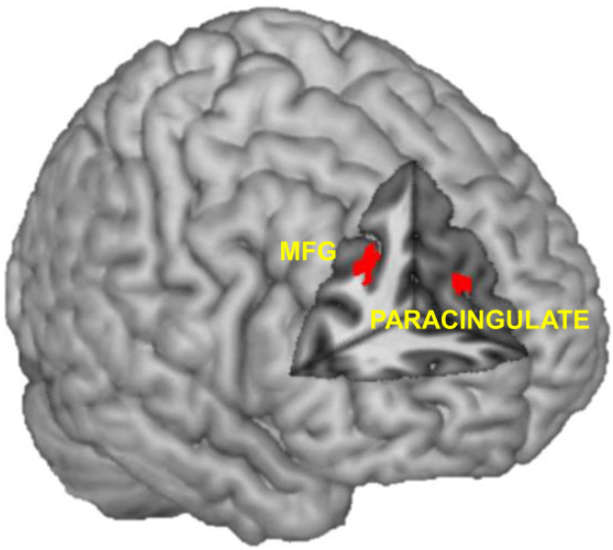

Fig. 3 Clusters with less activation in the rMDD group than the control group in the accept > reappraise contrast were found in the right paracingulate gyrus and the right MFG. MFG = middle frontal gyrus.

DISCUSSION

The purpose of this study was to examine the neural mechanisms of acceptance, compared with reappraisal, of sad images in unmedicated individuals with and without a history of MDD. Acceptance and reappraisal recruited overlapping brain circuits, including dorsal medial prefrontal cortex (dmPFC), dlPFC, vlPFC and anterior midcingulate. However, there were also key differences between these emotion regulation strategies. In both rMDD and control groups, acceptance was associated with less dlPFC and frontal pole activation than reappraisal. Within the control group, acceptance was associated with greater activation in the left precentral gyrus and insula than reappraisal. Greater activation to acceptance than reappraisal in the left insular cortex was associated with greater intensity of negative affect post-acceptance, suggesting that this activation reflected less effective emotion regulation, or alternately, reflected heightened emotional awareness rather than regulation. Acceptance was associated with less effective subjective regulation than reappraisal, which is consistent with some (Hofmann *et al.*, 2009; Szasz *et al.*, 2011) but not all (Keng *et al.*, 2013) previous comparisons of these strategies.

Most previous fMRI investigations of mindfulness broadly, or mindful acceptance specifically, have focused on mindfulness as a trait (Creswell *et al.*, 2007; Farb *et al.*, 2011) or as an outcome of mindfulness training (Farb *et al.*, 2007; Taylor *et al.*, 2011). Trait mindful observing, or noticing of internal and external stimuli (a component of the acceptance instructions administered in this study), is associated with activation in dorsal medial PFC during negative emotional imagery (Frewen *et al.*, 2010). Olsson and Ochsner (2008) have proposed that medial ACC and anterior insula support experiential awareness, with metacognitive awareness of that experience supported by dorsal and rostral PFC. By examining acceptance as state that can be brought forth with intention, the present findings broaden the understanding of the neural underpinnings of acceptance as an emotion regulation strategy. Greater activation in left insular cortex during awareness may reflect the task instructions to be aware of one's emotional states. In individuals with little training or experience in mindful acceptance

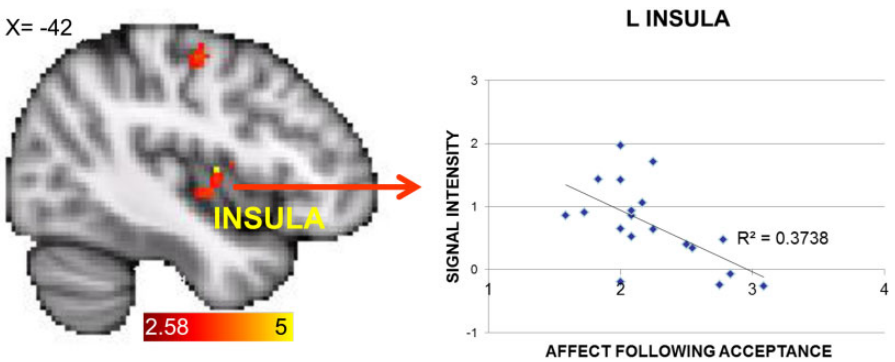

Fig. 4 The control group demonstrated greater activation during acceptance > reappraisal in the left precentral gyrus and the left insula, and greater signal intensity in this left insula cluster was associated with less change in negative affect following acceptance.

beyond brief experimental task instructions, this awareness may in itself be mildly distressing, or may interfere with other more practiced or preferred regulation strategies. In individuals with greater training and experience in mindful acceptance, emotional awareness may function differently. For example, in a study of pain perception in expert and novice meditators, increased insula activation was associated with higher ratings of pain unpleasantness in novice meditators but lower ratings in experts (Gard *et al.*, 2012), suggesting different effects of sensory processing on pain reduction. Similarly, mindfulness training in individuals with elevated depression symptoms was associated with reduced insula reactivity to sad stimuli, while heightened insula reactivity correlated with depression symptom severity, suggesting that mindfulness training may promote reduced neural reactivity to affective stimuli (Farb *et al.*, 2010).

The rMDD and control groups did not differ in self-reported affect following acceptance or reappraisal. However, the groups did differ in neural activation when implementing the emotion regulation strategies. Compared with the control group, acceptance in rMDD was associated with relatively reduced activation in the right frontal pole, a medial prefrontal region that has been linked to self-referential processing and rumination in individuals with rMDD (Farb *et al.*, 2011). Mindfulness training has been previously linked to reduced reactivity to sad stimuli in a cluster that included vmPFC (Farb *et al.*, 2010). Given that one of the key aims of mindfulness-based interventions targeting depressive relapse is to reduce rumination and maladaptive self-focus (Barnhofer *et al.*, 2009), the finding of relatively reduced medial prefrontal activation during acceptance is consistent with this therapeutic goal. Compared with controls, the rMDD group demonstrated relatively reduced activation in the right paracingulate and middle frontal gyrus when using acceptance than reappraisal. The middle frontal gyrus is recruited during tasks involving working memory, selective attention and successful emotion regulation (Ochsner *et al.*, 2004; Ochsner and Gross, 2008). Decreased middle frontal gyrus activity has been observed in MDD during tasks involving cognitive control (Okada *et al.*, 2009; Kikuchi *et al.*, 2012), emotion processing (Wang *et al.*, 2008; Dichter *et al.*, 2009; Feeser *et al.*, 2013) and during reappraisal in rMDD (Smoski *et al.*, 2013). Likewise, the rostral cingulate/paracingulate is thought to function as a 'hub' within the DMN (Shackman *et al.*, 2011) that mediates task switching with dorsal cognitive control networks in depression (Pizzagalli, 2011). Relatively decreased middle frontal gyrus and paracingulate activity in rMDD during acceptance may reflect decreased recruitment of neural resources to exert cognitive control during acceptance relative to reappraisal, with potential implications for the success of the strategy under more difficult task demands.

The relative effectiveness and neural underpinnings of different emotion regulation strategies in the rMDD group are relevant to informing treatments that focus on reducing vulnerability to MDD relapse. MDD is cyclical, with previous episodes serving as a powerful risk factor for future episodes (Lewinsohn *et al.*, 1988). Emotional acceptance and reappraisal mirror key elements of mindfulness-based cognitive therapy (MBCT; Segal *et al.*, 2002) and traditional cognitive behavioral therapy (CBT; Beck *et al.*, 1979), respectively. CBT reduces relapse risk and the need for further treatment among patients with acute MDD (Blackburn *et al.*, 1986; Evans *et al.*, 1992; Shea *et al.*, 1992), presumably through altering dysfunctional attitudes and thoughts that are vulnerability factors for MDD. MBCT reduces relapse rates among those with a history of three or more MDD episodes (Teasdale *et al.*, 2000; Ma and Teasdale, 2004; Kuyken *et al.*, 2008) and prolongs time to relapse (Bondolfi *et al.*, 2010), presumably by facilitating the ability to decenter from and accept thoughts and emotions non-judgmentally. Although both interventions are effective in reducing MDD relapse, less is known regarding the neural mechanisms by which these interventions improve clinical outcomes.

One limitation in our design is the lack of ratings of familiarity with, or ease of implementation of, acceptance *vs* reappraisal. With its roots in Eastern contemplative practices, mindfulness and mindful acceptance have until recently been relatively unfamiliar and under-studied as a means of promoting emotional health (Baer, 2003; Keng *et al.*, 2011), and the relatively reduced regulatory success of acceptance *vs* reappraisal may be in part related to the novelty of mindful acceptance. Although all participants were trained in acceptance and reappraisal before the scan and successfully articulated the use of the acceptance strategy during that training, measure of the extent to which the strategy was implemented correctly during the scan would further confirm correct implementation of the strategy. In addition, future studies that incorporate long-term clinical course will increase the translational implications for sustained MDD remission *vs* relapse.

Although the intent of this study was to examine the relative effectiveness and comparative neural activation of reappraisal and acceptance, it should be noted that these two strategies are not mutually exclusive. As shown in Figure 2, there is significant overlap in frontolimbic activation between the two strategies, consistent with prefrontal regions widely associated with emotion regulation (Ochsner and Gross, 2008). In practice, acceptance and reappraisal may mutually facilitate effective regulation. Cross-sectional (Jermann *et al.*, 2009; Desrosiers *et al.*, 2013) and intervention-based (Bormann and Carrico, 2009; M.J. Smoski, J.G. Brantley, M.M. Llabre, T.R. Lynch, E.C. Suarez, R.Q. Wolever and J.M. Greeson, submitted for publication) studies suggest that reappraisal use mediates the relationship between mindfulness and reduced depressive symptoms. Similarly, Garland *et al.* (2011) found a reciprocal relationship between positive reappraisal and mindfulness over the course of a mindfulness-based stress and pain reduction program, whereby increases in mindfulness predicted increases in reappraisal, and vice versa. Although reappraisal and acceptance are theoretically and empirically separable, they may be best thought of as complementary regulation strategies.

In summary, although both reappraisal and acceptance were associated with more effective subjective regulation than a no-regulation control condition, reappraisal was more effective than acceptance in regulating subjective negative affect. Both acceptance and reappraisal showed similar patterns of prefrontal cortex activation in both individuals remitted from depression as well as never-depressed controls, with a few notable exceptions. Acceptance was associated with greater activation in regions associated with somatic awareness (i.e. insula) and with less overall right-lateralized prefrontal cortex activation. Reappraisal was associated with greater regulatory success than acceptance, with no group differences in self-reported emotion regulation effectiveness. Currently, euthymic individuals with a history of MDD showed decreased right middle frontal gyrus and paracingulate activation during acceptance compared with reappraisal, and decreased medial prefrontal activation during acceptance compared with a control condition. These findings were evident despite the fact that the rMDD and control groups were matched to have equivalently low levels of current depressive symptom severity. These patterns of brain activity suggest complex implications regarding the use of acceptance as a regulation strategy in rMDD: less vmPFC activation that has been associated with rumination, a problematic process that is predictive of depressive relapse, but also less activation in cognitive control regions (i.e. paracingulate) generally associated with regulatory success. Further research is needed to determine whether these patterns of brain activation convey greater risk for future MDD episodes or are modifiable by interventions such as MBCT that target relapse prevention.

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