Neural Responses to Monetary Incentives in Major Depression

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Background: Reduced responsiveness to positive incentives is a central feature of Major Depressive Disorder (MDD). In the present study, we compared neural correlates of monetary incentive processing in unmedicated depressed participants and never-depressed control subjects.

Methods: Fourteen currently depressed and 12 never-depressed participants underwent functional magnetic resonance imaging while participating in a monetary incentive delay task. During the task, participants were cued to anticipate and respond to a rapidly presented target to gain or avoid losing varying amounts of money.

Results: Depressed and never-depressed participants did not differ in nucleus accumbens (NAcc) activation or in affective or behavioral responses during gain anticipation. Depressed participants did, however, exhibit increasing anterior cingulate activation during anticipation of increasing gains, whereas never-depressed participants showed increasing anterior cingulate activation during anticipation of increasing loss. Depressed participants also showed reduced discrimination of gain versus nongain outcomes.

Conclusions: The present findings indicate that although unmedicated depressed individuals have the capacity to experience positive arousal and recruit NAcc activation during gain anticipation, they also exhibit increased anterior cingulate cortex activation, suggestive of increased conflict during anticipation of gains, in addition to showing reduced discrimination of gain versus nongain outcomes.

Key Words: Accumbens, cingulate, depression, FMRI, human, incentive, prefrontal, reward

Depressive disorders are prevalent and burdensome, imposing enormous costs on individuals and society (1), because 16% of the general population develops clinically significant depression (2), and 80% of these individuals experiences recurrent depressive episodes (3). Major Depressive Disorder (MDD) is characterized by two primary affective symptoms: sustained negative affect and reduced positive affect. Cognitive and motivational research has traditionally focused on the first of these symptoms. Findings from this research suggest that depressed individuals attend more to negative than to neutral or positive material, and remember it better (4,5). Such negative biases have been proposed to account for the development and maintenance of depression (6,7).

Fewer studies have focused on the role of diminished positive affect in depression (8,9). These few studies suggest that, relative to nondepressed counterparts, depressed individuals report experiencing reduced positive affect (10) and show less autonomic and nonverbal (e.g., facial) responsiveness to positive material (11–13). Depressed individuals also show poorer memory for positive material (14) and fail to behaviorally respond faster for monetary reward (15–17). Finally, among depressed individuals, those who respond to positive material exhibit better symptomatic improvement over the following year, independent of initial symptom severity (12,18,19).

A substantial body of animal research implicates subcortical circuitry along the ascending trajectory of mesolimbic dopamine projections in appetitive motivation (20,21). This mesolimbic circuit includes midbrain nuclei that produce dopamine (e.g., the ventral tegmental area) as well as their subcortical (e.g., the nucleus accumbens [NAcc]) and cortical target regions (e.g., the mesial and orbital frontal cortices) (22). Unresponsiveness in this mesolimbic circuit has been hypothesized to contribute to depression (23). In fact, early studies using electroencephalography revealed decreased resting activity in the left prefrontal cortex of depressed individuals (24–28), which was interpreted to reflect reduced appetitive motivation (29). More recent studies using functional magnetic resonance imaging (FMRI), which enables visualization of changes in activation in small subcortical regions, have revealed reduced mesolimbic responsiveness to positive material in depressed individuals (30–33).

Incentive processing unfolds over time and includes multiple stages (e.g., cue identification, anticipation, behavioral execution, outcome processing, adjustment). Minimally, anticipation of incentives can be distinguished from consumption (34,35). The second-to-second resolution of event-related FMRI allows investigators to detect changes in subcortical activity during these distinct phases of incentive processing in behaving humans (36). With this method, investigators have found evidence for specialization within the mesolimbic circuit: although anticipation of both primary (e.g., juice) and secondary (e.g., money) rewards increases activation in ventral striatum (including the NAcc), rewarding outcomes instead increase activation in the mesial prefrontal cortex (MPFC), dorsomedial caudate, and posterior cingulate (37,38). To date, neural responses during reward anticipation and outcomes have not been examined in depressed individuals (although anticipatory activation has been examined in depressed children [39]). Thus, the primary goal of this preliminary study was to examine neural responses to anticipated and actual gain outcomes in a sample of unmedicated adults diagnosed with MDD.

In addition to the NAcc, recent findings have also implicated the dorsal anterior cingulate cortex (ACC) in incentive processing and, particularly in conflict monitoring, engagement of control and incentive-guided behavioral selection (40,41). Investigators have proposed that the ACC activates under conditions of risk (i.e., involving potential gains but also potential loss) when behavioral errors are more likely (42). In this context, a second goal of the present study was to examine ACC activation in a

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situation with the potential for affectively conflicting outcomes (i.e., anticipation of gain) in depressed individuals. To the extent that anticipation of gain introduces mood-incongruent conflict in depressed individuals (43), we predicted that they would show increased ACC activation.

Methods and Materials

Participants

Fourteen individuals (5 male) diagnosed with MDD but no other current Axis I Disorders with the Structured Clinical Interview for DSM (44) and 12 individuals (4 male) with no history of any Axis I disorder participated in the present study. All participants spoke fluent English and ranged in age from 18 to 48 years. Approximately one-half of the MDD participants were recruited from two outpatient university hospital psychiatry clinics, whereas the other one-half were self-referred from the community. Participants reported no reported lifetime history of brain injury or primary psychotic ideation, no current diagnoses of panic disorder or social phobia, and no behavioral indications of impaired mental status or mental retardation. Participants were also excluded if they met criteria for alcohol or substance dependence or showed signs of alcohol or substance abuse within the past 6 months. Participants who were currently taking psychotropic medication (including antidepressant drugs) or who had taken psychotropic medication < 3 months before the scan were excluded, so that potential group differences could not be attributed to medication effects. No participants had received electroconvulsive therapy. Potential control (CTL) participants were excluded from the study on the basis of the same general and medical criteria adopted for MDD participants or if they had a lifetime diagnosis of any Axis I disorder. The CTL and MDD participants did not differ in terms of age, handedness, or verbal ability (a proxy for general intelligence; Table 1).

Three trained psychology graduate students and 2 post-baccalaureate research assistants administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) to all participants. On the basis of a random sample of 15 diagnostic interviews, inter-rater reliability for the SCID was r = .96. The Global Assessment of Functioning Scale (GAF, Axis V, DSM-IV; American Psychiatric Association 1994) was also administered to all participants. The GAF provides a reliable rating of psychological, social, and occupational functioning that correlates robustly with other measures of illness severity (12,45). Inter-rater reliability for the GAF in the present study was high (r = .92). Participants also completed the Beck Depression Inventory II (46), which provided a continuous measure of depressive symptoms.

Table 1. Demographic and Clinical Information and Behavioral Results

	CTL (n = 12)	MDD (n = 14)
Age (yrs)	28.67 (4.25)	30.71 (8.80)
Handedness (EHI)	37.11 (20.49)	49.91 (10.13)
Shipley Vocabulary	34.75 (1.07)	34.62 (3.46)
GAF	86.92 (3.80)	51.79 (7.74)[a]
BDI	.50 (.80)	25.38 (7.88)[a]
Total Earnings ($)	53.94 (19.80)	65.07 (29.97)
Hit Rate (% overall)	68 (15)	74 (14)
RT (sec overall)	202.81 (19.31)	201.15 (18.46)

CTL, never-depressed control participants; MDD, Major Depressive Disorder; EHI, Edinburgh Handedness Inventory; GAF, Global Assessment of Functioning, BDI, Beck Depression Inventory; RT, reaction time.

[a]Significant difference at $p < .001$ (two-tailed).

Monetary Incentive Delay Task

The monetary incentive delay (MID) task was designed to elicit neural responses to monetary incentive anticipation and outcomes (47). Each of two MID task runs consisted of 90 6-sec trials, yielding a total of 180 trials. During each trial, subjects saw one of nine cue shapes (cue; 250 msec), fixated on a crosshair as they waited a variable interval (anticipation; 2000-2500 msec), and then attempted to respond with a button press during the presentation of a white target of variable duration (target; 160–360 msec). Feedback (outcome; 1650 msec) followed the disappearance of the target, which notified subjects how much money they had gained or lost that trial as well as their cumulative total up to that point. On incentive trials, subjects could either gain or avoid losing money by pressing the button during target presentation. Task difficulty was based on reaction times collected during the practice session before scanning and set such that participants would succeed on approximately 66% of their target responses. The FMRI volume acquisitions were time-locked to cue offset and thus were acquired during anticipatory delay and outcome periods (48).

Cues signaled potential gains (n = 72, denoted by circles), potential losses (n = 72; denoted by squares), or no response requirement (n = 36; denoted by triangles). Gain cues signaled the possibility of winning \$0.00 (n = 18; no lines), \$0.20 (n = 18; one horizontal line), \$1.00 (n = 18; two horizontal lines), or \$5.00 (n = 18; three horizontal lines). Similarly, loss cues signaled the possibility of losing \$0.00 (n = 18; no lines), \$0.20 (n = 18; one horizontal line), \$1.00 (n = 18; two horizontal lines), or \$5.00 (n = 18; three horizontal lines). "No response" trials (n = 36; a triangle) indicated that the subject should not respond during that trial and instead should wait until the appearance of the cue signaling the next trial. Trial types were pseudo-randomly ordered within each run, and runs were counterbalanced across subjects. Subjects were trained for at least 10 min, tested for explicit cue comprehension, and shown the cash they could make during the task before entering the scanner.

FMRI Acquisition

Imaging was performed with a 1.5-T General Electric MRI scanner with a standard quadrature head coil. Twenty-four 4-mm-thick slices (in-plane resolution 3.75 × 3.75 mm, no gap) extended axially from the mid-pons to the top of the skull, providing adequate spatial resolution of subcortical regions of interest (e.g., midbrain, ventral striatum) and omitting only the base of the cerebellum or crown of the skull in some subjects. Functional whole brain scans were acquired every 2 sec with a T2*-sensitive in-/out- spiral pulse sequence (echo time [TE] = 40 msec, flip = 90°) designed to minimize signal dropout at the base of the brain (49). Thus, even in artifact-prone regions (e.g., orbitofrontal cortex, ventral striatum, and amygdala), signal-to-noise ratio was > 40× and percent maximum signal was > 65%. High-resolution structural scans were subsequently acquired with a T1-weighted spoiled grass sequence (repetition time = 100 msec; TE = 7 msec, flip = 90°), which facilitated subsequent localization and co-registration of functional data.

FMRI Analysis

Analyses focused on changes in blood oxygen level dependent contrast (or "activation") that occurred during anticipatory

and outcome periods and were conducted with Analysis of Functional Neural Images (AFNI) software (50). For preprocessing, voxel time series were concatenated across task sessions, interpolated to correct for non-simultaneous slice acquisition within each volume (with sinc interpolation and the most ventral slice as a reference), corrected for three-dimensional motion (with the third volume of the first session as a reference), and slightly spatially smoothed (kernel full-width-at-half-maximal [FWHM] = 4 mm). Visual inspection of motion correction estimates ensured that no subject's head moved more than 2.0 mm in any dimension from one volume acquisition to the next. Data were preprocessed with bandpass filtering (admitting frequencies from 6 to 90 sec) and computation of percent signal change (calculated with respect to the mean activation over the entire experiment in each voxel).

Preprocessed time series data for each individual were analyzed with multiple regression (51). The regression model included a set of four orthogonal regressors of interest: anticipation of gain (i.e., +$0.20, +$1.00, or +$5.00) versus nongain (i.e., +$0.00, still requiring a response), anticipation of loss (i.e., −$0.20, −$1.00, or −$5.00) versus nonloss (−$0.00), gain versus nongain outcomes, and nonloss versus loss outcomes. Additional covariates included one regressor that contrasted anticipation of making a response (i.e., on incentive trials) versus no response; two orthogonal regressors highlighting each trial period of interest (i.e., anticipation and outcome); six regressors describing residual motion; and six regressors modeling baseline, linear, and quadratic trends for each experimental session. Regressors of interest were convolved with a γ-variate function that modeled a prototypical hemodynamic response (52) before inclusion in the model. Maps of t statistics representing each of the regressors of interest were transformed into Z scores, slightly spatially smoothed (kernel FWHM = 4 mm) and spatially normalized by warping to Talairach space. Statistical maps were then generated for the CTL and MDD groups with a meta-analytic formula and thresholded with a criterion adopted in prior studies of the MID task to correct for multiple comparisons in subcortical, anterior insular, and mesial prefrontal gray matter regions ($Z > 3.88$, $p < .05$ corrected for 500 comparisons, minimum cluster = four 4 mm^3 voxels) (47).

Group data were compared in two ways. First, direct t tests compared contrast coefficient maps across groups. Four 8-mm diameter spherical volumes of interest (VOIs) were compared in these t tests for gain versus nongain anticipation: bilateral NAcc, MPFC, and dorsal ACC. The t test comparisons tested for significant group differences in averaged activation extracted from each of these bilaterally averaged VOIs at $p < .0167$ (correcting for three comparisons). Second, for verification, peak signal change (4-sec lag) was extracted from these VOIs and averaged by trial type (53). Peak signal change was then compared with mixed-model analyses of variance (ANOVAs) with incentive valence (positive, negative) and magnitude ($0.00, $0.20, $1.00, $5.00) as within-subject factors and diagnostic group (CTL, MDD) as the between-subjects factor.

Behavior and Affect

Reaction times and hit rates were recorded on each trial of the MID task. Mixed-model ANOVAs of hit rates and reaction times were conducted for different trial types, with incentive valence (gain, loss) and magnitude ($0.00, $0.20, $1.00, $5.00) as within-subject factors and diagnostic group (CTL, MDD) as the between-subjects factor. After completing the MID task, participants rated their affective reactions to each of the incentive cues (i.e., happiness, excitement, unhappiness, fear) on 4-point Likert scales. Ratings for positive (i.e., happiness and excitement) and negative (i.e., unhappiness and fear) arousal were averaged to maximize reliability. Mixed-model ANOVAs of hit rate and affect were conducted, with incentive valence (gain, loss) and magnitude ($0.00, $0.20, $1.00, $5.00) as within-subjects factors and group (CTL, MDD) as the between-subjects factor. We also examined possible group differences in head motion by conducting t tests on the SDs of motion estimates (i.e., Right-Left [RL], Anterior-Posterior [AP], and Superior-Inferior [SI] displacements).

Results

Participant Characteristics

As expected, MDD participants scored lower in general functioning and higher in depressive symptomatology than CTL participants (Table 1). Whereas the GAF scores of the MDD participants indicated the presence of serious symptoms and impairment, the GAF scores of the CTL participants reflected absent or minor symptoms. The MDD participants had a mean of four previous depressive episodes. The groups did not differ in terms of age, handedness, or vocabulary scores.

Behavior and Affect

The three-way ANOVA conducted on hit rate yielded no significant main effects or interactions, indicating comparable performance on the MID task in the two groups. Similarly, the three-way ANOVA conducted on reaction time yielded only a significant main effect of magnitude [$F(3,69) = 6.65$, $p < .001$], with no other significant effects. The three-way ANOVA conducted on cue-elicited positive arousal yielded significant main effects of valence [$F(1,23) = 25.56$, $p < .001$] and magnitude [$F(3,69) = 19.70$, $p < .001$] and the predicted interaction of valence × magnitude [$F(3,69) = 7.57$, $p < .001$] but no effects of diagnosis. Similarly, the ANOVA conducted on cue-elicited negative arousal also yielded only significant main effects of valence [$F(1,23) = 23.11$, $p < .001$] and magnitude [$F(3,69) = 13.05$, $p < .001$], with a trend toward the predicted interaction of valence × magnitude [$F(3,69) = 2.72$, $p < .06$] but no effects of diagnosis. Finally, t tests indicated that there were no significant group differences in overall head motion in any of the three dimensions. Together, these findings indicated that MDD and CTL participants showed similar behavioral performance, similar affective reactions to cues, and similarly low levels of movement across different incentive conditions.

Brain Activation

Gain Versus Nongain Anticipation. Anticipation of gain (all amounts) versus nongain activated foci in the NAcc in both CTL and MDD participants (Figure 1), extending to other parts of the striatum (i.e., caudate and putamen) and thalamus. In addition, MDD participants showed prominent activation in dorsal mesial cortical regions extending from the ACC through the supplementary motor area to the more posterior motor cortex. The MDD participants also showed increased activation at foci in the parahippocampal gyri and parietal cortex (Supplement 1).

Loss Versus Nonloss Anticipation. Anticipation of loss (all amounts) versus nonloss activated foci in lateral cortical regions including the middle and inferior frontal gyri and parietal regions as well as subcortical foci in the insula, caudate, and thalamus for both CTL and MDD participants.

Gain Versus Nongain Outcomes. Gain versus nongain outcomes activated foci in the MPFC and posterior cingulate cortex in both CTL and MDD participants as well as subcortical foci in

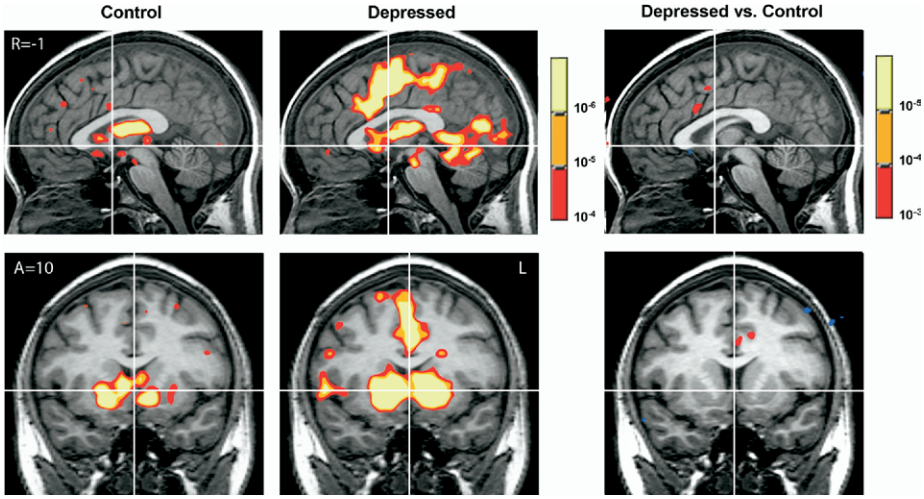

Figure 1. Gain versus nongain anticipation contrasts for control (n = 12; left), depressed (n = 14; middle), and depressed versus control participants (right).

the caudate and hippocampus. In addition, the putamen and sublenticular extended amygdala were activated in CTL participants.

Nonloss Versus Loss Outcomes. Nonloss versus loss outcomes activated the middle frontal gyri, parietal cortex, and sublenticular extended amygdala and putamen in CTL participants. Only the caudate head was activated in MDD participants.

Group Comparisons. Group analyses suggested greater activation in the anterior cingulate for MDD participants during gain anticipation and possibly in the striatum for CTL participants in response to gain outcomes. To verify these potential group differences, we conducted t tests to directly compare CTL and MDD participants' activation in bilateral VOIs in the NAcc, MPFC, and ACC. Consistent with the single group maps, these direct comparisons revealed greater activations for MDD than for CTL participants during gain versus nongain anticipation contrasts not in the NAcc but rather in regions occupying the mesial wall of the prefrontal cortex, including the dorsal ACC (Table 2). The CTL participants showed greater activation than did MDD participants in the MPFC, putamen, and insula in response to gain outcomes. There were no significant group differences in activation of these VOIs for other contrasts (Figure 1).

VOIs

NAcc (± 10, 10, −2). To verify an absence of group differences in NAcc activation during gain anticipation, we directly analyzed peak activation extracted from NAcc VOIs during anticipation. A mixed-model ANOVA (valence × magnitude × diagnostic group) yielded significant main effects of valence [$F(1,24) = 6.14$, $p < .05$] and magnitude [$F(3,72) = 12.78$, $p < .001$] and a significant interaction of valence × magnitude [$F(3,72) = 3.53$, $p < .05$] but no main effect or interactions involving diagnostic group (Figure 2).

ACC (± 8, 11, 34). To examine group differences in ACC activation, we directly analyzed peak activation extracted from ACC VOIs during anticipation. A mixed-model ANOVA (valence × magnitude × diagnostic group) yielded a significant main effect of magnitude [$F(3,72) = 4.43$, $p < .01$], qualified by a significant interaction of valence and diagnostic group [$F(1,24) = 4.70$, $p < .05$]. A linear trend analysis indicated that, whereas CTL participants showed a linear increase in ACC activation during anticipation of losses, MDD participants instead showed a linear increase in ACC activation during anticipation of gains [$F(1,24) = 4.25$, $p = .05$; Figure 2].

Table 2. Comparison of Depressed Versus Control Participants

	Region	R	A	S	Peak Z
Gain vs. Non Anticipation	L Superior Frontal Gyrus (BA 8)	−31	17	50	−4.10
	L Anterior Cingulate (BA 32)	−11	11	34	3.21
	L Precentral Gyrus (BA 6)	−51	−3	24	3.71
	R Postcentral Gyrus (BA 6)	43	−15	32	5.05
Loss vs. Non Anticipation	N/A				
Gain vs. Non Outcome	R MPFC (BA 32)	8	40	4	−3.20
	L Insula (BA 47)	−31	25	−6	−4.32
	R Putamen	13	9	8	−3.57
	L Putamen	−19	5	6	−4.48
	L Superior Frontal Gyrus (BA 6)	−17	3	62	−3.95
	L Insula (BA 13)	−41	−25	16	−3.30
	L Postcentral Gyrus (BA 3)	−33	−33	58	−3.74
	L Inferior Parietal Lobe (BA 40)	−47	−39	30	−3.91
Non vs. Loss Outcome	L Parahipp. Gyrus	−38	−45	−3	−3.49

Independent t; $p < .016$, uncorrected, cluster = 4; positive Z indicates depressed > control, negative Z indicates control > depressed. A, anterior; BA, Brodmann area; MPFC, mesial prefrontal cortex; R, right; S, superior.

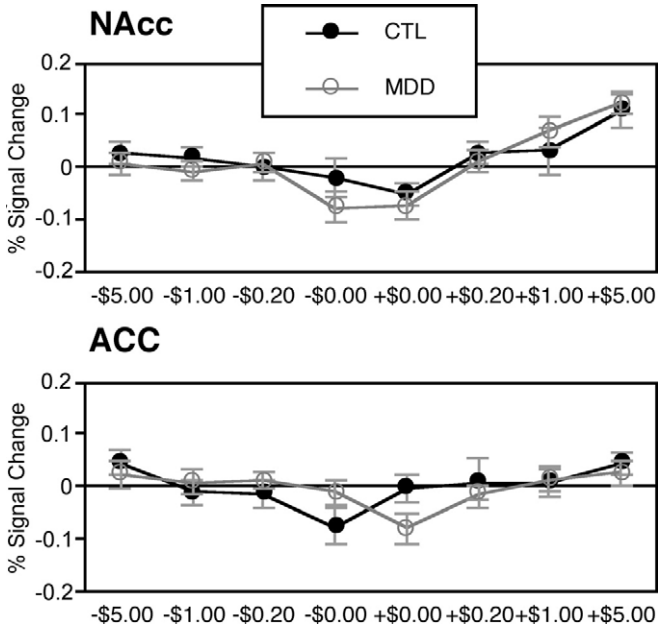

Figure 2. Peak activations by group in nucleus accumbens (NAcc; top) and anterior cingulate (ACC; bottom) volumes of interest (lag = 4 sec; mean ± SEM). CTL, control subjects; MDD, major depressive disorder.

MPFC (± 4, 50, −4). To examine potential group differences in MPFC activation, we directly analyzed peak activation extracted from MPFC VOIs in response to large gain (i.e., +$5.00) versus nongain (i.e., +$0.00) outcomes after anticipation of a +$5.00 gain. A mixed model ANOVA (outcome × diagnostic group) yielded a main effect of outcome [$F(1,24) = 5.03$, $p < .05$] but no significant main effect of diagnosis or interaction of diagnosis × outcome. Thus, unlike statistical maps in the other VOIs, analysis of MPFC peak activation did not support a robust interaction of depression status with responses to gain outcomes.

Brain/Affect Correlations

For each of the large incentive conditions that generated maximum signal (i.e., +$5.00 and −$5.00), cue-induced positive arousal and negative arousal were correlated with cue-induced anticipatory brain activation in the NAcc and ACC VOIs. The +$5.00 cue-induced positive arousal correlated with peak NAcc activation after presentation of the +$5.00 cue across groups [$r(25) = .53$, $p < .01$], replicating previous findings. This positive association did not significantly differ for CTL versus MDD subjects (Figure 3). In contrast, +$5.00 cue-induced negative arousal did not significantly correlate with peak NAcc activation. Neither did −$5.00 cue-induced positive or negative arousal correlate with peak NAcc activation. There were no significant correlations between +$5.00 or −$5.00 cue-induced positive or negative arousal and corresponding anterior cingulate activation in either group.

Discussion

The present study was designed to contrast neural and subjective responses to monetary incentives in unmedicated depressed participants and never-depressed participants. Because affective disturbances are central symptoms of MDD, incentive processing might be altered. Moreover, anticipation represents a critical phase of incentive processing, because it has the potential to influence subsequent thought and behavior (54).

This research yielded three relevant results. First, because depressed individuals have been found to report reduced positive affect (10,12), we predicted that they would show less NAcc activation and positive arousal during anticipation of monetary gains. In this sample of depressed participants, however, findings did not support our hypothesis. Neither NAcc activation nor self-reported levels of positive arousal differentiated depressed from never-depressed individuals during gain anticipation. Instead, both groups of participants showed increased NAcc activation and positive arousal while anticipating large monetary gains, and individual differences in NAcc activation correlated with positive arousal in both groups.

This lack of a difference between depressed and healthy individuals stands in contrast to recent findings comparing clinical samples of unmedicated schizophrenic patients with healthy adults. In event-related FMRI experiments featuring similar-sized samples and the same MID task, unmedicated schizophrenic patients showed marked blunting of NAcc activation during gain anticipation. Furthermore, in schizophrenic individuals, the degree of blunting correlated with severity of anhedonic symptoms (55,56). In contrast, the present findings suggest that unmedicated depressed individuals can recruit both NAcc activation and positive arousal during gain anticipation, at least in a highly structured and rapidly paced task with clearly defined monetary incentives. In the present sample of depressed individuals, anhedonic symptoms might not have been as prominent as in the sample of schizophrenic patients described earlier. Thus, it will be important for future studies to examine the effects of anhedonic symptoms in depressed individuals on incentive processing.

A second finding involved the ACC. Relative to CTL subjects, depressed participants exhibited increasing dorsal ACC activation as they anticipated increasing gains. Control subjects, in contrast, exhibited increasing dorsal ACC activation as they anticipated increasing losses. Anterior cingulate cortex activation has been observed in healthy individuals under conditions involving uncertainty and conflict, when errors are likely (40,57). Activation in a more dorsal and posterior region relative to ACC has been implicated in motor conflict. Because the same button press response was required in all incentive trials and depressed and never-depressed groups did not differ in reaction times or

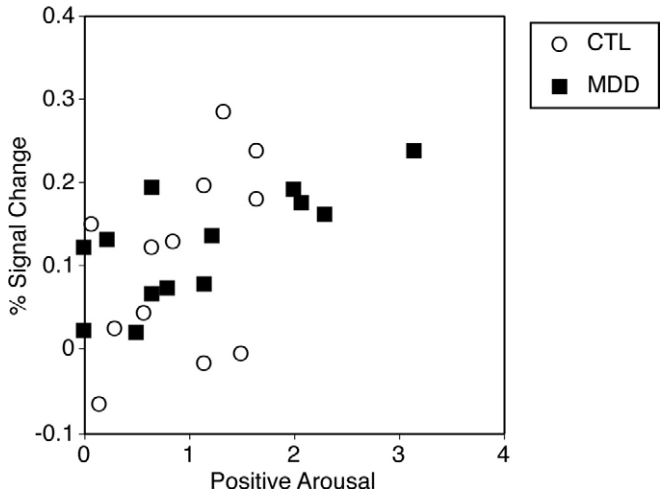

Figure 3. Correlation of +$5.00 cue-elicited peak activation with +$5.00 cue-elicited positive arousal for depressed (MDD) and control (CTL) participants [$r(25) = .53$, $p < .01$].

performance across different conditions, it is unlikely that differences in ACC activation were due to increased motor conflict (as reflected by reaction time). The present findings suggest that, whereas healthy individuals experience more affective conflict during anticipation of avoidable losses, depressed individuals experience more affective conflict during anticipation of attainable gains. If affective conflict in the face of uncertain gains characterizes depression, such a neural marker warrants further investigation.

Indeed, abnormal cingulate function has been implicated in previous research in depression. Cingulotomies (lesions of the ACC near regions observed in this study) are one of the few psychosurgical procedures used to treat intractable and therapeutically unresponsive depression (58). Furthermore, positron emission tomography (PET) studies of depressed patients have documented increased resting ACC activity in a more subgenual region (59,60), and inhibition of subgenual ACC activity can ameliorate refractory depression (61). Subgenual ACC activity has also been found to distinguish depressed from nondepressed individuals during exposure to emotional faces (62) and to predict the response of depressed individuals to therapy (63,64). The present study used event-related fMRI, which resolves faster changes in activation than other imaging modalities (e.g., PET, resting electroencephalogram, or block design fMRI). Further research must determine whether rapid changes in dorsal ACC activation observed in this study can predict therapeutic response or remission. Some brain imaging evidence points to decreased ACC activation in depressed individuals, but these findings might reflect activation in response to positive outcomes rather than anticipatory activation (30).

A third finding involved the MPFC. Although both depressed and nondepressed individuals showed MPFC and dorsal striatal responses to gain outcomes, direct comparisons suggested that this response was weaker for depressed individuals. Volume of interest analyses in predicted regions, however, did not yield a significant group difference, suggesting that this finding requires replication and further exploration. Nonetheless, such a finding would provide a replication in depressed adults of research suggesting reduced activation to gain outcomes in depressed children (39).

In the present study, we examined incentive processing in an unselected sample of individuals diagnosed with MDD. Because previous research suggests that the degree of NAcc activation during gain anticipation might specifically vary with anhedonic symptom profiles (17,33,55,65), future studies might profitably focus on depressed individuals with anhedonic symptom profiles. A strength of the present study is that none of the depressed participants were currently taking psychotropic medication. Future studies might also investigate depressed participants receiving versus not-receiving medication. Because NAcc activation has been linked to dopamine release, it is possible that pharmacotherapeutic interventions that target dopaminergic function might have a more pronounced effect on NAcc activation than drugs that target serotonergic function (66).

In conclusion, the present findings indicate that, although carefully diagnosed unmedicated depressed individuals show similarities to never-depressed CTL participants in their neural and affective responses to monetary incentives, they also show some differences involving increased recruitment of cortical midline structures during gain anticipation and decreased neural responsiveness to gain outcomes. Further research is needed to clarify the role of these differences in the maintenance of and recovery from depression.

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Supplementary material cited in this article is available online.

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