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FMRI of Alterations in Reward Selection, Anticipation, and Feedback in Major Depressive Disorder

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Abstract

The purpose of the present investigation was to evaluate reward processing in unipolar major depressive disorder (MDD). Specifically, we investigated whether adults with MDD demonstrated hyporesponsivity in striatal brain regions and/or hyperresponsivity in cortical brain regions involved in conflict monitoring using a Wheel of Fortune task designed to probe responses during reward selection, reward anticipation, and reward feedback. Functional magnetic resonance imaging (fMRI) data indicated that the MDD group was characterized by reduced activation of striatal reward regions during reward selection, reward anticipation, and reward feedback, supporting previous data indicating hyporesponsivity of reward systems in MDD. Support was not found for hyperresponsivity of cognitive control regions during reward selection or reward anticipation. Instead, MDD participants showed hyperresponsivity in orbitofrontal cortex, a region associated with assessment of risk and reward, during reward selection, as well as decreased activation of the middle frontal gyrus and the rostral cingulate gyrus during reward selection and anticipation. Finally, depression severity was predicted by activation in bilateral midfrontal gyrus during reward selection. Results indicate that MDD is characterized by striatal hyporesponsivity, and that future studies of MDD treatments that seek to improve responses to rewarding stimuli should assess striatal functioning.

Introduction

Anhedonia, a lack of interest or pleasure in normally rewarding experiences, is a defining symptom of Major Depressive Disorder (MDD; American Psychiatric Association, 1994).Anhedonia is also a central feature of a number of theories of MDD, particularly neurobiologic perspectives stating that deficits in emotional and motivational responses to affective stimuli are key to the disorder (e.g., Tomarken and Keener, 1998). Despite the centrality of anhedonia to MDD, the capacity of depressed individuals to experience anticipation of pleasurable events and enjoyment of pleasure during reward presentation has received little empirical attention, and the neurobiology of anhedonia in depression remains to be delineated.

Two non mutually-exclusive neurobiological mechanisms may contribute to anhedonia in MDD: *hypo*responsivity of structures within mesolimbic dopamine system related to processing rewards; and *hyper*responsivity in cortical regions associated with conflict monitoring. In support of the former hypothesis, lower activation in mesolimbic regions in response to positive stimuli in MDD (Schaefer et al., 2006; Epstein et al., 2006; Keedwell et al., 2005). However, these studies exclusively examined responses to reward presentation, and thus the contributions of mesolimbic/striatal hyporesponsivity during anticipation of rewards were unclear. In support of the cortical hyperresponsivity hypothesis, dorsal anterior cingulate cortex (dACC) activation has been implicated under conditions of uncertainty and affective conflict during the anticipation of potential positive outcomes (Botvinick et al., 1999; Carter et al., 1998). To the extent that individuals with MDD are less confident of potential positive outcomes (Beck and Clark, 1988), heightened dACC activation may be expected during reward anticipation. Knutson and colleagues

(2008) employed a Monetary Incentive Delay (MID) task to differentiate brain responses during reward anticipation and positive reward feedback. They reported that activation of the striatum, including the nucleus accumbens (NAc), did not differentiate MDD and control samples during monetary anticipation or during receipt of monetary rewards. Depressed participants did, however, exhibit dorsal anterior cingulate cortex (dACC) hyperactivation during anticipation of monetary rewards. The authors concluded that MDD may not be characterized by hypoactive anticipatory pleasure states during reward anticipation, but rather by increased affective conflict during anticipation of gains.

This key investigation by Knutson and colleagues (2008) warrants replication and further examination for at least two reasons: First, in the MID task, reward anticipation and preparation to engage in a behavior with potential reward (i.e., a speeded button press) occur simultaneously. Thus, brain functioning in MDD to a reward anticipation phase devoid of behavioral preparation has not been examined. Second, the MID task does not incorporate decision-making based on risk/reward trade-offs. Thus, it is unknown if MDD hyperactivity in regions associated with conflict monitoring extends to decision-making processes related to risk/reward behaviors, or, conversely, is purely linked to reward anticipation. Given the direct relevance of behavioral initiation/avoidance to the clinical presentation of MDD (Jacobson et al., 2001), a greater understanding of reward system activity while selecting a response option is of strong interest.

In the present investigation we employed a Wheel of Fortune (WoF) task to assess the functional neural correlates of reward selection, reward anticipation, and reward feedback in adults with MDD and in a matched adult control sample. The WoF has been shown to elicit activation in both striatum and ACC during reward anticipation (Ernst et al.,

2004). Based on the existing literature showing relatively lower levels of response in mesolimbic dopamine regions to positive stimuli in MDD (Schaefer et al., 2006; Epstein et al., 2006; Keedwell et al., 2005), we hypothesized hyporesponsivity in striatal regions across all three phases of the task, but most critically during reward anticipation because of preclinical evidence that reward-*seeking* behaviors are mediated by striatal structures (Salamone et al., 1994; Swerdlow and Koob, 1987). As highlighted earlier, Knutson and colleagues (2008) did not find striatal hypoactivation during reward anticipation, but we hypothesized that the an anticipatory phase devoid of a motor preparatory components may be more sensitive to anticipatory hedonic deficits in MDD. In addition, consistent with the findings of Knutson and colleagues (2008), we hypothesized hyperresponsivity of conflict monitoring regions, including dorsal ACC, during both the reward selection and reward anticipation phases.

Method

Participants

Study participants were recruited through the Duke Cognitive Behavioral Research and Treatment Program and advertisements at Duke University Medical Center and the University of North Carolina, Chapel Hill. In addition, nondepressed participants were recruited from lists maintained at the Duke-UNC Brain Imaging and Analysis Center. Potential participants received a Structured Clinical Interview for DSM-IV (SCID) conducted by licensed clinical psychologists or trained research assistants to assess for Axis I disorders, and completed several rating scales and interviews including the Hamilton Rating Scale for Depression (Hamilton, 1960) (HAM-D) and the North American Adult Reading Test (Blair and Spreen, 1989) (NAART). Participants in the depressed group met

DSM-IV criteria for a current episode of Major Depressive Disorder and scored 15 or above on the HAM-D. MDD participants were scanned before beginning a course of psychotherapy, and were not in treatment at the time of the scan. Participants in the control group scored 6 or lower on the HAM-D, and did not meet criteria for a current or lifetime episode of mood disorder. Exclusion criteria for both groups included: 1) current mood, anxiety, psychotic, or substance abuse disorder beyond unipolar depression or dysthymia in the MDD group, 2) current use of psychoactive medications, 3) history of psychosis or mania; 4) active suicidal ideation, 5) evidence of organicity, 6) estimated verbal IQ below 70, 7) magnetic resonance imaging contraindication (e.g., metal in body), 8) history of neurological injury or disease, and 9) current pregnancy. After a complete description of the study to the participants, written informed consent was obtained.

A total of 16 depressed (9 females) and 15 control participants (9 females) enrolled in the study. One depressed female withdrew after her initial interview, stating that her mood had improved substantially and she was no longer interested in participating. A depressed female who had frank abnormalities in her brain anatomy was withdrawn from the study. Thus the final sample for analyses was 14 depressed (7 females, average age 34.8 ± 14.3 years) and 15 control participants (9 females, average age 30.8 ± 9.7 years). Two MDD participants had prior hospitalizations. Three MDD participants were in their first depressive episode, four were in their second or third, and the remainder reported 4 or more episodes. One MDD participant met criteria for a past episode of PTSD. Two MDD and one control participant met criteria for past substance dependence. Groups did not differ in age, estimated verbal IQ as measured by the NAART (MDD=112.8, Control=117.7) or smoking status, *p's* > .05. MDD participants had greater HAM-D

depression symptom scores (MDD = 23.5, Control = 0.2), $p<0.00001$.

fMRI Task

The Wheel of Fortune (WOF) task is a computerized two-choice decision-making task involving probabilistic monetary outcomes (see Figure 1). Participants were instructed that they would take home up to $45 of the money they won ($40 minimum) and that they should try to win as much money as possible. In each trial, participants chose between two options, each with an assigned probability of winning a certain amount of money. If the computer randomly selected the same option as the participant, the participant won the designated amount of money; if the computer randomly selected the other option, the participant won nothing. Trial types and associated monetary values are shown in Figure 1.

Insert Figure 1 about here

Participants completed four runs of 46 trials, which lasted approximately 12 min each. Each trial lasted between 10.5 – 14.5 s and was composed of three phases: a selection phase (3 s), an anticipation phase (jittered between 3.5-7.5 s), and a feedback phase (4 s). All responses were recorded on two four-key button-boxes in the fMRI scanner, using three buttons per hand. All selection-phase responses were given with the right hand.

Immediately prior to the scanning session, participants were trained on the task. All stimuli were presented using E-Prime presentation software (PST Inc., Pittsburgh, PA) and displayed to participants in the scanner through magnet-compatible goggles (Resonance Technology, Inc., Northridge CA).

In-Scanner Behavior Analysis Approach

Following Ernst and colleagues (2004), responses with a low probability of winning

(10% and 30% chance responses) were combined into "risky" trials, with high-probability responses (70% and 90%) conditions combined into "safe" trials, unless otherwise noted. Not all participants had responses in all categories (e.g., one MDD participant chose only risky responses; another MDD participant made only one risky response, and therefore has no winning risky responses), so degrees of freedom reflect the number of participants in the analysis. Reaction times were square root transformed to normalize positive skew.

Imaging Methods

Scanning was performed on a General Electric 4T LX NVi MRI scanner system equipped with 41 mT/m gradients (General Electric, Waukesha, Wisconsin, USA). A quadrature birdcage radio frequency (RF) head coil was used for transmit and receive. A high resolution T1-weighted image with 68 slices was acquired using a 3D fast SPGR pulse sequence (TR = 500 ms; TE = 20 ms; FOV = 24 cm; image matrix = 256 × 256; voxel size = 0.9375 × 0.9375 × 1.9 mm) 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 an EPI pulse sequence sensitive to blood oxygenation level dependent (BOLD) contrast (TR, 1500 ms; TE, 31 ms; FOV, 24 cm; image matrix, 64 x 64; α= 62°; voxel size, 3.75 ×3.75 ×3.8 mm; 34 axial slices). The 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 4.0.2 (Oxford FMRIB, Oxford, U.K.) using the same protocol as we have published previously (Dichter et al., 2008). 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. Functional images were co-registered to structural images in native space, and structural images were normalized into MNI space. Voxel-wise temporal autocorrelation was estimated and corrected using FMRIB's Improved Linear Model (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. Group-wise activation and deactivation images were carried out using FEAT (FMRI Expert Analysis Tool) Version 5.92. Z (Gaussianised T/F) statistic images were thresholded using GRF-theory-based maximum height thresholding with a (corrected) significance threshold of z = 2.6 (Worsley, 2007). Clusters contained a minimum of 5 contiguous voxels and were localized using the Harvard-Oxford and Talairach atlases.

Results

In-Scanner Choices

Selection choices, confidence ratings, outcome valence ratings, and reaction times to respond were analyzed. Unless otherwise noted, 2 (Group: MDD, control) X 3 (Condition: safe, 50/50, risky) repeated measure MANOVAs were performed. For the sake of brevity, non-significant main effects and interaction terms are omitted. Reaction times to respond did not differ by group or condition in any phase.

To test for group differences in the propensity to make risky versus safe selections, a 2 (Group: MDD, control) X 2 (Condition: 10/90 or 30/70) repeated measure MANOVA was performed. A main effect of Condition, multivariate $F(1,27)=5.09$, $p<0.05$, indicated

that participants made more risky selections in the 30/70 condition than the 10/90 condition. No group-based differences were detected. Overall, the risky option was selected 54.2% of the time. A repeated measure MANOVA performed on confidence ratings from the anticipation phase revealed a main effect of Condition, multivariate $F(2,25)=64.0$, $p<0.0001$, reflecting the unsurprising pattern of greater confidence for safe relative to risky selections in both diagnostic groups.

For analyses of feedback valence ratings, win and non-win trials were examined separately. For win trials, a repeated measure MANOVA performed on outcome valence ratings revealed main effects of Condition, multivariate $F(2,23)=3.91$, $p<0.05$, and Group, $F(1,24)=6.30$, $p<.05$, as well as a Group x Condition interaction, multivariate $F(2,23)=4.32$, $p<.05$. The MDD group gave higher ratings overall, but ratings among the MDD group did not differ significantly by risk, $F(2,22)=2.99$, $p>.07$. In the control group, increased risk (and therefore increased earnings) was associated with higher ratings, $F(2,28)=3.39$, $p<.05$. For no-win trials, a similar MANOVA revealed a main effect of risk, multivariate $F(2,24)=3.79$, $p<.05$, reflecting less negative ratings for higher risk (and therefore less surprising losses).

Imaging Data

In order to maximize the number of trials contributing to each imaging analysis, trials were collapsed across risky, 50/50, and safe trial types.

Reward Selection

Selection phase contrasts for FSL mixed effects analysis included Money > Control comparisons between the control and MDD groups (see Table 1a for a summary of regions showing group differences). The key regions for which control participants showed greater

activation than MDD participants were the paracingulate gyrus (see Figure 2) and middle frontal gyrus (BA 8). In contrast, MDD participants showed relatively greater activation in left orbitofrontal cortex, superior frontal gyrus, BA 6, as well as fusiform gyrus and several other occipital regions. Table 1a lists regions with significant group differences during reward selection.

Insert Figure 2 about here

Reward Anticipation

Contrasts for the anticipation phase included Money > Control comparisons between the control and MDD groups. Controls showed greater activation in regions of basal ganglia associated with reward prediction and learning from positive feedback (right caudate) and memory (right hippocampus). See Figure 2. Only parietal operculum showed greater activation among MDD participants. Table 1b lists regions with significant group differences during reward anticipation.

Insert Table 1 about here

Reward Outcomes

Two sets of contrasts were performed for the reward outcome phase. Contrasts included both Win > Control and Non-win > Control comparisons between the control and MDD groups. For Win > Control contrasts, regions where the MDD group showed greater activation than controls included left inferior frontal gyrus (BA 9/45) and bilateral thalamus. For Non-win > Control contrasts, regions where the control group showed greater activation than the MDD group included in right caudate, auditory cortex, BA 41,

occipital regions, and frontal medial cortex, whereas the MDD group showed greater activation in middle, inferior, and orbitofrontal cortex. Table 1c and Figure 3 indicate regions with significant group differences during reward outcomes.

Insert Figure 3 about here

Brain Activation-Symptom Relations

We assessed relations between regional brain activation during each reward phase and depressive symptom severity in the MDD group in an exploratory fashion. A significant correlation was found between bilateral midfrontal activation to reward selection and HAM-D scores (R^2=0.5602).

Discussion

The goal of the present study was to map brain regions differentially recruited by individuals with and without MDD during reward selection, anticipation, and feedback. A primary question was the degree to which MDD is characterized by hyporesponsivity of mesolimbic structures related to reward processing, and/or hyperresponsivity in cortical regions associated with conflict monitoring across the phases of the reward response. Relative to affectively healthy control adults, MDD participants showed decreased activation during reward anticipation in the right caudate, a region that has been previously associated with reward prediction (Hsu et al., 2005) and reward response (Elliott et al., 2000) in healthy adults. This finding supports the hypothesis of hyporesponsivity in mesolimbic reward regions during reward anticipation.

Support for the conflict monitoring hypothesis was not found. The MDD group showed *less* activation in dorsal ACC, a region strongly associated with conflict monitoring

(Bush et al., 2002; Luks et al., 2007), than the control group during reward anticipation. Note that the present study was not designed to test a broad hypothesis of increased conflict monitoring in MDD across contexts, as the WoF task employed here requires multiple cognitive processes in addition to conflict monitoring. Rather, this study can be seen as a first step in demonstrating that regions associated with conflict monitoring did not show increased activation in a reward context. MDD participants did show greater activation during reward selection and in response to non-winning feedback in orbital frontal cortex, a region involved in the indexing of contingency relationships (Luks et al., 2007) and updating of learned associations with both rewarding and punishing stimuli (Luks et al., 2007; Stalnaker et al., 2007; Schoenbaum et al., 2007). Thus in the current study, frontal hyperactivation in MDD occurred in regions associated with indexing risk and reward rather than in regions that resolve conflicts between those states.

The nature of the task employed in the present investigation may account for our differing results from those of Knutson et al. (2008). In the present investigation, choice selection and assessment of the likeliness of a positive outcome may be based on a probability calculation (i.e., an assessment of pie slice size to give a rough estimation of one's chance of winning on a given trial.) By comparison, chances of winning in the MID task are based on reaction times, are equivalent across all trials, and do not lend themselves to a similar computational comparison. Dorsal and middle frontal regions, including BA 8 and 9, as well as dorsal ACC, are associated with computational processes (Cowell et al., 2000; Gruber et al., 2001), and showed relatively decreased activation in the MDD group during both reward selection and anticipation. This pattern of activation may reflect less reliance on computational analysis than monitoring of affective conflict over potential

reward on the part of MDD participants.

This is the first neuroimaging study to examine functional brain responses to reward selection among individuals with MDD. Processes involved in selecting and initiating behaviors may have particular clinical relevance in MDD, as both a lack of approach motivation and heightened behavioral inhibition are thought to be key components of MDD (Kasch et al., 2002). We found that individuals with MDD showed relatively less activity in areas associated with cognitive and computational processes during reward selections. Less use of these processes while selecting a course of action in MDD may contribute to behavioral inhibition or lack of approach due to a relative lack of information on which to base actions, or may be reflective of decreased effort due to more distal anhedonic processes. Likewise, a heightened focus on assessing the potential for risk or reward (as reflected in relatively greater orbital frontal activation) without concomitant computational information processing to optimize response selection may contribute to poor decision-making in reward contexts on the part of individuals with MDD. Further studies are needed to validate and extend these findings, and to make more direct links to patient behaviors.

There are several limitations to the current study. First, the modest sample size may limit interpretability of null results. Second, this study used representations of money earned as the rewarding stimulus. Although monetary reward is thought to be a relatively strong reinforcer in humans (Kirsch et al., 2003), it is unclear if gustatory, social, or other types of rewarding stimuli would reveal more robust group differences. Finally, as outlined above, the nature of the experimental task included a computational component to determining relative risk that may have produced differential activation between the MDD

and control groups during reward selection and anticipation.

The present study represents an important extension of the existing literature on multiple aspects of reward system functioning in MDD. Consistent with previous studies using presentations of positive stimuli, MDD appears to be associated with hypoactivation of mesolimbic reward regions when anticipating rewards. In addition, MDD is characterized by hyperactivation in regions associated with motor preparation during reward selection, but not cognitive control or ongoing monitoring of potential reward as reported previously in the literature. Future studies will be needed to determine the functional impact of these patterns of brain functioning, as well as to determine if group differences in activation normalize with treatment and symptom remission.

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TABLES

Table 1a. Between-groups activation differences for the selection phase (Money > Control).

Comparison	Region	Size	Z Max	Coordinates X	Y	Z
MDD>Control	Central Opercular Cortex (Left)	10	2.95	48	-10	8
	Cuneal Cortex (Left)	13	3.02	8	-86	26
	Frontal Gyrus (Middle, Right)	12	3.18	-34	36	20
	Frontal Gyrus (Superior, Left)	73	3.64	24	24	52
	Frontal Orbital Cortex (Left *)	25	2.94	26	30	-16
	Frontal Pole					
	Left *	101	4.11	22	48	-20
	Right	7	3.02	-16	34	-12
	Hippocampus (Left)	6	2.93	22	-6	-28
	Lateral Occipital Cortex (Inferior, Left)	35	3.48	56	-72	-8
	Lingual Gyrus (Right)	8	2.93	-4	-62	4
	Occipital Cortex (Lateral, Inferior)					
	Left	9	2.93	52	-72	14
	Right	5	2.71	-40	-64	6
	Occipital Cortex (Lateral, Superior)	123				
	Left *	123	3.71	14	-70	56
	Right *	100	3.57	-14	-72	58
	Occipital Pole					
	Left	20	3.24	8	-90	14
	Right *	150	3.77	-8	-90	30
	Parahippocampal Gyrus (Anterior, Right)	5	2.83	-38	-12	-22
	Parietal Operculum Cortex (Left)	133	3.85	44	-36	32
	Planum Temporale (Left)	125	4	64	-18	8
	Postcentral Gyrus (Left)	31	3.45	6	-50	76
	Precentral Gyrus (Left*)	19	2.96	6	-28	80
	Precuneous Cortex					
	Left	7	2.76	8	-50	58
	Right *	56	3.59	-16	-50	54
	Supramarginal Gyrus (Anterior, Right)	28	3.1	-50	-28	34
	Supramarginal Gyrus (Posterior, Left)	18	3.04	50	-42	44
	Temporal Fusiform Cortex (Posterior, Right)	12	2.88	-44	-24	-14
	Temporal Gyrus (Inferior, Temporooccipital)					
	Left *	82	3.82	48	-56	-6
	Right	173	4.43	-46	-56	-10
	Temporal Gyrus (Inferior, Left)	9	3.03	44	-22	-32
	Temporal Gyrus (Superior, Anterior)	21	3.08	-60	-8	0
Control>MDD	Angular Gyrus (Right)	9	3.07	-52	-54	28
	Caudate (Right)	15	3.18	-8	6	6
	Frontal Gyrus (Middle, Right)	57	3.67	-48	26	38
	Frontal Gyrus (Superior, Right)	9	3.37	-18	26	60
	Frontal Pole (Right *)	122	3.78	-14	44	48
	Paracingulate Gyrus (Right)	16	3.1	0	48	2
	Precentral Gyrus (Left)	5	3.08	52	-2	52
	Supramarginal Gyrus (Posterior, Right)	6	2.99	-62	-52	38
	Temporal Gyrus (Middle, Posterior, Right)	13	3.78	-70	-14	-22

Table 1b. Between-groups activation differences for the anticipation phase (Money > Control).

Comparison	Region	Size	Z Max	Coordinates		
				X	Y	Z
MDD>Control	Parietal Operculum Cortex (Right)	22	3.38	-52	-28	24
Control>MDD	Caudate (Right *)	160	4.1	-18	-16	22
	Cingulate Gyrus (Anterior, Right)	95	3.38	-16	36	14
	Cingulate Gyrus (Posterior)					
	Left	183	3.51	10	-44	12
	Right	90	3.74	-10	-30	-38
	Frontal Gyrus (Inferior, Pars triangularis, Right *)	930	4.91	-28	24	26
	Frontal Gyrus (Middle)					
	Left	49	3.57	34	12	30
	Right *	41	3.54	-32	12	52
	Frontal Pole (Right *)	96	3.57	-34	34	12
	Hippocampus (Right)	59	3.38	-34	-26	-14
	Lingual Gyrus (Left *)	584	4.76	-10	-76	-4
	Occipital Cortex (Lateral, Inferior)					
	Left *	70	3.56	22	-74	36
	Right	40	3.07	-32	-66	46
	Occipital Cortex (Lateral, Superior, Right)	124	3.63	-34	-80	22
	Occipital Fusiform Gyrus (Right)	17	2.9	-32	-70	-2
	Postcentral Gyrus (Left *)	83	3.57	42	-22	48
	Precentral Gyrus					
	Left *	125	3.74	24	-10	72
	Right	12	2.98	-40	-4	54
	Precuneous Cortex					
	Left	9	2.82	16	-66	42
	Right	58	3.53	-22	-54	22
	Subcallosal Cortex (Right)	6	2.93	-2	12	2
	Temporal Gyrus (Inferior, Posterior, Right)	8	3.03	-58	-28	-22
	Temporal Gyrus (Middle, Posterior, Right)	5	2.85	-70	-22	-20
	Temporal Pole (Right)	27	3.16	-54	14	-34
	Thalamus					
	Left	63	3.51	18	-22	14
	Right	23	2.92	-12	-10	14

Table 1c. Between-groups activation differences for the reward feedback phase.

Winning > Control Trials	Region	Size	Z Max	Coordinates X	Y	Z
MDD > Control	Angular Gyrus (Left)	14	2.93	48	-58	20
	Cuneal Cortex (Left)	14	2.97	6	-88	24
	Frontal Gyrus (Inferior , Pars opercularis, Left)	49	3.79	58	14	22
	Occipital Fusiform Gyrus (Left)	8	2.8	30	-76	2
	Precuneous Cortex (Left)	15	3.08	8	-56	18
	Temporal Pole (Right)	19	3.38	-30	10	-24
	Thalamus					
	Left	11	3.15	18	-30	-4
	Right	22	3.03	-22	-30	0
Control > MDD	Cuneal Cortex (Right)	12	3.13	-2	-88	42
	Frontal Gyrus (Middle, Left)	7	2.89	44	22	42
	Lingual Gyrus (Right)	13	3.02	-18	-66	-8
	Occipital Cortex (Lateral, Superior)					
	Left	7	2.96	24	-70	32
	Right	19	2.92	-30	-72	34
Non-win> Control Trials	Frontal Gyrus (Inferior, Pars opercularis, Left)	20	3.05	60	14	22
	Frontal Gyrus (Middle, Left)	11	3.01	52	34	22
MDD > Control	Frontal Orbital Cortex (Right)	5	2.8	-24	22	-24
Control > MDD	Amygdala (Left)	11	3.34	24	2	-18
	Caudate (Right *)	57	2.89	-16	2	20
	Central Opercular Cortex (Right)	11	3.18	-42	-16	12
	Cingulate Gyrus (Posterior, Right)	27	3.65	-6	-34	18
	Frontal Operculum Cortex (Right)	21	3	-30	12	16
	Frontal Pole (Right)	16	3.05	-16	38	-20
	Heschl's Gyrus (Left)	14	3.14	52	-20	6
	Hippocampus (Right *)	31	3.46	-28	-18	-18
	Insular Cortex (Right)	5	2.98	-32	12	-8
	Lingual Gyrus (Right *)	54	3.11	-10	-74	2
	Occipital Cortex (Lateral, Inferior, Right)	26	2.87	-30	-72	6
	Occipital Cortex (Lateral, Superior, Right *)	57	3.6	-34	-72	20
	Parietal Lobule (Superior, Right)	23	3.18	-24	-48	48
	Planum Temporale (Left)	96	3.38	36	-36	14
	Postcentral Gyrus (Right *)	23	3.22	-2	-42	66
	Precuneous Cortex (Left *)	19	3.09	20	-56	8
	Putamen (Left)	11	2.78	26	-2	-4
	Subcallosal Cortex (Right)	8	3	-6	6	-12
	Temporal Gyrus (Middle, Posterior, Left)	2.77	3	56	-20	-6
	Temporal Pole (Right)	14	2.88	-54	8	-32
	Thalamus (Left)	13	3.39	18	-18	16

* Multiple non-continuous clusters were identified within this region. Cluster size represents the total number of voxels within clusters meeting threshold criteria in the region. Z-max and coordinate values represent the cluster with the strongest activation within the region.

Figure Legends

Figure 1. The Wheel of Fortune (WoF) task (Ernst et al., 2004). (a) The four different types of wheels; (b) The timing of three processes that occurred during the task, i.e., reward selection, reward anticipation, and reward feedback.

Figure 2. Reward selection (**top**) and anticipation (**bottom**) fMRI results (money vs. control). Red areas depict regions with greater activation in the control than the depressed group; blue areas depict regions with greater activation in the depressed than the control group.

Figure 3. Reward feedback fMRI results for win (**top**) and non-win (**bottom**) trials relative to control feedback. Red areas depict regions with greater activation in the control than the MDD group; blue areas depict regions with greater activation in the MDD than the control group.

Figure 1

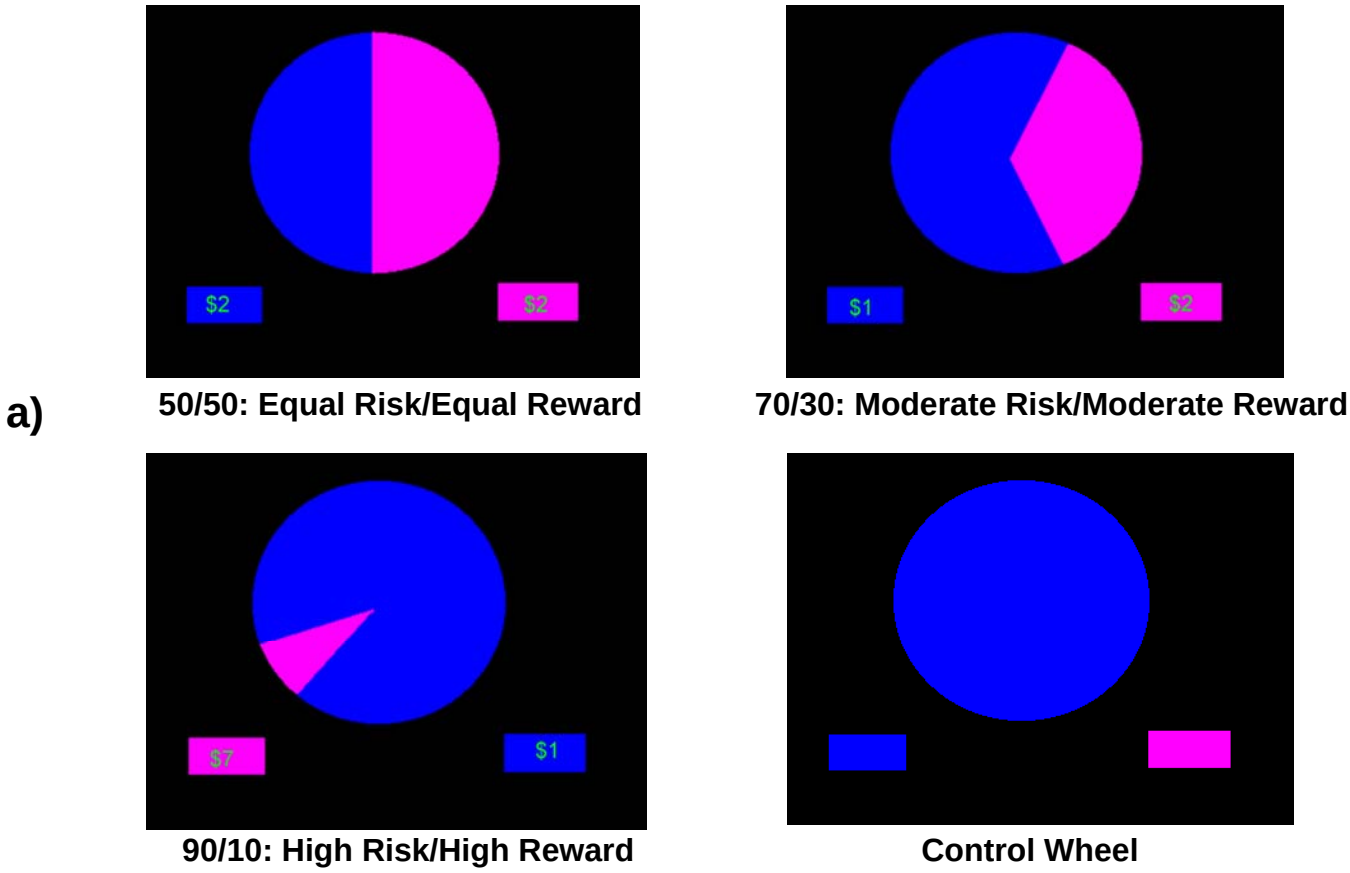
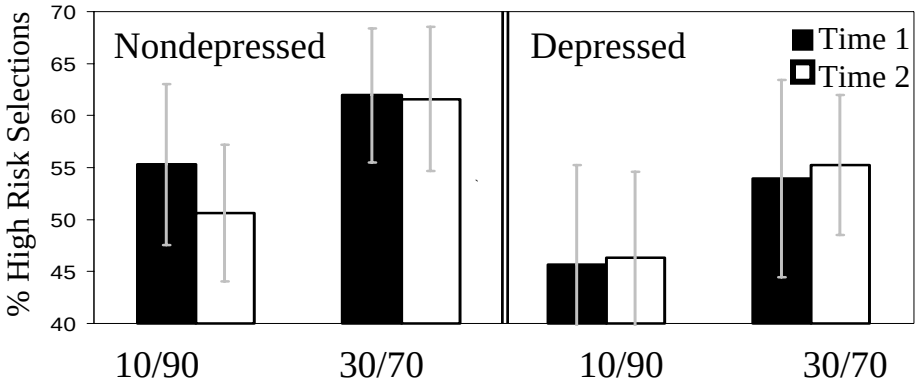
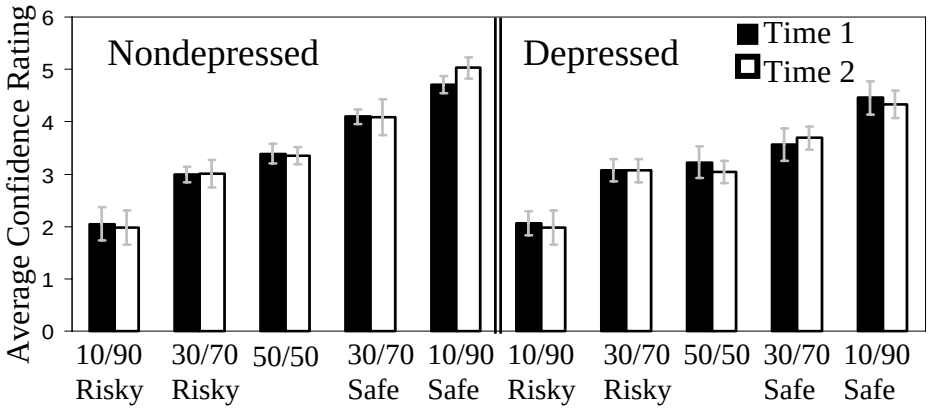
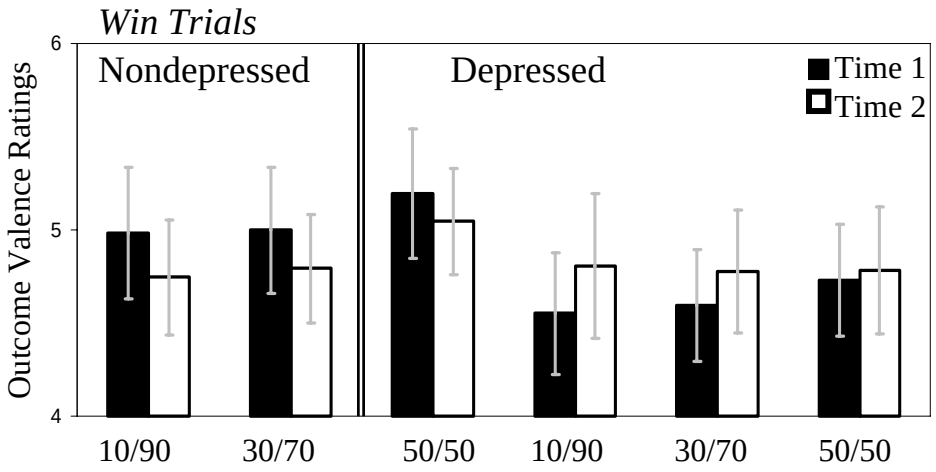

a)
$2
$2
50/50: Equal Risk/Equal Reward
$1
$2
70/30: Moderate Risk/Moderate Reward
$7
$1
90/10: High Risk/High Reward
Control Wheel
b)
$7
$1
How Sure Are You?
Unsure
Sure
1
2
3
4
5
6
You Win $7
Total $18
How do you feel?
Selection Phase, 3 sec
Anticipation Phase, 3.5 sec
Feedback Phase, 4 sec

Figure 2


% High Risk Selections
70
65
60
55
50
45
40
Nondepressed
Depressed
Time 1
Time 2
10/90
30/70
10/90
30/70


Average Confidence Rating
6
5
4
3
2
1
0
Nondepressed
Depressed
Time 1
Time 2
10/90 Risky
30/70 Risky
50/50
30/70 Safe
10/90 Safe
10/90 Risky
30/70 Risky
50/50
30/70 Safe
10/90 Safe


Win Trials
Outcome Valence Ratings
6
5
4
Nondepressed
Depressed
Time 1
Time 2
10/90
30/70
50/50
10/90
30/70
50/50

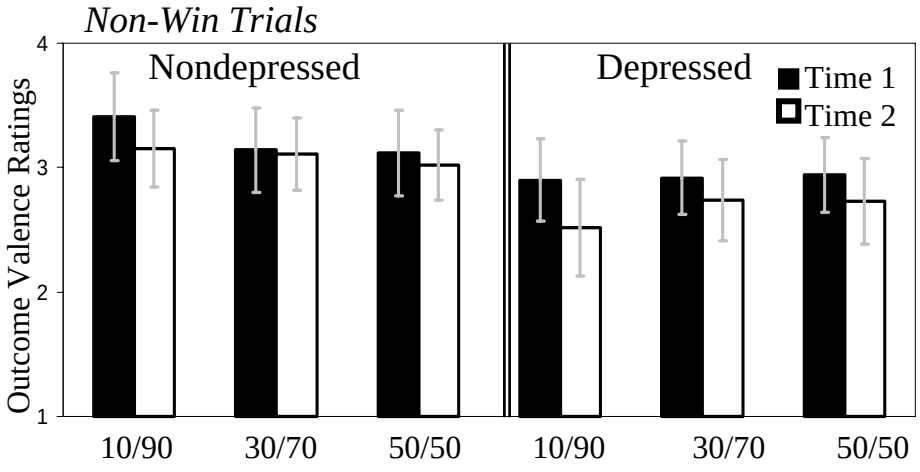

Non-Win Trials
Outcome Valence Ratings
4
3
2
1
Nondepressed
Depressed
Time 1
Time 2
10/90
30/70
50/50
10/90
30/70
50/50

Figure 3

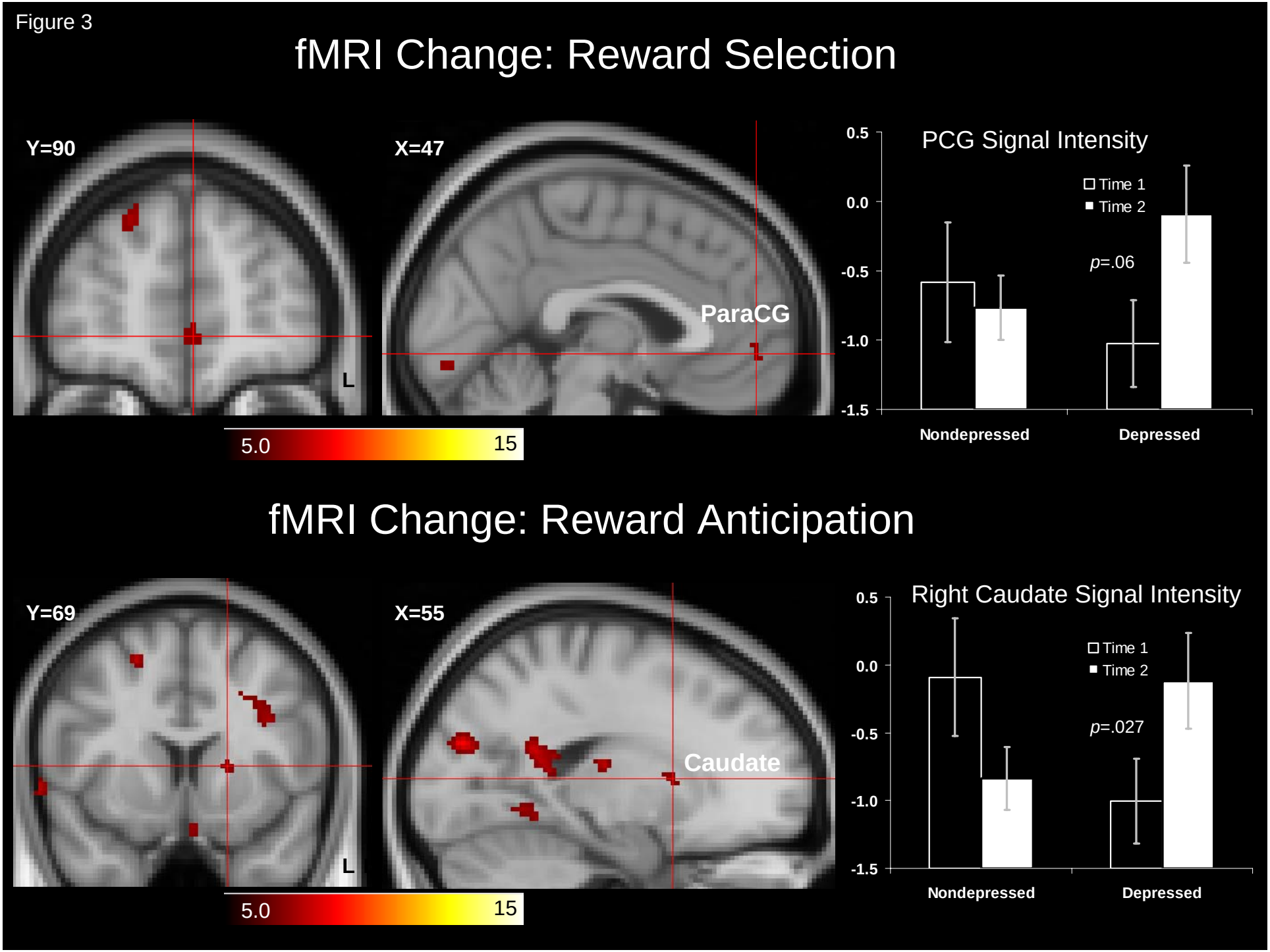
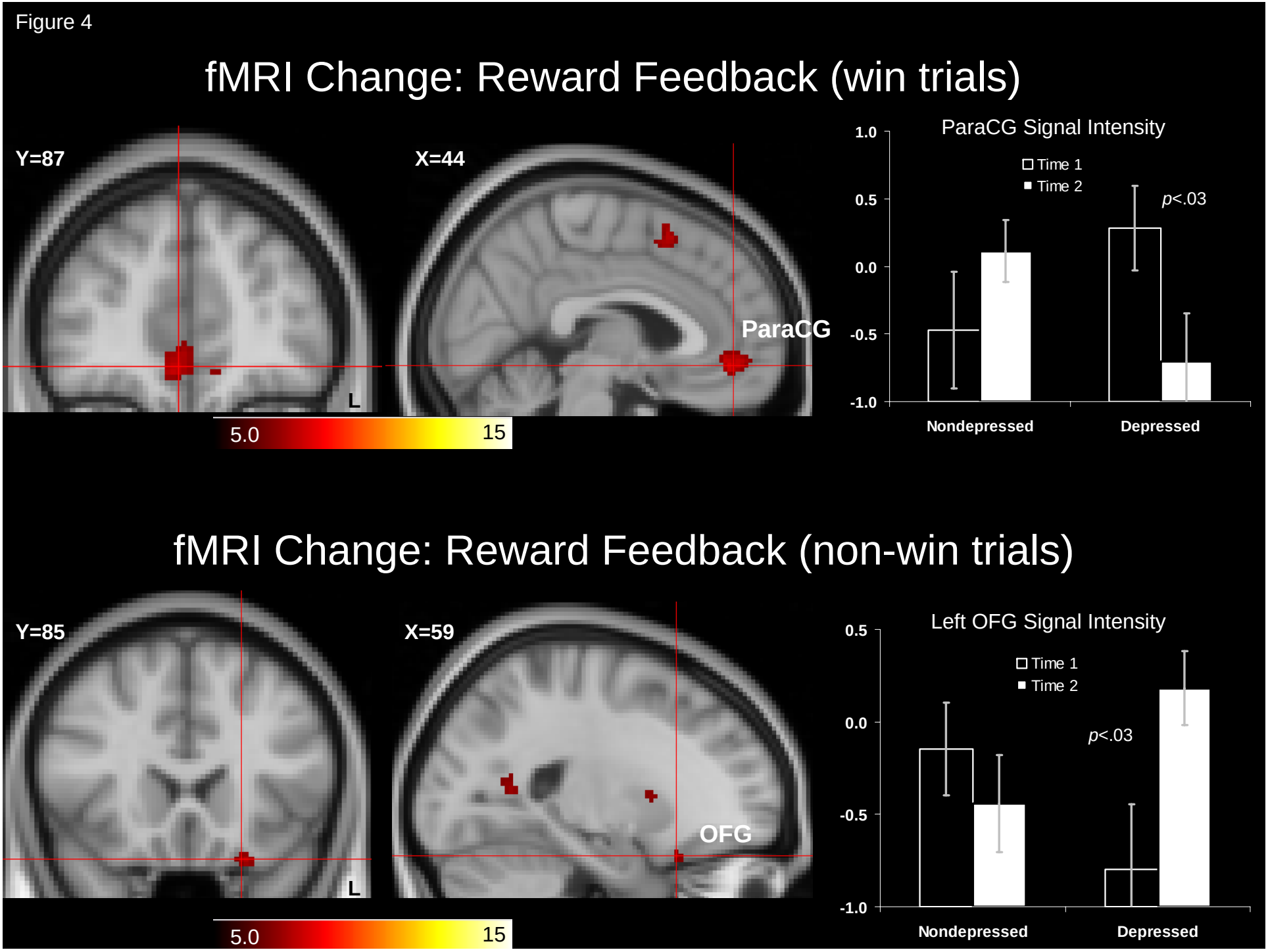
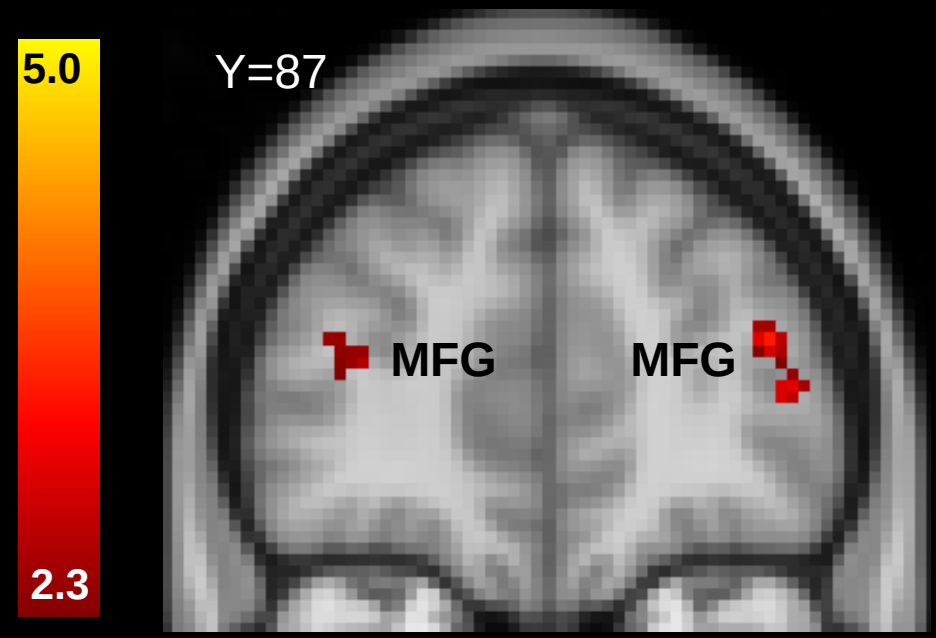
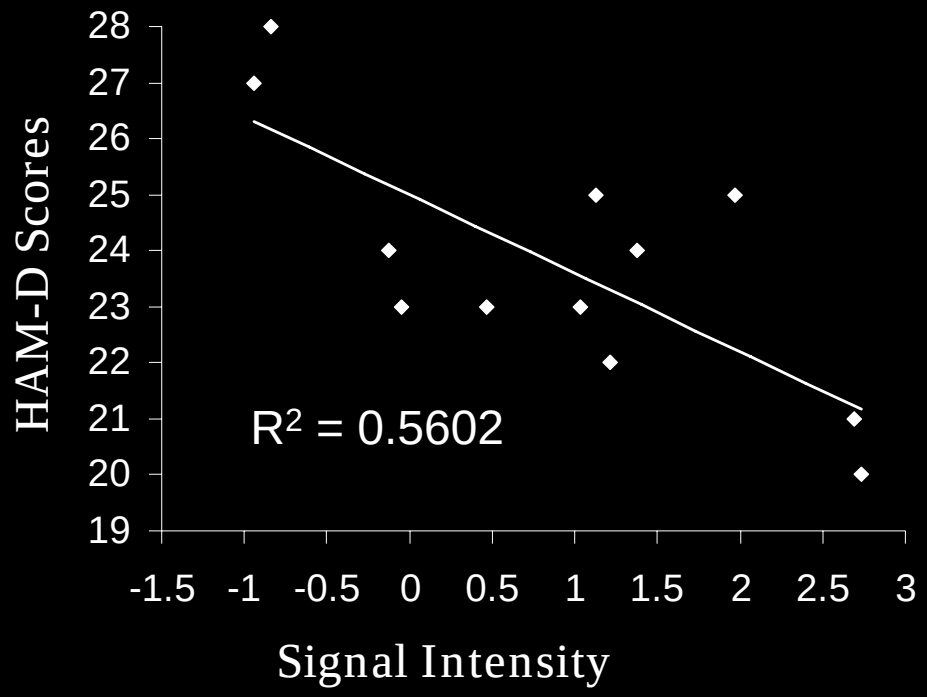

fMRI Change: Reward Selection
Y=90
X=47
L
ParaCG
5.0
15
PCG Signal Intensity
0.5
0.0
-0.5
-1.0
-1.5
Time 1
Time 2
p=.06
Nondepressed
Depressed
fMRI Change: Reward Anticipation
Y=69
X=55
L
Caudate
5.0
15
Right Caudate Signal Intensity
0.5
0.0
-0.5
-1.0
-1.5
Time 1
Time 2
p=.027
Nondepressed
Depressed

Figure 4


fMRI Change: Reward Feedback (win trials)
Y=87
X=44
ParaCG
L
5.0
15
ParaCG Signal Intensity
Time 1
Time 2
p<.03
1.0
0.5
0.0
-0.5
-1.0
Nondepressed
Depressed
fMRI Change: Reward Feedback (non-win trials)
Y=85
X=59
OFG
L
5.0
15
Left OFG Signal Intensity
Time 1
Time 2
p<.03
0.5
0.0
-0.5
-1.0
Nondepressed
Depressed


5.0
2.3
Y=87
MFG
MFG


HAM-D Scores
28
27
26
25
24
23
22
21
20
19
R² = 0.5602
-1.5
-1
-0.5
0
0.5
1
1.5
2
2.5
3
Signal Intensity