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Preliminary communication

Remitted major depression is characterized by reward network hyperactivation during reward anticipation and hypoactivation during reward outcomes

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ABSTRACT

Background: Although functional brain imaging has established that individuals with unipolar major depressive disorder (MDD) are characterized by frontostriatal dysfunction during reward processing, no research to date has examined the chronometry of neural responses to rewards in euthymic individuals with a history of MDD.
Method: A monetary incentive delay task was used during fMRI scanning to assess neural responses in frontostriatal reward regions during reward anticipation and outcomes in 19 participants with remitted major depressive disorder (rMDD) and in 19 matched control participants.
Results: During the anticipation phase of the task, the rMDD group was characterized by relatively greater activation in bilateral anterior cingulate gyrus, in right midfrontal gyrus, and in the right cerebellum. During the outcome phase of the task, the rMDD group was characterized by relatively decreased activation in bilateral orbital frontal cortex, right frontal pole, left insular cortex, and left thalamus. Exploratory analyses indicated that activation within a right frontal pole cluster that differentiated groups during reward anticipation predicted the number of lifetime depressive episodes within the rMDD group.
Limitations: Replication with larger samples is needed.
Conclusions: Results suggest a double dissociation between reward network reactivity and temporal phase of the reward response in rMDD, such that rMDD is generally characterized by reward network hyperactivation during reward anticipation and reward network hypoactivation during reward outcomes. More broadly, these data suggest that aberrant frontostriatal response to rewards may potentially represent a trait marker for MDD, though future research is needed to evaluate the prospective utility of this functional neural endophenotype as a marker of MDD risk.

1. Introduction

Major Depressive Disorder (MDD) is characterized by anhedonia, the loss of interest or pleasure in normally rewarding activities (American Psychiatric Association, 1994). A growing body of literature has linked frontostriatal dysfunction during reward processing to anhedonia in MDD (Forbes et al., 2006, 2009; Keedwell et al., 2005a, 2005b; Knutson et al., 2008; Kumari et al., 2003; Mitterschiffthaler et al., 2003; Schaefer et al., 2006; Smoski et al., 2009, in press). This literature has established not only the general hyporesponsivity of frontostriatal regions with dense dopaminergic projections to rewards in MDD, but also that the topography of frontostriatal dysfunction

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to rewards in MDD is critically dependent both on the temporal phase of the reward response and on the type of reward processed.

A critical next step to evaluate whether this marker of MDD status is potentially a trait marker of MDD vulnerability is the evaluation of individuals with a history of MDD but who do not currently meet criteria for the disorder (Alloy et al., 1999; Mednick and McNeil, 1968). Although such a design is not sufficient to establish a trait marker, given that the sequelae of past illness and treatments on brain function may not be conclusively ruled out, it is nevertheless a necessary initial step to identify a disease trait. This approach allows for an examination of relations between heightened risk for MDD and patterns of brain function while mitigating the potential confounding effects of current mood state,[1] illness severity, nonspecific effects of chronic illness and stress, and the effects of psychotropic medication usage (Kerestes et al., 2011; McCabe et al., 2010). Thus, examining linkages between brain function and a history of MDD holds the ultimate promise of aiding in the identification of trait-like endophenotypic vulnerability markers predictive of disease onset prior to the manifestation of clinically impairing symptoms. Furthermore, functional brain imaging is a powerful tool to evaluate a potential marker of disease vulnerability given that brain-based endophenotypes may hold relatively greater promise as predictors of disease manifestation and progression due to the closer association between such measures and the genetic and environmental causes of psychiatric illness than observable behavior (Peterson and Weissman, 2011).

Euthymic individuals with a history of MDD show a range of altered neurocognitive and neurobiological profiles, including deficits in measures of attention and executive functions (Paelecke-Habermann et al., 2005), larger event-related potential feedback-related negativities (Santesso et al., 2008), increased ventral striatal–cortical connectivity (Pail et al., 2011), and decreased resting regional homogeneity in frontal, temporal and parietal lobes and increased regional homogeneity in the putamen, frontal and parietal lobes (Yuan et al., 2008).

Most relevant in the present context are task-based functional brain imaging studies in rMDD. The clear majority of such studies indicate that rMDD is characterized by brain hypoactivation relative to individuals with MDD or controls, including reduced DLPFC activation to maternal critical remarks (Hooley et al., 2005), reduced right DLPFC and left VLPFC activation to positive emotional distracters during a working memory task (Kerestes et al., 2011), decreased medial prefrontal activity to sad film clips (Farb et al., 2011), decreased pregenual anterior cingulate cortex activation to sad autobiographical memories (Liotti et al., 2002), decreased activation in right middle frontal gyrus during an emotional oddball task (Wang et al., 2008), and reduced left middle frontal gyrus activation during a verbal fluency task (Okada et al., 2009). However, a small subset of studies has reported brain hyperactivation in MDD. Schoning et al. (2009) reported increased cingulate cortex activation during a working-memory task in rMDD, Kerestes et al. (2011) reported greater left DLPFC activity to negative emotional distracters during a working memory task, and Farb et al. (2011) reported higher calcarine cortex activity to sad film clips. These findings have been interpreted to reflect possible compensatory activation to maintain adequate task performance in the rMDD samples. Finally, we are aware of one published study of reward processing in rMDD: McCabe et al. (2009) found decreased activation in the ventral striatum in response to the sight and flavor of chocolate. However, no study to date has examined response to rewards during both anticipation and outcome phases of the reward response.

The purpose of the present study was to extend research on reward processing deficits in MDD to individuals with a history of MDD using a functional magnetic resonance imaging (fMRI) task that has been shown to differentiate MDD and nondepressed control samples. Hypotheses were informed by data from our laboratory (Dichter et al., 2009; Smoski et al., 2009, in press) and other research groups (Forbes et al., 2006, 2009; Keedwell et al., 2005a, 2005b; Kumari et al., 2003; McCabe et al., 2009; Mitterschiffthaler et al., 2003; Schaefer et al., 2006) demonstrating frontostriatal hypoactivation to rewards in MDD, and more specifically, hyporesponsivity in ventral striatal regions during reward anticipation and in ventromedial prefrontal cortex during reward outcomes. However, given that treatments for MDD may increase or decrease brain function (Goldapple et al., 2004; Kennedy et al., 2001, 2007) and given that the extant fMRI ligature reviewed above has documented both brain hypo- and hyper-activation in rMDD, hypotheses about the specific direction of group differences were tentative in nature. Exploratory follow-up analyses examined relations between clinical correlates in the rMDD sample and neural response to rewards during the fMRI task.

2. Method

2.1. 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 lists of potential participants maintained by the Duke-UNC Brain Imaging and Analysis Center (BIAC). Nineteen adults with rMDD (4 male; 13 Caucasian; 24.5 ± 5.4 years old; 17 right-handed) were recruited via the Cognitive Behavioral Research and Treatment Program at Duke University Medical Center. Exclusion criteria for both groups included age <19 or >55 years, current Axis I psychopathology, psychiatric medication use within the past month, estimated verbal IQ scores <80, BDI >8, or MRI contraindications. None of the control participants and two rMDD participants were receiving psychotherapy at the time of participation. Five rMDD participants had previously used psychotropic medications. Inclusion in the rMDD group was contingent on a prior diagnosis of MDD based on SCID I semi-structured interview (First et al., 1996). Control participants were lifetime-free of MDD. All participants consented to a protocol approved by the local Human Investigations Committees at both UNC-Chapel Hill and Duke University Medical Centers and were paid at least $35 for completing the imaging portion of the study. All

[1] Though clearly the goal of neurobiologic research into the pathophysiology of MDD is to identify the causes of clinically depressed mood, the presence of sad mood states may actually impede the identification of linkages between brain endophenotypes and depression vulnerability because the neural correlates of sad mood and of MDD are not completely concordant.

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participants had normal or corrected-to-normal vision and completed a mock scan session prior to imaging. Information about demographics and prior MDD episodes are presented in Table 1.

2.2. fMRI task

The fMRI task was a modified from the Monetary Incentive Delay (MID) task as implemented in Knutson et al. (2000) and used previously by our research group (Smoski et al., in press). Participants practiced the task outside the scanner prior to the scan session. Participants completed four functional imaging runs. On two runs, money could be won or not won, but money could not be lost; on the other two runs, money could be lost or not lost, but money could not be won. Only results from runs with potential monetary wins are presented here. Each run began with a 10-s instructional screen indicating whether the forthcoming run would be a "win" or a "loss" run. Run types (i.e., win or loss runs) were presented in alternating order, and the run type presented first was counter-balanced across participants.

Task conditions and trial timings are summarized in Fig. 1. Each trial consisted of: (1) a 2000 ms cue that indicated whether adequately quick responses to the forthcoming target bulls-eye could result in a "win" (a triangle) or could not (a circle); (2) a delay period during which a crosshair was presented for 2000–2500 ms; (3) a target bulls-eye that required a speeded button press presented for up to 500 ms; (4) 3000 ms of feedback that indicated whether that trial was a "win" or not; and (5) a variable length ITI crosshair presented such that the total duration of each trial was 12 s. Trial types (i.e., potential win or not potential win) were aperiodic and pseudorandomly ordered.

Participants could win $1 per trial, and feedback was a text display of the amount of money won ("+$1"). Coincident with this feedback, a cumulative count of the number of dollars won within the run was presented. Participants were instructed to respond to all target bulls-eyes as quickly as possible, and outcomes on win trials were contingent on reaction times. The task was adaptive such that participants were successful on two-thirds of trials, regardless of individual differences in reaction times. Each 8-minute run contained 40 trials: 20 were potential win trials, 20 were non-win control trials. Prior to entering the scanner, participants were shown the money they could win based on scanner task performance. Stimuli were presented using E-Prime presentation software

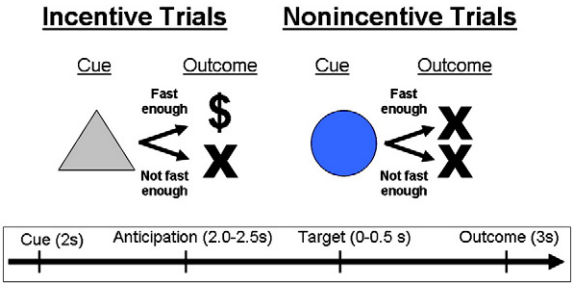

Fig. 1. The MID task. Each trial consisted of a cue (i.e., a triangle indicated an incentive trial, a circle indicated a non-incentive trial), an anticipatory delay, a target, and outcome feedback.

v. 1.1 (Psychology Software Tools Inc., Pittsburgh, PA) and displayed in the scanner through magnet-compatible goggles (Resonance Technology, Inc., Northridge CA).

2.3. Imaging methods

Scanning was performed on a General Electric (Waukesha, Wisconsin, USA) MR750 3.0 Tesla scanner. This scanner is 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 quadrature birdcage radio frequency head coil was used for transmit and receive. A high resolution T1-weighted image with 166 slices was acquired using a 3D FSPGR pulse sequence (TR = 7.484 ms; TE = 2.984 ms; FOV = 256 mm; image matrix = 256 × 256; voxel size = 1 mm^3) and used for coregistration 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, 2000 ms; TE, 30 ms; FOV, 256 mm; image matrix, 64 × 64; $\alpha = 60°$; 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.

2.4. 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, U.K.). Timing files

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

	Remitted MDD (n = 19; 4 ♂)	Controls (n = 19; 7 ♂)	t (*p*) (two-tailed)
Age	23.6 (4.09)	27.9 (6.3)	1.89 (0.072)
RRS	1.42 (0.303)	1.25 (0.19)	2.079 (0.045)
NAART: verbal IQ	110.36 (5.01)	110.7 (3.30)	0.24 (0.81)
BDI	2.63 (4.91)	1.37 (2.29)	1.016 (0.32)
Number with prior hospitalization for MDD	3	0	
Average number of MDD episodes	1.56 (0.86)	0	
Average duration of most recent MDD episode in months	6.84 (5.20)	0	
Average number of months since most recent MDD episode	40.8 (44.9)	0	

Note: RRS: Ruminative Responses Scale (Nolen-Hoeksema et al., 1993); NAART: North American Adult Reading Test (Blair and Spreen, 1989); BDI: Beck Depression Inventory (Beck et al., 1996).

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were converted to FSL-compatible format and NIFTI image data files were generated. 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), as implemented by the FSL FEAT preprocessing utility. 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 intersubject comparison. 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 response type, 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 (FLAME,Woolrich et al., 2001; Smith et al., 2004). Following the guidelines of Lieberman and Cunningham (2009), clusters of ten or more voxels with minimum values of $z>2.58$ ($p<.005$) were classified as significant activations.

The anticipation and outcome phases of the task were analyzed separately. For both phases, the primary method of analysis was to identify clusters that showed significant interactions of group (control vs rMDD) and trial type (potential win versus non-potential win during the anticipatory phase, and wins versus non-wins during the outcome phase). This whole-brain analytic approach identified clusters that differentiated groups on the basis of potential responses to reward (during the anticipation phase) and on the basis of reward outcomes (during the outcome phase). To constrain activation maps to brain areas responsive to the task, planned analyses included masking group-difference activation maps by activations maps of responses averaged for all participants regardless of group membership thresholded by the same criteria.

Activation localizations were based on Harvard–Oxford cortical and subcortical structural probabilistic atlases, with Brodmann area identification via Talairach Daemon, as implemented in FSLView v3.1.8.

3. Results

3.1. Imaging data: anticipatory responses

Group (control vs rMDD) × trial type (potential win versus non-potential win) interaction mixed effect analyses were performed on anticipatory phase data. Activation maps were masked by anticipatory responses averaged for all participants regardless of group membership. Results revealed no brain areas with significantly decreased activation in the rMDD group, relative to the control group.[2] However, there were a number of frontostriatal clusters reflecting relatively greater activation in the rMDD group, including bilateral pregenual anterior cingulate gyrus (ACG), the right midfrontal gyrus (MFG), and a large cluster in the right cerebellum (see Fig. 2 and Table 2).

3.2. Imaging data: outcome response

Group (control vs rMDD) × trial type (wins versus non-wins) interaction mixed effect analyses were performed on outcome phase data. Activation maps masked by responses averaged for all participants regardless of group membership revealed no group differences in any brain regions. Exploratory analyses of unmasked group differences were conducted, which yielded two clusters outside of the reward network with significantly increased activation in the rMDD group, relative to the control group. There also were a number of unmasked frontostriatal clusters reflecting relatively decreased activation in the rMDD group, including bilateral orbital frontal cortex (OFC), right frontal pole, left insular cortex, and left thalamus (see Fig. 3 and Table 3).

3.3. In-scanner reaction times

In-scanner reaction times to target bulls-eyes were analyzed via a Group (Control, rMDD) × Condition (Gain, Non-gain) repeated measures MANOVA. The Group × Condition interaction effect was not significant, multivariate $F(1,36)=1.98$, $p>.15$, there was no main effect of Condition, multivariate $F(1,36)=0.93$, $p>.30$, and there was no main effect of Group, $F(1,36)=2.19$, $p>.10$. Within-condition comparisons revealed that groups did not differ in reaction times during unrewarded trials, $t(36)=0.24$, $p>.81$, but there was a trend towards differences on rewarded trials, $t(36)=1.96$, $p<.06$, with slower responses in the rMDD group (mean(SE) = 145 (4.87) than the control group mean(SE) = 133 (3.81)) (see the left side of Fig. 4).

3.4. Clinical correlations

To test for relations between brain activation magnitudes and clinical features of the rMDD group, correlations between brain activation clusters that predicted group differences (see Tables 2 and 3), clinical measures, and in-scanner reaction times within the rMDD sample were evaluated. These analyses were exploratory in nature and thus not corrected for multiple comparisons to minimize statistical Type II errors. The only significant relation that emerged was a significant positive correlation between the number of lifetime MDD episodes and the magnitude of frontal pole activation during anticipation, $r=0.61$, $p<.006$. This relation indicates that greater frontal pole activation during gain anticipation predicted a greater number of lifetime MDD episodes (see the right side of Fig. 4).

[2] This result (no brain areas with significantly decreased activation in the rMDD group, relative to the control group) remained even when unmasked results were examined.

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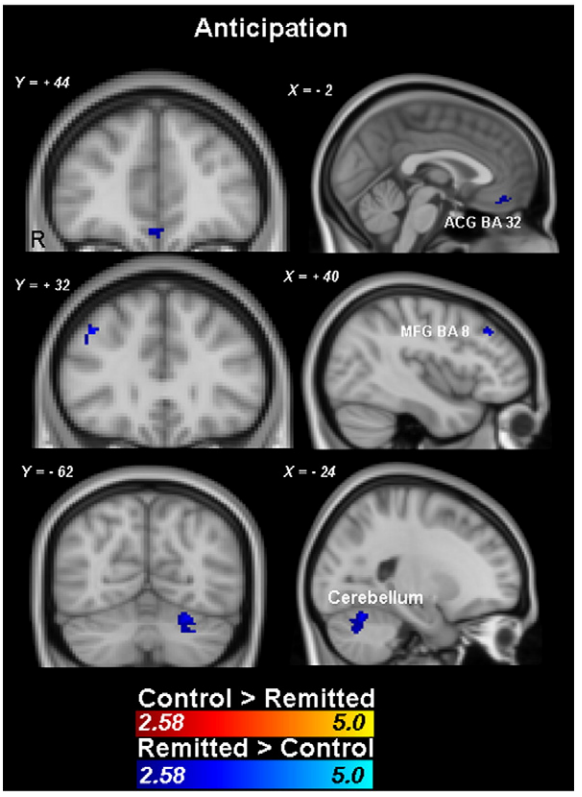

Fig. 2. Clusters showing significant group differences during reward anticipation ($z > 2.58$, with a minimum of 10 voxels/cluster). Responses are masked by the responses of both groups combined thresholded by the same criteria.

4. Discussion

The purpose of this study was to extend the sizeable literature documenting reward system dysfunction in MDD to individuals with rMDD (i.e., a history of MDD but without current MDD). This approach has the potential to inform whether aberrant frontostriatal responses to rewards may represent a trait-like marker of vulnerability to MDD, given that individuals with a history of MDD are at increased risk of developing subsequent episodes of MDD (Hollon et al., 2005). This approach may also aid in elucidating potential neurobiological mechanisms of MDD while mitigating the possible confounding effects of current mood state, illness severity, nonspecific effects of chronic illness and stress, and of psychotropic medication usage (Kerestes et al., 2011; McCabe et al., 2010; Peterson and Weissman, 2011).

Based on data from our own research group (Dichter et al., 2009; Smoski et al., 2009, in press) and others (Forbes et al., 2006, 2009; Keedwell et al., 2005a, 2005b; Kumari et al., 2003; McCabe et al., 2009; Mitterschiffthaler et al., 2003; Schaefer et al., 2006) demonstrating frontostriatal hypoactivation to rewards in MDD, we hypothesized that the rMDD group would be characterized by frontostriatal hypoactivation during both temporal phases of reward responding. Results from the anticipatory phase of the task were contrary to this prediction: there were no brain regions with significantly decreased activation in the rMDD group, relative to the control group, during reward anticipation. However, there were a number of frontostriatal regions known to be responsive to rewards with relatively greater activation in the rMDD group, including the pregenual aspect of the ACG, the right MFG, and the right cerebellum.

The pregenual anterior cingulate has a central role in processing emotion (Etkin et al., 2011) and rewards (Liu et al., 2011). This region in particular codes for deriving the specific value of an expected reward and for value representations of forthcoming rewards (Wallis and Kennerley, 2010). The midfrontal gyrus plays a critical role in monitoring incentive-based behavioral responses (Haber and Knutson, 2010), and activation of this region has been found to be decreased in MDD during reward-based decision making and to predict depression severity in MDD (Smoski et al., 2009). Finally, although the cerebellum is not typically considered part of the

Table 2
Clusters showing significantly greater activation in the rMDD group relative to the control group during reward anticipation (there were no regions showing decreased activation in the rMDD group relative to the control group). All voxels within these clusters are $z > 2.58$, with a minimum of 10 voxels/cluster. Responses are masked by the responses of both groups combined thresholded by the same criteria.

	Side	Brodmann area	Size (mm^3)	Z max	MNI coordinates		
					X	Y	Z
Caudate	Left		304	3.26	−14	−4	+22
Cerebellum (anterior)[a]	Right		168	3.12	+6	−54	−16
Cingulate gyrus (anterior)	Right		48	2.78	+4	−10	+26
	Left	32	224	3.01	−2	36	22
Frontal gyrus (middle)	Right	8	176	3.46	+40	+30	+38
Frontal orbital cortex	Right		72	2.97	+22	+34	−12
Occipital fusiform gyrus	Left[a]		1008	3.86	−16	−86	−24
	Right		240	4.28	+10	−90	−18
Paracingulate gyrus[b] (Anterior)	Right	32	344	3.06	+2	+42	−14
Parahippocampal gyrus (anterior)	Left		200	3.61	−10	−6	−22
Parietal lobule (superior)	Left	40	168	3.37	−40	−50	+58
Precuneous cortex, lingual gyrus	Right		64	2.96	28	−54	+8
Supplementary motor cortex	Right		64	3.36	+2	+4	+74
Supramarginal gyrus (posterior)	Right		384	3.76	+36	−48	+38
	Left	40	176	3.04	−40	−44	+42

[a] Two clusters within same region, coordinates and peak activation reported for highest peak activation.
[b] Three clusters within same region, coordinates and peak activation reported for highest peak activation.

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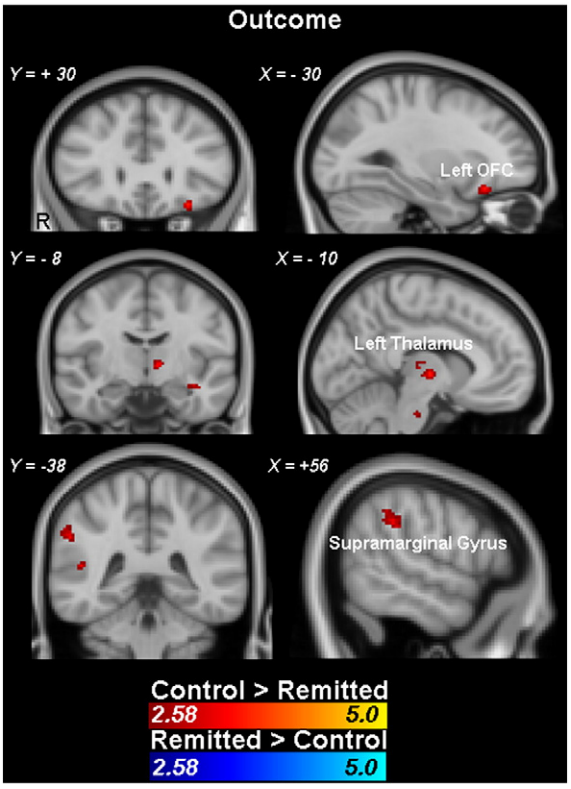

Fig. 3. Clusters showing significant group differences during reward outcomes ($z > 2.58$, with a minimum of 10 voxels/cluster). Responses are unmasked.

reward network, it has been shown to be involved in aspects of emotion regulation and cognition (Fusar-Poli et al., 2009) and to be functionally impaired in a range of psychiatric disorders (Baldacara et al., 2008). Our finding of increased activation in this region in rMDD requires replication, but may be linked to the extensive projections from this region to aspects of the reward network (Schmahmann, 2010).

Although the overall direction of effects during the anticipatory phase of the task (i.e., greater activation in the rMDD group relative to the control group) was not predicted, it should be noted that there is evidence of ACG hyperactivation during reward anticipation in individuals with frank MDD, though in the dorsal rather than pregenual aspect of the ACG (Knutson et al., 2008), a finding interpreted to reflect possibly increased uncertainty and conflict during anticipation of attainable gains. Given the localization of the present finding to the pregenual ACC, it may be that case that rMDD is characterized by relatively greater neural resources recruited to represent the value of anticipated rewards. Further, given that rewards were uncertain during the anticipation phase of the task, greater responses in this region in the rMDD group may reflect greater on-line monitoring of speeded button responses to obtain the forthcoming reward (Knutson et al., 2008).

Analyses of outcome phase responses were consistent with hypotheses of reward network hypoactivation in rMDD and revealed a number of frontostriatal brain regions with relatively decreased activation in the rMDD group, including the OFC, right frontal pole, left insular cortex, and left thalamus. The OFC codes the magnitude and affective value of positive and negative rewards and primary reinforcers (Bechara et al., 2000), tracks the subjective utility of delayed rewards (Kable and Glimcher, 2007), and facilitates decision-making based

Table 3
Clusters showing significantly less activation in the rMDD group relative to the control group during reward outcomes (unmasked). All voxels within these clusters are $z > 2.58$, with a minimum of 10 voxels/cluster.

	Side	Brodmann area	Size (mm^3)	Z max	MNI coordinates		
					X	Y	Z
rMDD < control							
Angular gyrus	Right		608	2.98	+54	−46	
Central opercular cortex	Left[a]		328	3.10	−58	−20	
	Right		64	2.80	+46	+4	+20
Cingulate gyrus (posterior)	Left		72	2.92	−4	−46	+4
Frontal orbital cortex	Left[a]	47	400	3.52	−28	+28	0
	Right		48	2.78	+38	+32	−18
Frontal pole	Right		144	3.06	+38	+46	−8
Insular cortex[a]	Left		200	2.91	−36	+16	+24
Intracalcarine cortex	Right		200	2.94	+16	−62	−2
Planum polare	Left		136	3.05	−46	+2	+10
Precentral gyrus	Left		80	2.93	−58	−4	−22
Superior lateral occipital cortex	Right		424	3.45	+44	−68	+14
Supramarginal gyrus (anterior)	Left	40	136	2.80	−56	−28	+16
Supramarginal gyrus (posterior)[a]	Right		1864	3.71	+48	−38	+24
Temporal fusiform cortex (posterior)	Left		120	2.95	−32	−36	+12
Temporal gyrus (posterior, superior)	Left	22	88	3.03	−70	−34	−28
Temporal pole	Right		48	2.89	+48	+18	+4
Thalamus	Right		64	2.76	+16	−8	−10
Thalamus	Left		1448	3.67	−10	−12	+4
Control < rMDD							
Precuneous cortex	Left		56	2.82	−4	−70	+48
Supramarginal gyrus (posterior)	Left		176	3.31	−48	−46	+56

[a] Two clusters within same region, coordinates and peak activation reported for highest peak activation.

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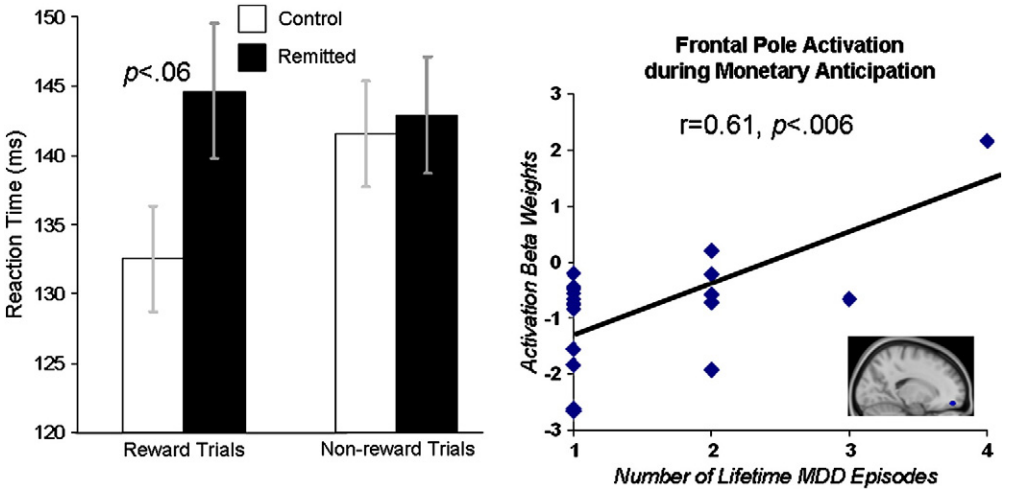

Fig. 4. *Left*: Average reaction times to targets. Error bars reflect standard errors of the mean. *Right*: Significant relation between frontal pole activation during monetary anticipation and the number of lifetime MDD episodes in the rMDD group. The frontal pole cluster was defined on the basis of group difference in activation during this phase of the task.

on cost-benefit gradients (de Lafuente and Romo, 2006), particularly in ambiguous contexts (Hsu et al., 2005). As such, the OFC codes hedonic value and abstract representations of positive and negative outcomes and responds similarly to obtained rewards and avoided losses (Kim et al., 2006; Rolls, 1996). Thus, decreased OFC activation in the rMDD group may reflect diminished tagging of this reward stimulus with affective value. Because a major function of the OFC in incentive contexts is to influence future decision making (Deco and Rolls, 2006), this has implications for the downstream effects of decreased OFC activation on goal-oriented behaviors. We note that these results require replication given the possibility of susceptibility artifact above the sinus cavities.

In reward contexts, the frontal pole in believed to code not for incentive motivation or reward-based decision making, but rather for monitoring and evaluating decisions after the presentation of reward or punishment (Tsujimoto et al., 2010). As such, this region is believed to promote learning associations between behaviors to attain goals as well as costs to attain them (Tsujimoto et al., 2011).

The insular cortex mediates coding both the anticipation and experience of negative outcomes (Knutson et al., 2007; Samanez-Larkin et al., 2008) and insula activity in reward contexts has been linked to anxiety and avoidance learning (Paulus and Stein, 2006; Samanez-Larkin et al., 2008). The thalamus is an integral component of the cortico-basal ganglia system and holds a large glutamatergic projection to the ventral striatum, medial prefrontal cortex, and amygdala (Akert and Hartmann-von Monakow, 1980) and that mediates motivation and emotional drive, planning and cognition for the development and expression of goal-directed behaviors (Haber and Calzavara, 2009; Krebs et al., 2011). Thus, outcome phase data revealed hypoactivation in multiple nodes of the reward network, although we note that outcome phase results were evident only when between-group activations were not masked by grand average task-based activations, and thus we consider these findings exploratory in nature.

Analysis of in-scanner task-related behavior revealed a trend towards relatively slower responses in the rMDD group during only potential reward trials, suggesting a possible behavioral component to altered reward circuitry brain function in rMDD. Exploratory analyses indicated that greater frontal pole activation during monetary anticipation was associated with a greater number of lifetime depressive episodes within the rMDD sample. Given the role of this brain region for monitoring and evaluating decisions after the presentation of rewards (Tsujimoto et al., 2010), it may be the case that greater decision monitoring predicts greater vulnerability for MDD, perhaps due to linkages with rumination during reward outcomes (Koster et al., 2011). It should be noted that there were no significant correlations between brain activation and profiles on the Ruminative Responses Scale (Nolen-Hoeksema et al., 1993) in this rMDD sample, and thus, such effects may be evident only during active task conditions, though this interpretation is highly speculative.

Study limitations include a small sample size, the fact that two rMDD participants were receiving psychotherapy at the time of participation, and the fact that five rMDD participants had previously used psychotropic medications. Additionally, we recently reported that reward network dysfunction in MDD may be more pronounced in response to pleasant images rather than monetary rewards, and thus future studies should examine the effects of positive image reward in individuals with rMDD.

In summary, results are suggestive of reward network dysfunction in currently euthymic individuals with a history of MDD. Specifically, results indicate reward network hyperactivation during the anticipation of rewards and reward network hypoactivation during reward network outcomes. These results imply a double dissociation between reward network activity and the temporal phase of the reward response in rMDD, highlighting the importance of considering the chronometry of the reward response when evaluating reward network function related to MDD. More broadly, these findings suggest that aberrant frontostriatal response to rewards may represent a trait endophenotype for MDD, although future studies in other high risk groups, particularly first-degree relatives of MDD patients with no history of

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MDD, will be critical to establish this potential marker of MDD vulnerability.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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