

# Reduced Caudate and Nucleus Accumbens Response to Rewards in Unmedicated Individuals With Major Depressive Disorder

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**Objective:** Major depressive disorder is characterized by impaired reward processing, possibly due to dysfunction in the basal ganglia. However, few neuroimaging studies of depression have distinguished between anticipatory and consummatory phases of reward processing. Using functional MRI (fMRI) and a task that dissociates anticipatory and consummatory phases of reward processing, the authors tested the hypothesis that individuals with major depression would show reduced reward-related responses in basal ganglia structures.

**Method:** A monetary incentive delay task was presented to 30 unmedicated individuals with major depressive disorder and 31 healthy comparison subjects during fMRI scanning. Whole-brain analyses focused on neural responses to reward-predicting cues and rewarding outcomes (i.e., monetary gains). Secondary analyses focused on the relationship between anhedonic symptoms and basal ganglia volumes.

**Results:** Relative to comparison subjects, participants with major depression showed significantly weaker responses to gains in the left nucleus accumbens and the caudate bilaterally. Group differences in these regions were specific to rewarding outcomes and did not generalize to neutral or negative outcomes, although relatively reduced responses to monetary penalties in the major depression group emerged in other caudate regions. By contrast, evidence for group differences during reward anticipation was weaker, although participants with major depression showed reduced activation to reward cues in a small sector of the left posterior putamen. In the major depression group, anhedonic symptoms and depression severity were associated with reduced caudate volume bilaterally.

**Conclusions:** These results suggest that basal ganglia dysfunction in major depression may affect the consummatory phase of reward processing. Additionally, morphometric results suggest that anhedonia in major depression is related to caudate volume.

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Anhedonia—lack of reactivity to pleasurable stimuli—is a core symptom of major depressive disorder (1, 2). Relative to healthy comparison subjects, depressed individuals display reduced positive attentional biases (3), weaker positive affect in response to pleasant stimuli (4), and reduced reward responsiveness (5). Neuroimaging indicates that these deficits may reflect dysfunction in the basal ganglia, including the striatum (nucleus accumbens, caudate, putamen) and the globus pallidus (6–11). However, the functional significance of basal ganglia dysfunction in major depression remains poorly understood. Specifically, whether dysfunction is more closely associated with deficits in the anticipatory or the consummatory phase of reward processing is unclear.

Dissociating these phases is important for two reasons (12). First, they reflect different psychological states: anticipation is characterized by goal-directed behavior, whereas

consummation involves pleasure experience (13). Second, they make separable contributions to goal-directed behavior (14). In nonhuman primates, unexpected rewards elicit phasic bursts in dopamine neurons projecting from the midbrain to the basal ganglia (14). However, the bursts eventually shift from the rewards to reward-predicting cues. Because the basal ganglia are critical for motor control (15), this constitutes a mechanism by which reward-predicting cues can elicit motivated behavior. Given dopamine abnormalities in major depression (16), depression may involve impairments in the anticipatory and/or consummatory components of this mechanism.

To explore this issue, a recent study (17) used a monetary incentive delay task to investigate anticipatory versus consummatory phases of reward processing in 14 participants with major depression and 12 comparison subjects. Surprisingly, there were no group differences in basal gan-

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**TABLE 1. Demographic and Clinical Characteristics of Participants With Major Depressive Disorder and Healthy Comparison Subjects in a Study of Reward Processing**

Characteristic	Comparison Group (N=31)		Major Depression Group (N=30)	
	Mean	SD	Mean	SD
Age (years)	38.80	14.48	43.17	12.98
Education (years)	15.19	1.96	14.87	2.37
Age at onset of major depression (years)			29.39	15.98
Duration of current major depressive episode (months)			37.13	78.24
Number of prior major depressive episodes			3.69	2.64
Beck Depression Inventory–II score <sup>a</sup>	2.20	2.41	27.48	10.60
Hamilton Depression Rating Scale (17-item) score	—	—	17.97	4.90
	N	%	N	%
Female	13	41.9	15	50.0
Caucasian	24	77.4	21	70.0
Married	7	22.6	7	23.3
Employed	18	58.1	12	40.0

<sup>a</sup> Significant difference between groups ( $p < 0.001$ ). Scores were not available for three participants in the major depression group and one in the comparison group.

glia responses to reward cues. Furthermore, although participants with major depression showed bilateral reductions in putamen responses to gains, no outcome-related differences emerged in the accumbens or the caudate, regions implicated in processing reward feedback (18, 19), particularly when reward delivery is unpredictable (20). However, there were also no group differences in behavior. Thus, these null results may have reflected intact reward processing in that particular sample of patients with major depression and/or limited statistical power.

In this study, we used a similar task to probe anticipatory and consummatory phases of reward processing in a larger group of unmedicated depressed individuals (N=30) and healthy comparison subjects (N=31). To permit a balanced design, the task was modified such that 50% of reward and loss trials ended in monetary gains and penalties, respectively (21). Given the role of dopamine and the basal ganglia in reward anticipation (22), we predicted that depressed individuals would show blunted responses to reward cues, particularly in the ventral striatum. However, based on prior findings (17), and because gains would be delivered in only 50% of reward trials (20), we hypothesized that participants with major depression might primarily show impaired striatal responses to rewarding outcomes. Finally, in light of recent work (23), we predicted that greater anhedonic symptoms would be associated with smaller caudate volumes.

## Method

### Participants

Depressed individuals were recruited from a treatment study comparing the effectiveness of the dietary supplement S-adenosyl-L-methionine and escitalopram. Comparison subjects were recruited from the community. Participants with major depression had a DSM-IV diagnosis of major depressive disorder according to the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID; 24) and had a score  $\geq 16$  on the 21-item Hamilton Depression Rating Scale (HAM-D; 25). Exclusion criteria were any psychotropic medication in the past 2 weeks, fluoxetine in the past 6 weeks, or dopaminergic drugs or neuroleptics in the past 6 months; a current or past history of major depressive disorder

with psychotic features; and presence of other axis I diagnoses (including lifetime substance dependence and any substance use disorder in the past year), with the exception of anxiety disorders. Comparison subjects reported no medical or neurological illness, no current or past psychopathology (according to the SCID), and no use of psychotropic medications. All participants were right-handed.

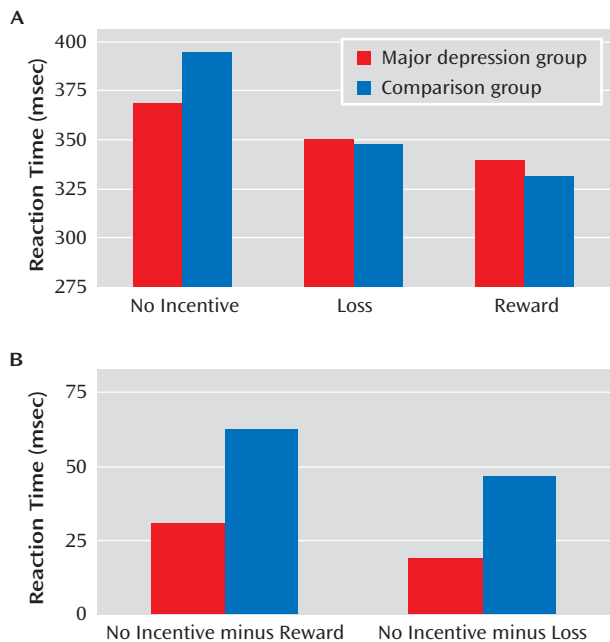
The final sample included 30 participants with major depression and 31 demographically matched comparison subjects (Table 1). Participants with major depression were moderately depressed, as assessed by the Beck Depression Inventory–II (BDI; 26) (mean score=27.48 [SD=10.60]) and the 17-item HAM-D (mean score=17.97 [SD=4.19]). Eleven depressed participants had a current anxiety disorder, and three had subthreshold anxiety symptoms. In the major depression group, 11 participants (37%) had never received antidepressants and 16 (53%) reported prior antidepressant use; information about prior antidepressant treatment was unavailable for three individuals. Only three individuals reported resistance to a prior antidepressant. All participants provided written informed consent to a protocol approved by the Committee on the Use of Human Subjects in Research at Harvard University and the Partners Human Research Committee.

### Monetary Incentive Delay Task

The task has been described previously (21). Trials began with a visual cue (1.5 seconds) indicating the potential outcome (reward: +\$; loss: -\$; no incentive: 0\$). After a variable interstimulus interval (3–7.5 seconds), a red target square was briefly presented, to which subjects responded by pressing a button. After a second delay (4.4–8.9 seconds), visual feedback (1.5 seconds) indicated trial outcome (gain, penalty, no change). A variable interval (3–12 seconds) separated the trials. The task involved five blocks with 24 trials (eight per cue), yielding 40 and 20 trials for cue- and outcome-related analyses, respectively.

Participants were told that responding rapidly would maximize their chances of obtaining gains and avoiding penalties. However, gains and penalties were actually delivered in a predetermined pattern to allow a balanced design. For each block, half the reward trials yielded a monetary gain (range=\$1.96–\$2.34; mean=\$2.15) and half ended with no-change feedback. Similarly, half the loss trials yielded a monetary penalty (range=\$1.81–\$2.19; mean=\$2.00), and half resulted in no change. No-incentive trials always ended with no-change feedback. To maximize feedback believability, target duration was longer for trials scheduled to be successful (i.e., gains on reward trials) than for those scheduled to be unsuccessful (i.e., no-change feedback on reward trials). Furthermore, target durations were individually titrated on the basis of data collected on re-

**FIGURE 1. Behavioral Findings During the Monetary Incentive Delay Task in Participants With Major Depression (N=30) and Healthy Comparison Subjects (N=31)<sup>a</sup>**



<sup>a</sup> Panel A, reaction time in response to the target as a function of reward, loss, or no-incentive cue. Panel B, reaction time difference scores (no-incentive minus reward cue; no-incentive minus loss cue) reveal significantly reduced relative reaction time speed in the major depression group for reward trials ( $p < 0.047$ ) and a similar tendency for loss trials ( $p = 0.053$ ).

action time during a practice session (see the data supplement that accompanies the online edition of this article).

### Procedure

Data collection occurred prior to start of treatment. After blocks 2 and 4, participants rated their affective response to cues and outcomes for valence (on a scale ranging from 1=most negative to 5=most positive) and arousal (from 1=low intensity to 5=high intensity). Participants were compensated \$80 for their time and “earned” \$20–\$22 from the task.

### Data Acquisition

Data were collected on a 1.5-T Symphony/Sonata scanner (Siemens Medical Systems, Iselin, N.J.) and consisted of a  $T_1$ -weighted MPRAGE acquisition (repetition time=2730 msec; echo time=3.39 msec; field of view=256 mm; voxel dimensions=1×1×1.33 mm; 128 slices) and gradient echo  $T_2^*$ -weighted echoplanar images, which were acquired using an optimized pulse sequence (21) (repetition time=2500 msec; echo time=35 msec; field of view=200 mm; voxel dimensions=3.125×3.125×3 mm; 35 interleaved slices).

### Data Reduction and Statistical Analyses

**Reaction time and affective ratings.** After removal of outliers (responses exceeding three standard deviations from the mean), reaction time data were entered into a group-by-cue-by-block analysis of variance (ANOVA). For brevity, only effects involving group or cue are reported. Affective ratings were averaged across the two assessments and entered into group-by-cue or group-by-outcome ANOVAs.

**Functional and structural MRI.** Analyses were conducted using FreeSurfer and FreeSurfer Functional Analysis Stream (FS-FAST) (27; <http://surfer.nmr.mgh.harvard.edu>). Preprocessing included slice-time and motion correction, removal of slow trends with a second-order polynomial, intensity normalization, and spatial smoothing (6 mm full width at half maximum); a temporal whitening filter was used to correct for autocorrelation in the noise. Data for four participants in the major depression group were lost because of excessive motion (>5 mm), leaving 26 individuals with major depression and 31 comparison subjects for fMRI analysis. Before group analyses were conducted, the data were resampled into the Montreal Neurological Institute MNI305 space (voxel size=2 mm<sup>3</sup>).

Functional data were analyzed using the general linear model. The hemodynamic response was modeled as a gamma function and convolved with stimulus onsets; motion parameters were included as nuisance regressors. Between-group whole-brain random-effects comparisons were computed for reward anticipation (reward cue versus no-incentive cue) and reward outcome (gain versus no-change feedback on no-incentive trials) contrasts. Note that because of the double subtraction, clusters exceeding the statistical threshold show a significant group-by-condition interaction. Secondary analyses of loss-related contrasts are reported in the online data supplement. Because of a priori hypotheses about the basal ganglia, activation maps were thresholded using a peak voxel criterion of  $p < 0.005$  with a minimum cluster extent of 12 voxels; Monte Carlo simulations were performed to confirm that the primary findings held after correction for multiple comparisons (see the online data supplement). Findings emerging outside the basal ganglia should be considered preliminary. To assess whether findings in a priori regions were specific to rewards, follow-up group-by-condition ANOVAs were conducted on averaged beta weights (including for penalties) extracted from clusters showing group differences.

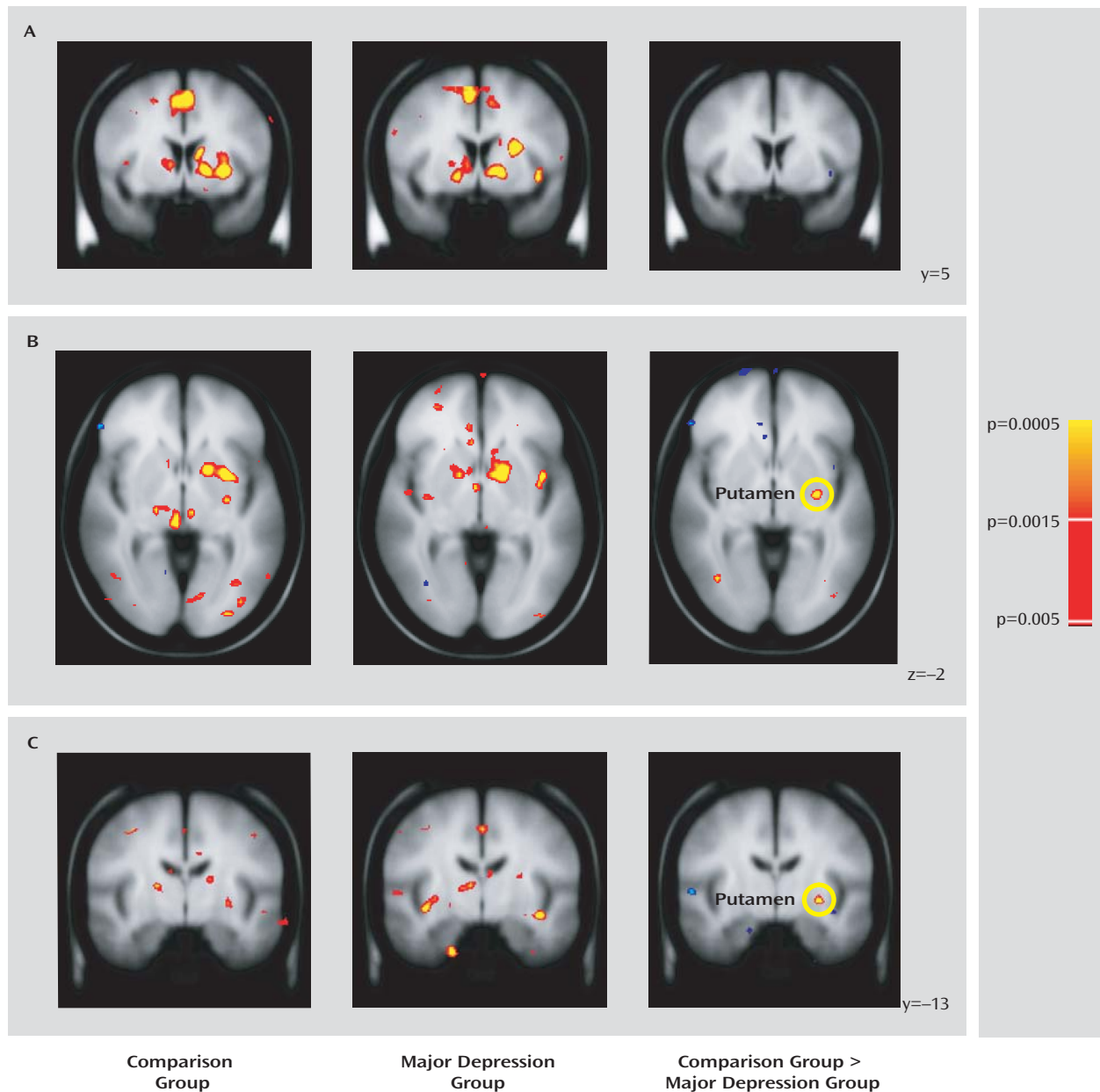
**Structural MRI.** Morphometric analyses used FreeSurfer’s automated parcellation approach (27, 28; see Table S1 in the online data supplement) and focused on the basal ganglia. To account for differences in cranial size, volumes were divided by the intracranial volume and entered into a group-by-hemisphere-by-region (nucleus accumbens, caudate, putamen, and globus pallidus) ANOVA. Significant effects were followed up with post hoc  $t$  tests. For participants with major depression, Pearson correlations and hierarchical regressions (controlling for age and gender) were conducted to examine relationships between volumes and anhedonic symptoms or depression severity. As in prior work (29), anhedonia was assessed by computing a BDI anhedonia subscore (loss of pleasure, interest, energy, and libido; reliability coefficient:  $\alpha = 0.85$ ).

## Results

### Reaction Time

A main effect of cue emerged ( $F = 30.15$ ,  $df = 2, 118$ ,  $p < 0.0001$ ), reflecting motivated responding (shorter reaction time) on reward and loss trials versus no-incentive trials. The main effect of group was not significant, indicating that the comparison and major depression groups showed similar overall reaction time (mean=350.38 msec [ $SD = 68.91$ ] and mean=357.01 msec [ $SD = 75.60$ ], respectively; see the online data supplement). These effects were qualified by a significant group-by-cue interaction ( $F = 3.98$ ,  $df = 2, 118$ ,  $p < 0.045$ ). As evident from Figure 1A, the interaction reflected smaller reaction time differences on incentive versus no-incentive trials in the major depression

**FIGURE 2. Reward-Related Anticipatory Activation in Participants With Major Depression (N=26) and Healthy Comparison Subjects (N=31)<sup>a</sup>**



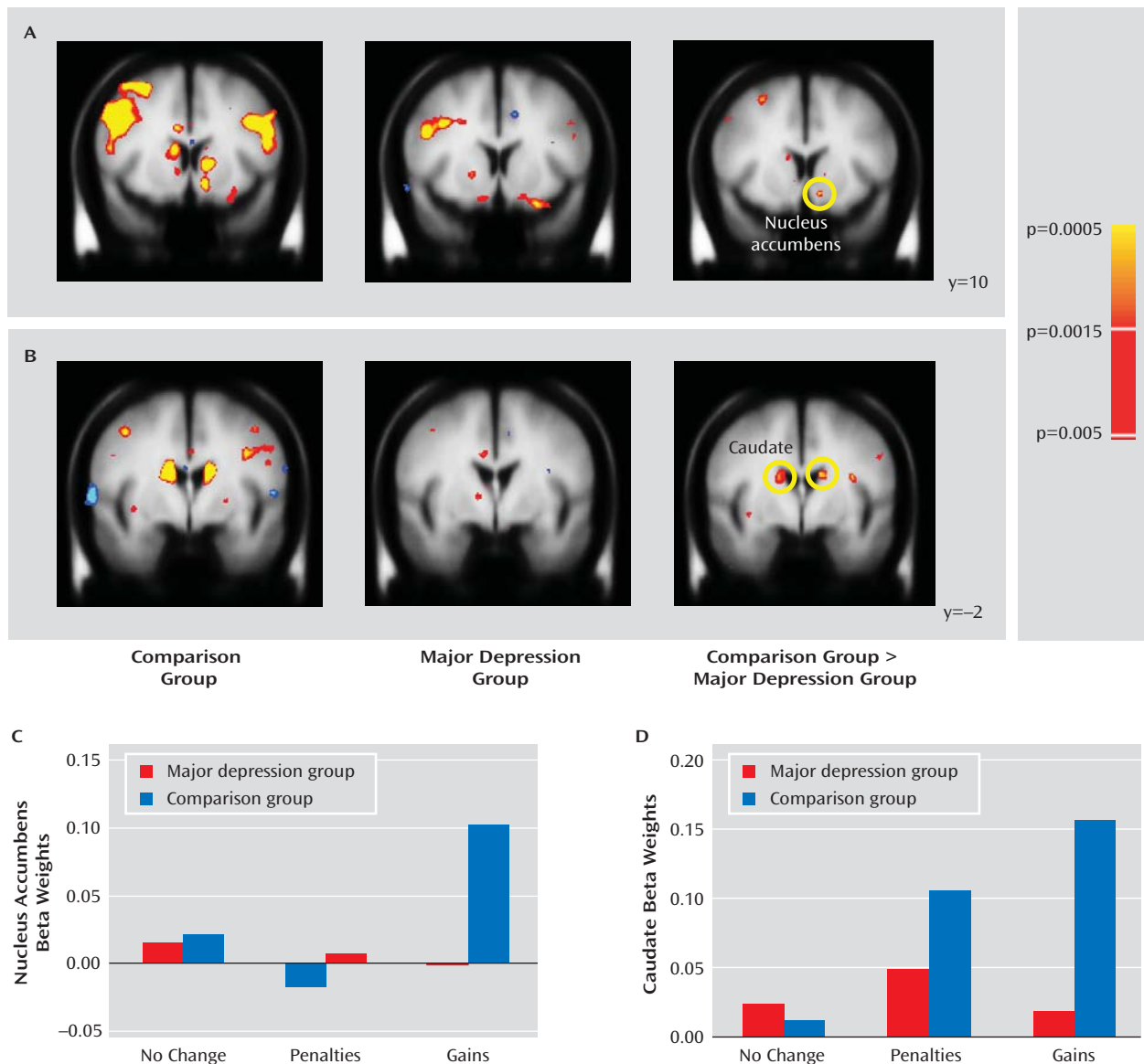
<sup>a</sup> Coronal (panels A, C) and axial (panel B) slices showing anticipatory reward activity (reward cue minus no-incentive cue) in basal ganglia regions are displayed for both groups as well as for the random-effects analyses comparing the two groups. Panel A shows robust activation of ventral striatal regions, including the nucleus accumbens, in both groups, leading to a lack of group differences. In panels B and C, relative to the comparison group, the major depression group shows significantly reduced activation during reward anticipation in the left putamen ( $x=-28$ ,  $y=-13$ ,  $z=-2$ ). All contrasts are thresholded at  $p<0.005$ . Left hemisphere is displayed on the right.

group. Relative to comparison subjects, participants with major depression showed weaker reward-related reaction time modulation (reaction time in no-incentive trials minus reaction time in reward trials;  $t=-2.09$ ,  $df=59$ ,  $p<0.047$ ), with a similar tendency for loss-related reaction time modulation ( $t=-1.97$ ,  $df=59$ ,  $p=0.053$ ) (Figure 1B). However, no group differences in reaction time emerged for reward, loss, or no-incentive trials ( $p$  values  $>0.21$ ).

Moreover, both groups showed the shortest reaction time to reward cues, followed by loss and no-incentive cues ( $p$  values  $<0.002$ ).

Mirroring the lack of group effect in reaction times collected during scanning, groups did not differ in target durations linked to successful or unsuccessful outcomes, which were selected on the basis of reaction time during practice (see the online data supplement). There were also

FIGURE 3. Reward-Related Consummatory Activation in Participants With Major Depression (N=26) and Comparison Subjects (N=31)<sup>a</sup>



<sup>a</sup> Coronal slices showing consummatory reward activity (gain feedback minus no-change feedback) in basal ganglia regions are displayed for both comparison subjects and participants with major depression as well as for the random-effects analyses comparing the two groups. Relative to the comparison group, the major depression group showed significantly reduced activation in response to gain feedback in the left nucleus accumbens (panel A) and the caudate bilaterally (panel B). Follow-up analyses on beta weights extracted from the nucleus accumbens (panel C) and caudate regions bilaterally (panel D) (averaged across three clusters that survived correction for multiple comparisons) indicated that group differences were specific to reward outcome. All contrasts are thresholded at  $p < 0.005$ . Left hemisphere is displayed on the right.

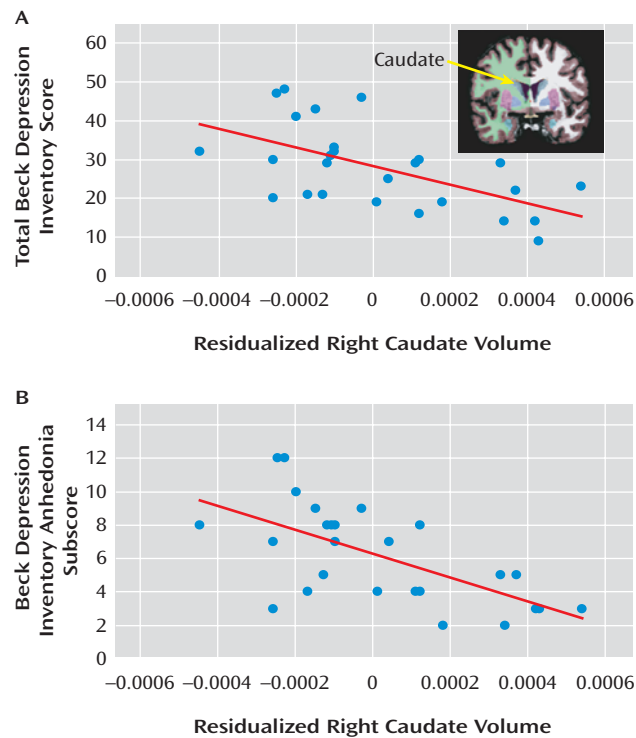
no group differences in the percentage of reward trials ending in gains or of loss trials ending in penalties, or in total money earned (see Table S2 in the online data supplement). Thus, fMRI findings were not confounded by group differences in task difficulty.

**Affective Ratings**

Participants' ratings data indicated that the cues and outcomes elicited the intended responses (see Figure S1

in the online data supplement). Critically, relative to the comparison group, the major depression group reported overall reduced positive affect in response to both cue (group:  $F=5.62$ ,  $df=1, 58$ ,  $p < 0.021$ ) and feedback (group:  $F=12.26$ ,  $df=1, 59$ ,  $p < 0.001$ ) stimuli, as well as reduced arousal in response to gains ( $p < 0.045$ ) but not to penalties or no-change feedback ( $p$  values  $> 0.42$ ; group-by-outcome interaction,  $F=3.20$ ,  $df=2, 118$ ,  $p < 0.045$ ).

**FIGURE 4. Relationship Between Clinical Symptoms and Caudate Volume in Participants With Major Depression (N=26)<sup>a</sup>**



<sup>a</sup> Scatterplot and Pearson correlation between residualized right caudate volume (adjusted for age and gender) and (panel A) total score of the Beck Depression Inventory–II (BDI) ( $r=-0.579$ ,  $p<0.002$ ) and (panel B) BDI anhedonia subscore ( $r=-0.635$ ,  $p<0.0001$ ) for participants with major depression. Similar correlations emerged for the left caudate (total BDI:  $r=-0.489$ ,  $p<0.015$ ; BDI anhedonia subscore:  $r=-0.553$ ,  $p<0.004$ ). The BDI anhedonia subscore was computed by summing items 4 (loss of pleasure), 12 (loss of interest), 15 (loss of energy), and 21 (loss of interest in sex).

### Functional MRI Data

**Reward anticipation (reward cue minus no-incentive cue).** A complete list of regions showing group differences is provided in Table S3 of the online data supplement. Surprisingly, both groups showed robust basal ganglia responses to reward cues (Figure 2A). However, the major depression group showed relatively weaker activation in the left posterior putamen (Figure 2B and C).

**Reward outcome (gain minus no-change feedback).** Relative to comparison subjects, the major depression group showed significantly weaker responses to gain versus no-change feedback in the left nucleus accumbens and the dorsal caudate bilaterally, including two subregions in the right caudate and two in the left caudate (Figure 3A and B). Both clusters in the right caudate and one in the left caudate remained significant after correction for multiple comparisons (see Table S4 in the online data supplement); accordingly, differences in the nucleus accumbens should be considered preliminary. To test whether group differences were specific to reward out-

comes, mean beta weights were extracted from each cluster and entered into group-by-condition (gains, penalties, and no-change feedback) ANOVAs; for the caudate regions of interest, the factor subregion was added. For brevity, only effects involving group are reported.

In the accumbens (Figure 3C), a main effect of condition ( $F=3.46$ ,  $df=2$ ,  $110$ ,  $p<0.040$ ) was qualified by the group-by-condition interaction ( $F=2.94$ ,  $df=2$ ,  $110$ ,  $p=0.063$ ); the main effect of group was not significant. Because of a priori hypotheses regarding the accumbens, and given the significant group-by-condition interaction in the whole-brain analysis, follow-up tests were performed to clarify the source of the interaction. Relative to the comparison group, the major depression group showed significantly weaker responses to gains ( $p<0.005$ ) but not to penalties or no-change feedback. Furthermore, within-group tests showed that while comparison subjects responded more strongly to gains compared with both penalties ( $p<0.004$ ) and no-change ( $p<0.001$ ) feedback, in participants with major depression left accumbens activation was not modulated by condition.

In the caudate (Figure 3D), the ANOVA revealed significant main effects of subregion, condition, and group ( $p$  values  $<0.013$ ), a significant condition-by-subregion interaction and, most important, a significant group-by-condition interaction ( $F=7.89$ ,  $df=2$ ,  $110$ ,  $p<0.002$ ). This interaction was due to significantly greater activation in the comparison versus the major depression group in response to gains ( $p<0.0002$ ) but not to penalties or no-incentive feedback. Moreover, whereas comparison subjects showed increased caudate activation bilaterally in response to both gains and losses ( $p$  values  $<0.0002$ ) relative to no-change feedback, participants with major depression failed to show any feedback-dependent caudate modulation. No correlations emerged between activation in the left putamen, left accumbens, or caudate and anhedonic symptoms in either group.

### Morphometric Data

The group-by-hemisphere-by-region ANOVA revealed no group differences (see Table S5 in the online data supplement). In the major depression group, correlations were run between 1) proportional left accumbens and bilateral caudate volumes and 2) anhedonic symptoms and depression severity. For the left accumbens, no significant effects emerged. For the left and right caudate, volume was inversely related to total BDI score (left:  $r=-0.489$ ,  $p<0.015$ ; right:  $r=-0.579$ ,  $p<0.002$ ) and BDI anhedonia subscore (left:  $r=-0.553$ ,  $p<0.004$ ; right:  $r=-0.635$ ,  $p<0.0001$ ) (Figure 4). Critically, both left and right caudate volumes predicted total BDI score and BDI anhedonia subscore after adjusting for age and gender (total BDI score: left caudate,  $\Delta R^2=0.203$ ; right caudate,  $\Delta R^2=0.309$ ; BDI anhedonia subscore: left caudate,  $\Delta R^2=0.281$ ; right caudate,  $\Delta R^2=0.387$ ; all  $\Delta F >6.09$ ,  $p$  values  $<0.025$ ).

### Control Analyses

In light of group differences in valence ratings for reward cues and valence and arousal ratings for gains, control analyses evaluated whether group differences in left putamen reward cue responses and left accumbens and bilateral caudate gain responses remained after controlling for affective ratings (see the online data supplement). Regression analyses confirmed that this was the case. Moreover, group differences in accumbens and caudate gain responses remained after controlling for the volumes of these structures and group differences in reward-related reaction time modulation. In addition, no significant correlations between reward-related accumbens and caudate activation and the volume of these regions emerged. Finally, there were no differences in basal ganglia activation for participants with major depression with comorbid anxiety (N=14) compared to those without (N=16).

### Discussion

This study investigated anticipatory and consummatory phases of reward processing in depression. Behaviorally, the major depression group showed evidence of anhedonia, reporting generally reduced positive affect to reward stimuli and less arousal following gains. These findings were mirrored by group differences in basal ganglia responses to rewarding outcomes, as participants with major depression showed weaker responses to gains in the caudate bilaterally and in the left nucleus accumbens. By contrast, there was less evidence of differences during reward anticipation. Both groups showed robust basal ganglia responses to reward cues, and although comparison subjects activated the left posterior putamen more strongly than did participants with major depression, the size of the cluster was relatively small. Also, groups did not differ in reaction time as a function of cue, although relatively weaker modulation by reward was seen in participants with major depression (see difference scores). Finally, negative correlations between anhedonic symptoms (and depression severity) and caudate volume emerged in participants with major depression. These findings, which extend previous reports of basal ganglia dysfunction in major depression (6–11, 30), suggest that this dysfunction is more closely associated with consummatory than anticipatory deficits and emphasize a role for reduced caudate volume in anhedonia.

#### **Reduced Basal Ganglia Response to Rewarding Outcomes in Major Depression**

The strong caudate response to gains in comparison subjects fits human (18, 20, 31) and animal (32) studies demonstrating this structure's sensitivity to reward-related information. The caudate responds maximally when rewards are unpredictable (e.g., when delivered on 50% of reward trials, as was done here) and subjects believe that outcomes are contingent on their actions (31). Accordingly,

the between-group caudate difference suggests a weaker perceived action-outcome relationship and/or weaker responses to unpredictable rewards in depression.

Evidence for the first interpretation is mixed. Although groups differed in reward-related reaction time modulation (reaction time difference scores), there was no group difference in reactions on reward trials, and both groups responded faster on reward trials than on loss or no-incentive trials. Thus, both groups behaved as though their responses influenced the chances of receiving gains. Alternatively, the impact of the gains may have been weaker in participants with major depression. This is consistent with the fact that participants with major depression reported overall blunted affective responses and decreased arousal to gains. In addition, group differences were also observed in the left nucleus accumbens, a region that responds strongly to rewarding stimuli (33). Activity in the accumbens appears to track the hedonic value of outcomes (31, 34). Thus, while the group difference in caudate responses suggests a depression-related deficit in expressing goal-directed behaviors, the finding in the accumbens indicates a more primary deficit in hedonic coding. These results are consistent with evidence indicating that deep brain stimulation to the accumbens (35) and ventral capsule/ventral striatum (36) significantly reduced symptom severity and anhedonia in treatment-resistant patients with major depression. Collectively, these findings indicate that dysfunction in regions mediating hedonic impact (accumbens) and reinforcement of actions (caudate) plays an important role in the pathophysiology of major depression.

The group differences in gain responses are intriguing in light of reports of reduced ability to modulate behavior as a function of intermittent rewards in major depression (5). Using a probabilistic reward task, we found that depressed subjects, particularly those reporting anhedonic symptoms, showed a reduced response bias toward a more frequently rewarded stimulus relative to comparison subjects. Furthermore, healthy comparison subjects with blunted response bias in the probabilistic task also generated weak basal ganglia responses to gains in the fMRI task used here (37). These considerations suggest that weak basal ganglia responses to unpredictable rewards may contribute to poor learning of action-reward contingencies in major depression.

#### **Intact Basal Ganglia Responses to Reward Cues in Major Depression**

Surprisingly, both groups showed robust basal ganglia responses to reward cues. However, in contrast to results in a prior study (17), the major depression group in the present study showed weaker reward-related reaction time modulation and affective responses to reward-related stimuli relative to comparison subjects. Thus, behavioral evidence of reward processing deficits can coexist with significant basal ganglia responses to reward-predicting cues.

The nature of the intact basal ganglia response to reward cues in individuals with major depression is unclear. In incentive delay tasks, anticipatory ventral striatal activity is typically regarded as related to the dopamine signal seen in response to reward cues in electrophysiological studies (38). In nonhuman primates, this signal is first elicited by unpredicted rewards and travels back to cues only when a cue-outcome contingency is learned (14). In our study, the comparison group showed a significantly stronger basal ganglia response to gains than the major depression group, yet the two groups showed few differences in response to reward cues. This suggests two possibilities: 1) the unlikely possibility that the dopamine signal traveled from the gains (consummatory phase) to the cues (anticipatory phase) more rapidly in individuals with major depression or 2) the more likely possibility that the reward cues elicited a ventral striatal response on their own that was similar across groups and possibly independent of transmission of the dopamine signal elicited by gains. This possibility is rarely considered in studies using incentive delay tasks, but because participants know that reward cues can lead to gains, it is possible that the cues elicit ventral striatal activation from the outset. However, even if this is the case, a group difference in ventral striatal response to reward cues might still be expected (8). Studies in which participants learn cue-reward associations over time are needed to investigate this issue.

### ***Reduced Caudate Volume and Anhedonia***

Replicating findings with nonclinical subjects (23), participants with major depression who had elevated anhedonic symptoms showed reduced caudate volumes bilaterally. This relationship provides impetus for continued investigation of depressive endophenotypes (1, 2), because it is unclear whether reduced caudate volume predisposes individuals to anhedonic or more severe depression or instead represents a state-related correlate of these symptoms.

### ***Limitations***

Several limitations of this study should be emphasized. First, although the *a priori* hypothesis about the nucleus accumbens (8, 10, 11) was confirmed by a group-by-condition interaction at  $p < 0.005$ , this difference was not significant after correction for multiple comparisons because of the small cluster size (see the online data supplement). Moreover, no correlations between striatal activation and anhedonic symptoms emerged. Consequently, additional studies are needed to confirm the role of the nucleus accumbens in reward dysfunction in major depression. Given mounting interest in the role of the accumbens in the pathophysiology of major depression, as exemplified by recent deep brain stimulation studies targeting this region (35, 36), our finding of reduced reward-related accumbal responses is nevertheless intriguing. Second, correlations between caudate volume and de-

pression severity emerged for BDI score but not HAM-D score. Although the reason for this discrepancy is unclear, it is possible that several BDI items tapping anhedonia contributed to this finding. In spite of these limitations, the current findings indicate that anhedonia, a core component of major depression, may reflect weak reward consummatory responses in the basal ganglia, particularly the nucleus accumbens and the caudate, and is related to reduced caudate size.

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## **Methods**

### Individual titration and optimization of monetary incentive delay task

To increase the believability of the feedback manipulation, the target presentation duration was varied across successful trials (gains on reward trials, no-change on loss trials) and unsuccessful trials (no-change on reward trials, penalties on loss trials). To this end, prior to fMRI collection, participants completed 40 practice trials. For each subject, the 85th and 15th percentiles of the reaction time distribution during practice were used as the target durations on successful and unsuccessful trials, respectively. Because participants were instructed that the outcome of a trial depended on how fast they pressed a button after the appearance of the target, this manipulation served to justify outcome delivery (e.g., unsuccessful outcomes were associated with short target durations to which participants would have difficulty responding to quickly enough). Finally, to maximize task engagement, participants were instructed that good performance would yield an opportunity to play a sixth bonus block associated with increased gains (\$3.63-\$5.18) and infrequent penalties. Every participant “qualified” for the bonus block. This combination of instructions and task design has been shown to lead to sustained task engagement and robust recruitment of brain reward circuitry (S1). Throughout the task, no information regarding cumulative earnings was provided.

The trial sequence was determined using Optseq (<http://surfer.nmr.mgh.harvard.edu/optseq/>) to optimize de-convolution of the hemodynamic response (S2). In addition, inter-stimulus interval and inter-trial interval durations were selected using a genetic algorithm to

maximize the statistical orthogonality of the design and optimize estimation of hemodynamic responses (S3).

#### Functional and structural MRI data collection

Functional data were collected with z-shimming and a tilted slice acquisition (30° from the AC-PC line). This sequence has been shown to increase signal recovery in the orbitofrontal cortex and medial temporal lobes without compromising temporal resolution or overall coverage (S1, S4). Data from the sixth “bonus” block were collected using non-optimized acquisition parameters to assess signal recovery in the behavioral blocks of interest, and are not included in the present analyses. Head movement was minimized with padding.

#### Methods and quality control of the MRI segmentation procedure

Structural labeling of the basal ganglia was achieved using FreeSurfer’s subcortical segmentation procedure (S5), which was run along with the accompanying cortical parcellation algorithms (S6). FreeSurfer’s segmentation processes work by incorporating information about the image intensity of different tissue classes with probabilistic information about the relative location of different brain regions, such that each voxel in a participant’s structural image is assigned a neuroanatomical label (S5, S7). Importantly, the probabilistic information is derived from a training data set that was manually labeled using validated techniques developed by the Center for Morphometric Analysis at Massachusetts General Hospital (e.g., S8, S9). Although FreeSurfer’s steps can be run in fully automated mode and are designed to permit segmentation of very large numbers of brains per day (S5), in the present study they were run in stages and quality control was implemented at three separate points. The first set of quality controls

involved checking that: 1) the participant's T1 image was correctly cross-registered to the MNI305 atlas in Talairach space (to increase the reliability of the probabilistic labeling); 2) a skull stripping procedure used to remove the skull and dura from the image was completed correctly; and 3) intensity normalization of the images was correct such that subsequent intensity-based segmentation steps would be accurate. Problems were rarely detected at any of the quality control points, but they were most frequent at this point and usually consisted of an inaccurate cross-registration and/or incomplete stripping of dura or eyes from around the orbitofrontal cortex. These problems were manually corrected by the second and third authors and the first stage was re-run and re-checked afterwards. The second set of quality controls was done to confirm that: 1) outlines of the pial and white matter surfaces of the brain were correctly drawn; 2) segmentation of white matter was accurate; and 3) the subcortical segmentation—including the segmentation of basal ganglia structures—was complete. Problems at this stage were generally minor and involved small errors in the pial and white matter surfaces (e.g., dura included in the pial surface, incomplete coverage of white matter in the superior temporal lobes). Again, these problems were manually corrected and the stage was re-run and re-checked afterwards. The final set of quality controls consisted of inspection of inflated cortical surfaces and accompanying cortical parcellations (S6). Errors were very rarely detected at this stage, probably due to the careful checks implemented at points one and two.

### Comparisons between manual and automatic anatomical tracings

Findings emerging from recent studies indicate that FreeSurfer's automated approach provides segmentation accuracy comparable to expert manual labeling. For the caudate (i.e., the region emerging from the current study as being significantly related to anhedonic symptoms),

the percent spatial overlap between manual and automated tracings in prior studies ranged from satisfactory (0.76: S10) to excellent ( $>0.85$ ; S5; 0.88: S11). Moreover, the test-retest reliability of FreeSurfer's dorsal striatum volume in a prior study was excellent (0.96; S12).

Of particular relevance to the current study, the Center for Morphometrical Analysis (Massachusetts General Hospital, Boston) recently performed a comparison between FreeSurfer automatic tracing and manual tracing methods of the basal ganglia for a sample of 20 adults recruited from the community (age:  $26.72 \pm 4.83$ , 11 females, 75% Caucasian). Data were collected at the same neuroimaging facility and using a similar MPAGE acquisition protocol (TR/TE: 2530/3.30 voxel dimensions:  $1.33 \text{ mm}^3$ ; flip angle = 7 degrees) as done in the current study. Before tracing, structural data were motion-corrected. As shown in Table S1, Pearson's correlations between the manual and automatic tracing methods were highly significant for the regions emerging from the current study (caudate, putamen, nucleus accumbens). With the exception of the left nucleus accumbens ( $r=0.556$ ) all correlations exceeded  $r=0.78$  (courtesy of Dr. Nikos Makris, Center for Morphometric Analysis, Massachusetts General Hospital, Boston, MA).

#### Correction for multiple comparisons using Monte Carlo simulations

In addition to evaluating results using the voxel and extent thresholds reported in the main text ( $p < .005$ , 12 voxels), between-groups differences in the contrast of primary interest (gains - no change feedback) were examined following correction for multiple comparisons using Monte Carlo simulations (mri\_glmfit program in FS-FAST). To this end, the fMRI data for each subject was replaced with white Gaussian noise that was spatially smoothed to the same degree as the fMRI data, as measured from the residuals from the group analysis. The full

analysis was then performed on this synthetic data set. Clusters were defined as connected sets of voxels whose p-values were less than 0.005 (the voxel-wise threshold). This was repeated 10,000 times to empirically determine the null distribution of the largest cluster size under our experimental conditions. This distribution was then used to compute the p-values of the clusters when the real data were analyzed.

Given our a priori interest in basal ganglia reward responses, the simulation only considered the basal ganglia. A mask of the four basal ganglia regions of interest (nucleus accumbens, caudate, putamen, pallidus) was generated by running the FreeSurfer subcortical segmentation on the high resolution “Collins” brain and then transforming the mask to Talairach space, and the Monte Carlo simulation was restricted to this mask volume. Accordingly, the results of this simulation were used only to determine the significance of findings in basal ganglia regions.

## Results

### Target Presentation Duration

MDD and comparison subjects had very similar 15th and 85th percentile reaction time values during practice, which were used to set target durations on unsuccessful and successful trials, respectively, during the experimental blocks (15th:  $270.43 \pm 42.55$  ms vs.  $272.32 \pm 27.24$  ms,  $t = -0.21$ ,  $df = 59$ ,  $p > 0.83$ ; 85th:  $370.27 \pm 66.46$  ms vs.  $385.52 \pm 83.72$  ms;  $t = -0.79$ ,  $df = 59$ ,  $p > 0.43$ ). In addition, analyses of reaction times collected during fMRI scanning revealed no main effects of *Group* ( $F = 0.17$ ,  $df = 1, 59$ ,  $p > 0.68$ ; see Main Text), due to comparable overall reaction times in comparison ( $350.38 \pm 68.91$ ) and MDD ( $357.01 \pm 75.60$ ) subjects.

### General performance in the Monetary Incentive Delay task

To further evaluate possible group differences in task difficulty, we computed 1) the percentage of reward trials ending in gains, 2) the percentage of loss trials ending in penalties, 3) the total number of errors committed (e.g., pressing the button in response to the cue instead of the target), and 4) the total money won, lost, and earned (i.e., won minus lost). As summarized in Table S2, no group differences emerged. Collectively, analyses of both reaction time and “accuracy” data collected during both the practice and imaging session suggest that fMRI findings were not confounded by group differences in task difficulty.

### Affective ratings

*Anticipation phase.* Due to technical problems, the valence ratings for reward cues were lost for one comparison subject. The ANOVA revealed a main effect of *Group* ( $F = 5.62$ ,  $df = 1, 58$ ,  $p < 0.021$ ) due to overall reduced positive affect in MDD versus comparison subjects ( $2.78 \pm 0.57$

vs.  $3.08 \pm 0.42$ ) (Figure S1, panel A). The *Group* x *Cue* interaction was not significant ( $F=1.54$ ,  $df=2,116$ ,  $p>0.22$ ). A trend for a main effect of *Cue* also emerged ( $F=2.99$ ,  $df=2,116$ ,  $p<0.054$ ), due to significantly more positive valence ratings for the reward ( $3.07 \pm 0.87$ ) versus loss cue ( $2.77 \pm 0.79$ ;  $p<0.035$ ).

For arousal ratings, the ANOVA revealed a main effect of *Cue* ( $F=4.50$ ,  $df=2,118$ ,  $p<0.013$ ), due to increased arousal in response to both reward ( $3.05 \pm 0.69$ ;  $p<0.017$ ) and loss ( $3.07 \pm 0.75$ ;  $p<0.015$ ) cues relative to neutral cues ( $2.81 \pm 0.83$ ). There was no difference in arousal elicited by reward and loss cues ( $p>0.84$ ). Neither the main effect of *Group* ( $F=0.13$ ,  $df=1,59$ ,  $p>0.71$ ) nor the *Group* x *Cue* interaction ( $F=2.32$ ,  $df=2,118$ ,  $p>0.10$ ) was significant (Figure S1, panel B).

*Outcome phase.* For valence ratings, there was a main effect of *Group* ( $F=12.26$ ,  $df=1,59$ ,  $p<0.001$ ) due to significantly less positive ratings in MDD than comparison subjects ( $2.79 \pm 0.44$  vs.  $3.16 \pm 0.38$ ) (Figure S1, panel C). The *Group* x *Outcome* interaction was not significant ( $F=1.38$ ,  $df=2,118$ ,  $p>0.25$ ). Additionally, the main effect of *Outcome* was significant ( $F=191.57$ ,  $df=2,118$ ,  $p<0.0001$ ). As expected, gains elicited significantly more positive ratings ( $4.16 \pm 0.77$ ) than penalties ( $1.80 \pm 0.82$ ;  $p<0.0001$ ) or no-change feedback ( $2.97 \pm 0.47$ ;  $p<0.0001$ ). Moreover, penalties were rated as significantly more negative than no-change feedback ( $p<0.0001$ ).

For arousal ratings, the ANOVA revealed a main effect of *Outcome* ( $F=9.02$ ,  $df=2,118$ ,  $p<0.0005$ ) that was qualified by a significant *Group* x *Outcome* interaction ( $F=3.20$ ,  $df=2,118$ ,  $p<0.045$ ). The main effect of *Group* was not significant ( $F=0.24$ ,  $df=1,59$ ,  $p>0.87$ ). The *Outcome* effect reflected the fact that gains elicited significantly greater arousal ( $3.48 \pm 0.85$ ) than penalty ( $3.08 \pm 1.13$ ;  $p<0.015$ ) or no-change feedback ( $2.87 \pm 0.89$ ;  $p<0.0001$ ), which did not differ from each other ( $p>0.15$ ). Critically, however, relative to comparison subjects, MDD subjects reported



significantly less arousal in response to gains ( $p < 0.045$ ) but not penalties or no-change feedback ( $p > 0.42$ ) (Figure S1, panel D). Moreover, within-group follow-up analyses indicated a lack of modulation for MDD subjects ( $p > 0.16$ ). For comparison subjects, on the other hand, gains elicited significantly more arousal ( $3.69 \pm 0.79$ ) than penalties ( $2.97 \pm 1.12$ ;  $p < 0.0002$ ) or no-change feedback ( $2.81 \pm 0.75$ ;  $p < 0.0002$ ). Collectively, these results show that cue and outcome stimuli generally elicited the intended affective responses, and indicate that MDD subjects experienced less positive affect during the anticipatory and consummatory phases of the task. Moreover, after receiving gains, MDD subjects reported less intense affective responses.

### Secondary fMRI findings

Complete lists of regions showing group differences during incentive anticipation and consummation are presented in Tables S3 and S4, respectively.

*Reward Anticipation (Reward cue – No-incentive cue).* As described in the main text, relative to comparison subjects, MDD subjects showed relatively weaker activation to reward cues in the left posterior putamen. To further investigate this finding, a *Group x Cue* (reward, loss, no-incentive) ANOVA on beta weights extracted from this region was performed. The only significant finding was the *Group x Cue* interaction ( $F = 5.10$ ,  $df = 2, 110$ ,  $p < 0.008$ ). Follow-up tests revealed that, for comparison subjects, both reward (mean =  $0.032 \pm 0.08$ ;  $p < 0.005$ ) and loss (mean =  $0.031 \pm 0.06$ ;  $p < 0.007$ ) cues elicited stronger activation compared to the no-incentive cue (mean =  $-0.019 \pm 0.08$ ). For MDD subjects, on the other hand, reward cues (mean =  $-0.002 \pm 0.10$ ), loss cues (mean =  $0.021 \pm 0.08$ ), and no-incentive cues (mean =  $0.022 \pm 0.07$ ) elicited similar responses, and no cue-related modulation was observed ( $p > 0.21$ ). Follow-up tests revealed that groups differed in their responses to no-incentive ( $p < 0.05$ ) but not reward ( $p > 0.15$ ) or loss

( $p > 0.60$ ) cues. However a between-groups *t*-test of the reward minus no-incentive cue difference was also significant,  $t(55) = -2.96$ ,  $p = .005$ , directly confirming the whole-brain result (comparison: mean= $0.050 \pm 0.09$ ; MDD: mean= $-0.024 \pm 0.10$ ).

Relative to comparison subjects, MDD subjects were characterized by significantly increased bilateral activation in various dorsolateral prefrontal cortex regions encompassing the middle and inferior frontal gyri (Figure S2). For the bilateral clusters ( $x=24, y=22, z=40$ ;  $x=-28, y=24, z=40$ ), beta weights were extracted and entered in a *Group x Hemisphere x Condition* ANOVA. The only significant finding was the *Group x Condition* interaction ( $F=11.00$ ,  $df=2,110$ ,  $p < 0.0001$ ). Follow-up analyses indicated that, relative to comparison subjects, MDD subjects had significantly greater bilateral dorsolateral prefrontal activation to reward ( $p < 0.009$ ) but not loss ( $p > 0.78$ ) or no-incentive ( $p > 0.16$ ) cues (Figure S2). Within-group analyses revealed that comparison subjects were characterized by significantly reduced activation in response to reward relative to no-incentive cues ( $p < 0.015$ ). MDD subjects, on the other hand, showed significantly greater activation in response to reward cues compared to both loss ( $p < 0.025$ ) and no-incentive ( $p < 0.005$ ) cues. The remaining two prefrontal clusters (left inferior frontal gyrus:  $x=-46, y=16$ , and  $z=28$ ; right middle frontal gyrus:  $x=30, y=26, z=29$ ) showed similar patterns.

*Reward Outcomes (Gains – No-change feedback)*. In addition to showing a weaker striatal response to gains relative to comparison subjects, the MDD group also showed significantly weaker activation in the dorsal anterior cingulate cortex ( $x=10, y=18, z=30$ ; Figure S3), a region that has been implicated in integrating reinforcement history over time (S13-S16). Analysis of beta weights (gains, penalties, no-change feedback) extracted from the dorsal anterior cingulate cortex revealed a significant *Group x Condition* interaction ( $F=6.61$ ,  $df=2,110$ ,  $p < 0.002$ ), due to a significant between-group difference (comparison > MDD) for gains

( $p < 0.001$ ) but not penalty or no-change feedback ( $ps < 0.42$ ). Whereas comparison subjects showed significantly greater cingulate activation in response to gains versus no-change feedback ( $p < 0.015$ ), MDD subjects showed a significantly weaker response to gains compared to both penalties and no-change feedback ( $ps < 0.05$ ; Figure S3).

*Loss Anticipation (Loss cue – No-incentive cue).* Relative to comparison subjects, MDD subjects showed significantly increased activation during anticipation of a potential loss in various regions, including the left insula ( $x = -38, y = -7, z = -6$ ), right middle frontal gyrus ( $x = 40, y = 44, z = 8$ ), and dorsal anterior cingulate cortex ( $x = 2, y = 23, z = 16$ ) (Figure S4). Follow-up analyses indicated that MDD subjects activated these regions more strongly in response to loss (and reward) cues relative to no-incentive cues, whereas comparison subjects generally did not show any cue-specific modulation. These observations were corroborated by significant *Group x Condition* interactions for all three regions ( $F_s > 3.39, df = 2, 110, ps < 0.045$ ); for the left insula and right middle frontal gyrus, the main effect of *Condition* was also significant ( $F_s > 6.64, df = 2, 110, ps < 0.002$ ). Within-group analyses indicated that MDD subjects activated the left insula, right middle frontal gyrus, and dorsal anterior cingulate cortex more strongly in response to both loss and reward cues compared to the no-incentive cue (all  $ps < 0.009$ ; Figure S4). Comparison subjects, on the other hand, showed no condition-specific modulation in the right middle frontal gyrus or cingulate (all  $ps > 0.25$ ); for the left insula, comparison subjects showed significantly higher activation to the reward compared to loss cue ( $p < 0.015$ ). The only region showing significantly higher activation for comparison relative to MDD subjects was the cerebellum (Table S2).

*Loss Outcomes (Penalties – No-change feedback).* Relative to comparison subjects, the MDD group was characterized by significantly reduced activation in response to penalties in

various regions, including the bilateral caudate, thalamus, and right prefrontal cortex, among other regions (Table S3). For all these regions, including the left ( $x=-8, y=-2, z=12$ ) and right ( $x=14, y=23, z=11$ ) caudate, the ANOVA revealed significant *Group x Condition* interactions ( $F_s > 3.17, df=2, 110, p_s < 0.047$ ) in the absence of *Group* main effects (Figure S5). Within-group analyses showed that comparison subjects activated both the left and right caudate significantly more to penalties (and gains) versus no-change feedback ( $p_s < 0.05$ ), whereas MDD subjects showed no modulation ( $p_s > 0.15$ ). Moreover, in this left caudate cluster, comparison subjects showed significantly higher activation than MDD subjects to penalties ( $p < 0.015$ ); there was no between-group difference in response to penalties in the right caudate. Relatively increased activation for MDD relative to comparison subjects was observed only in the right cerebellum and left precuneus.

#### Morphometrical Basal Ganglia Data

The absolute and proportional volumes of single basal ganglia regions are listed in Table S5. The *Group x Hemisphere x Region* ANOVA revealed a significant main effect of *Structure* and a *Structure x Hemisphere* interaction, which were not explored further. The main effect of *Group* was not significant ( $F=0.73, df=1, 59, p > 0.35$ ). The only other effect approaching significance was the *Group x Hemisphere x Structure* interaction ( $F=2.47, df=3, 177, p=0.086, \epsilon=0.67$ ). However, follow-up analyses revealed no volumetric group differences (all  $p_s > 0.18$ ).

#### Control analyses

*Analyses comparing MDD subject with (N=14) vs. without (N=16) comorbid anxiety disorders.* For the reaction time data, a *MDD Subgroup* (MDD with vs. without comorbid

anxiety disorder) x *Cue* ANOVA revealed no effects involving *MDD Subgroup* ( $F_s < 0.40$ ,  $p_s > 0.50$ ). For the affective ratings, the only effects of interest were main effects of *MDD Subgroup* for the arousal ratings for both the anticipatory ( $F = 8.57$ ,  $df = 1, 28$ ,  $p < 0.008$ ) and consummatory ( $F = 7.83$ ,  $df = 1, 28$ ,  $p < 0.009$ ) phase, which were due to higher arousal rating for MDD subjects with comorbid anxiety relative to MDD subjects without anxiety comorbidity. No effects involving *MDD Subgroup* emerged for the left putamen (anticipatory phase), left nucleus accumbens (consummatory phase), or caudate (consummatory phase) clusters (all  $F_s < 1.24$ , all  $p_s > 0.29$ ).

*Functional MRI findings adjusted for affective ratings.* For the main regions-of-interest emerging from the whole-brain between-group analyses, hierarchical regression analyses were performed to evaluate whether differences remained after accounting for group differences in the affective ratings. For the left posterior putamen region implicated in reward anticipation, valence ratings in response to the reward cues were entered in the first step, whereas *Group* (dummy-coded) was entered in the second step. For the left nucleus accumbens and bilateral caudate regions emerging from the analyses of gains, valence and arousal ratings in response to gains were entered in the first step, and *Group* was entered in the second step (data from the caudate were first averaged across hemispheres). For all regions the model was significant, indicating that *Group* predicted differences in left putamen ( $\Delta R^2 = 0.104$ ), left nucleus accumbens ( $\Delta R^2 = 0.094$ ), and caudate ( $\Delta R^2 = 0.187$ ) activation above and beyond group differences in affective ratings (all  $\Delta F > 5.74$ , all  $p_s < 0.020$ ).

*Functional MRI findings adjusted for striatal volume.* A second set of hierarchical regression analyses were performed to evaluate whether the group differences in left nucleus accumbens and bilateral caudate responses to gains remained after adjusting for proportional

volume. For both regions (left nucleus accumbens:  $\Delta R^2=0.116$ ; caudate:  $\Delta R^2=0.243$ ), *Group* predicted activation to gains after controlling for volume (all  $\Delta Fs > 7.33$ ,  $ps < 0.009$ ).

*Functional MRI findings adjusted for reward-related reaction time modulation.* A final set of hierarchical regression analyses were performed to evaluate whether the group differences in left nucleus accumbens and bilateral caudate responses to gains remained after adjusting for group differences in reward-related reaction time modulation (no-incentive – reward difference score). For both regions, *Group* uniquely predicted activation to gains after controlling for reaction time differences (left nucleus accumbens:  $\Delta R^2=0.130$ ; caudate:  $\Delta R^2=0.212$ ), (all  $\Delta Fs > 8.10$ ,  $ps < 0.007$ ).

*Corrections for multiple comparisons using Monte Carlo simulations.* Of the five basal ganglia clusters evident at  $p < .005$ , 12 voxel extent, three were significant at  $p < .05$  following correction for multiple comparisons: both clusters in the right caudate and one in the left caudate (Table S4). The second cluster in the left caudate and the left nucleus accumbens cluster were not significant,  $p > .05$ , likely due to their smaller size.

*Correlations between functional MRI and volumetric data.* At the request of an anonymous reviewer, correlational analyses between functional and volumetric data were performed. To this end, beta weights in response to gains were extracted from structurally defined left nucleus accumbens and bilateral caudate regions. The mean beta weight across the entire structure was then correlated with the volume of the region. For both MDD and comparison subjects, no significant correlations emerged for either the nucleus accumbens (MDD:  $r=0.35$ ,  $p > 0.075$ ; comparison:  $r=-0.03$ ,  $p > 0.88$ ) or bilateral caudate (MDD:  $r=0.06$ ,  $p > 0.78$ ; comparison:  $r=-0.09$ ,  $p > 0.65$ ).

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Table S1: Summary of Pearson's correlations between basal ganglia volumes determined by FreeSurfer automatic tracing and manual tracing methods for a sample of 20 community adults (courtesy of Dr. Nikos Makris, Center for Morphometric Analysis, Massachusetts General Hospital, Boston, MA).

<b>Basal Ganglia Volume</b>	<b>Pearson r</b>	<b>p</b>
Right Caudate	0.880	0.0000003
Left Caudate	0.875	0.0000005
Right Putamen	0.932	0.0000001
Left Putamen	0.795	0.0000279
Right Accumbens	0.784	0.0000435
Left Accumbens	0.556	0.0108939

Table S2: Summary of task “performance” in the MID task.

	<b>Comparison</b>	<b>MDD</b>	<b>T</b>	<b>p</b>
	<b>subjects</b>	<b>subjects</b>	<b>statistic</b>	
% Reward trials ending in gains	48.68 (1.76)	48.31 (1.91)	-0.76	0.45
% Loss trials ending in penalties	47.94 (2.68)	47.62 (2.86)	-0.44	0.67
Total number of errors	4.06 (3.92)	4.92 (4.81)	0.74	0.46
Total \$ won	41.72 (1.59)	41.10 (2.46)	-1.14	0.26
Total \$ lost	47.05 (6.50)	49.00 (9.16)	-0.91	0.37
Total \$ earned	-5.13 (7.19)	-7.91 (9.93)	-1.22	0.23

Note: the overall net loss reflects the fact that while gains were slightly larger than penalties, participants were penalized \$2 for each error. The sixth “bonus” block included three large gains (\$3.68, \$4.72, and \$5.18) against one scheduled loss (-\$1.53), so that most participants would experience a net gain. Each participant was paid \$20-22 dollars for playing the game.

TABLE S3. Regions Showing Group Differences Between MDD (N=26) and Comparison Subjects (N=31) During the Anticipation of a Potential Reward or Loss

Region	x	y	z	Volume (mm <sup>3</sup> )	Peak Voxel p value
<b>A. Reward Cue – No Incentive Cue</b>					
<i>Comparison Subjects &gt; MDD</i>					
L Putamen	-28	-13	-2	192	0.0001
R Occipitofrontal Fasciculus	30	-34	32	144	0.0010
R Middle Occipital Gyrus	38	-65	1	136	0.0002
<i>MDD &gt; Comparison Subjects</i>					
R. Uncus/Parahippocampal gyrus	34	-2	-28	128	0.0011
R Inferior Frontal Gyrus	55	34	-3	504	0.0002
L Inferior Frontal Gyrus	-46	16	28	176	0.0012
R Middle Frontal Gyrus	24	22	40	432	0.0001
	30	26	29	304	0.0001
L Middle Frontal Gyrus	-28	24	40	480	0.0003
R. Subgenual Cingulate	12	32	-9	176	0.0004
R. Superior Temporal Gyrus	57	-10	5	120	0.0004
L. Occipitofrontal Fasciculus/Cingulum	-24	30	1	688	0.0002
L. Inferior Parietal Lobule	-24	-36	30	96	0.0007
R. Lingual Gyrus	12	-51	5	352	0.0009
R. Cerebellum	32	-71	-34	160	0.0013
<b>B. Loss Cue – No Incentive Cue</b>					
<i>Comparison Subjects &gt; MDD</i>					
R. Cerebellum	20	-56	-17	96	0.0009
<i>MDD &gt; Comparison Subjects</i>					
L Insula	-38	-7	-6	472	0.0000
R Medial Frontal Gyrus	2	30	40	224	0.0001
L Postcentral Gyrus	-40	-17	31	96	0.0003
Dorsal Anterior Cingulate	2	23	16	176	0.0011
R Posterior Cingulate	6	-20	41	96	0.0002
L Middle Temporal Gyrus	-34	-65	12	248	0.0001
L Lingual Gyrus	-28	-61	-1	296	0.0001

Note: x, y, and z correspond to the Talairach coordinates of the peak voxel. Talairach coordinates

were computed from MNI space using the formula proposed by Brett and coworkers (S9).

Volume = Size of the region exceeding the statistical threshold ( $p < 0.005$ ); R= right; L=left.

TABLE S4. Regions Showing Group Differences Between MDD (n = 26) and Comparison Subjects (n = 31) In Response to Gains and Penalties

Region	x	y	Z	Volume (mm <sup>3</sup> )	Peak Voxel p-value
<b>A. Gain – No-Change Feedback</b>					
<i>Comparison Subjects &gt; MDD</i>					
R Caudate	14	15	11	320	0.0001†
	16	0	19	424	0.0005†
L Caudate	-12	-4	21	336	0.0004†
	-20	-27	19	104	0.0017
L Nucleus Accumbens*	-8	10	-8	64	0.0002
R Insula	32	17	2	120	0.0006
L Insula	-32	-4	20	128	0.0004
R Inferior Frontal Gyrus	50	24	24	160	0.0002
R Middle Frontal Gyrus	20	48	8	384	0.0001
	51	18	37	896	0.0001
	28	15	48	344	0.0001
R Medial Frontal Gyrus	4	47	30	216	0.0005
L Precentral Gyrus	-51	-3	31	264	0.0002
R Rostral Anterior Cingulate	6	29	9	280	0.0005
R Dorsal Anterior Cingulate	10	18	30	136	0.0006
L Posterior Cingulate	-2	-29	28	136	0.0003
R Middle Temporal Gyrus	51	-57	0	408	0.0002
L Cerebellum	-8	-62	-20	208	0.0002
	-16	-76	-24	160	0.0002
<i>MDD &gt; Comparison Subjects</i>					
L Fusiform Gyrus	-40	-14	-25	456	0.00024
<b>B. Penalty vs. No-Change Feedback</b>					
<i>Comparison Subjects &gt; MDD</i>					
R Caudate	14	23	11	296	0.0007
L Caudate	-8	-2	12	168	0.0005
L Thalamus	-18	-25	15	576	0.0001
R Inferior Frontal Gyrus	44	29	20	1472	0.0000
R Middle Frontal Gyrus	30	15	43	152	0.0007
L Precentral Gyrus	-53	-3	31	224	0.0004
L Posterior Cingulate	-2	-13	27	96	0.0012
R Superior Temporal Gyrus	50	10	-11	144	0.0001
R Middle Temporal Gyrus	67	-40	3	640	0.0000
L Middle Temporal Gyrus	-61	-51	7	128	0.0005
L Inferior Occipital Gyrus	-34	-81	-7	128	0.0003
<i>MDD &gt; Comparison Subjects</i>					
L Precuneus	-16	-54	22	440	0.0000
R Cerebellum	30	-76	-26	168	0.0013

Note: x, y, and z correspond to the Talairach coordinates of the peak voxel. Talairach coordinates were computed from MNI space using the formula proposed by Brett and coworkers (S9).

Volume = Size of the region exceeding the statistical threshold ( $p < 0.005$ ); R= right; L=left.

\*8 voxels, did not reach cluster size significance threshold. † Significant at  $p < .05$  following correction for multiple comparisons with Monte Carlo simulation restricted to basal ganglia volume.

TABLE S5. Absolute and proportional volume (adjusted for total intracranial volume) for the four basal ganglia regions for MDD (n = 26) and Comparison (n = 31) subjects. Volumes are expressed in cubic millimeters.

	<b>Comparison</b>		<b>MDD</b>	
	<b>subjects</b>		<b>subjects</b>	
	Mean	SD	Mean	SD
Intracranial volume	1562421	191574	1520071	150388
Absolute volumes				
Left Caudate	3433	447	3427	507
Left_Putamen	5472	732	5550	697
Left_Pallidus	1718	252	1659	248
Left_NAcc	630	114	617	118
Right_Caudate	3592	520	3645	516
Right_Putamen	5369	717	5364	697
Right_Pallidus	1781	279	1658	287
Right_NAcc	548	74	560	128
Proportional volume				
Left_Caudate	0.00221	0.00025	0.00226	0.00027
Left_Putamen	0.00353	0.00044	0.00366	0.00037
Left_Pallidus	0.00111	0.00015	0.00109	0.00013
Left_NAcc	0.00041	0.00009	0.00041	0.00008
Right_Caudate	0.00231	0.00027	0.00240	0.00027
Right_Putamen	0.00346	0.00040	0.00354	0.00038
Right_Pallidus	0.00114	0.00015	0.00109	0.00016
Right_NAcc	0.00035	0.00006	0.00037	0.00007

NAcc = nucleus accumbens

FIGURE S1. Affective ratings during the monetary incentive delay task in MDD (N=30) and comparison (N=31) subjects. **(A)** Cue-related valence ratings; **(B)** cue-related arousal ratings; **(C)** outcome-related valence ratings; and **(D)** outcome-related arousal ratings collected during the task (averaged across the assessments occurring after blocks 2 and 4). Ratings were made using 5-point scales to evaluate affective response to the cues and outcomes with respect to valence (e.g., “Please rate how you felt while waiting to push the button on a reward trial”; 1=most negative feeling, 5=most positive feeling) and arousal (e.g., “Please rate the strength of this feeling”; 1=low intensity, 5=high intensity).

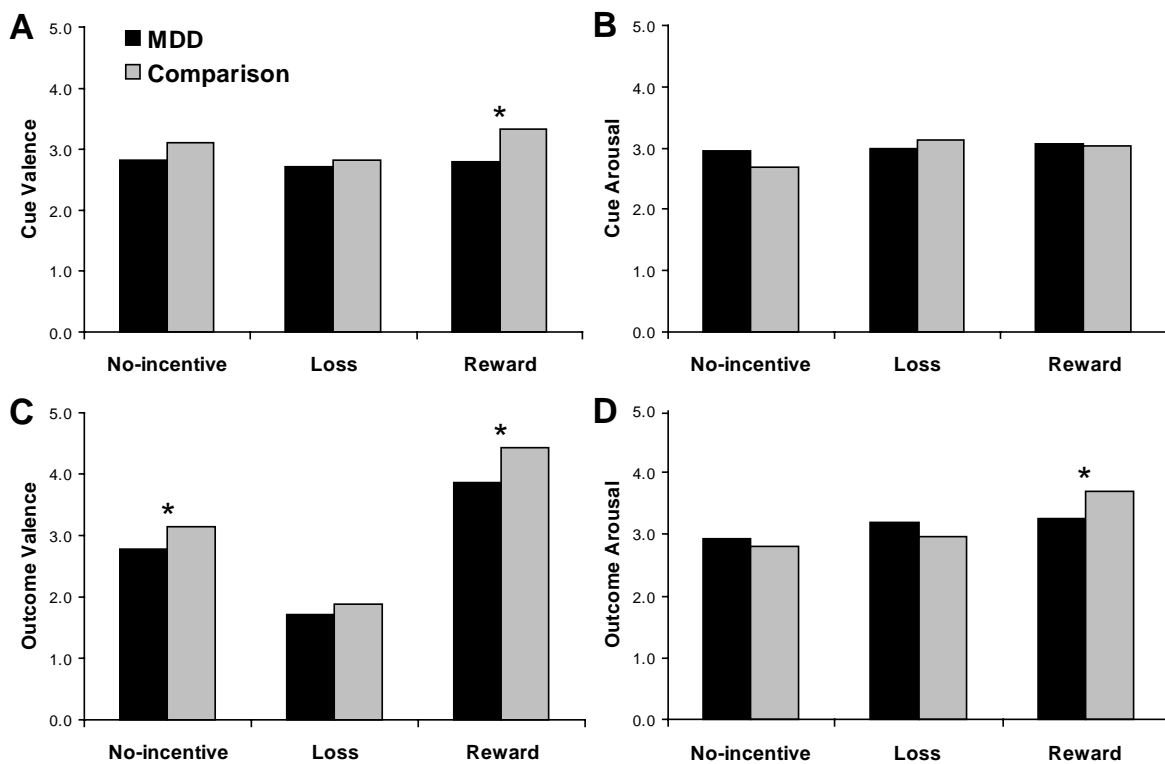




FIGURE S2. Secondary findings emerging from analyses investigating reward-related anticipatory activation in MDD (N=26) and comparison (N=31) subjects.

Relative to comparison subjects, the MDD group showed relatively higher activation to reward cues [Reward cue – No-incentive cue] in bilateral dorsolateral prefrontal cortex (PFC) ( $x=24$ ,  $y=22$ ,  $z=40$  and  $x=-28$ ,  $y=24$ ,  $z=40$ ). Follow-up analyses revealed group differences for reward cues ( $p<0.009$ ) but not loss or no-incentive cues. L = Left.

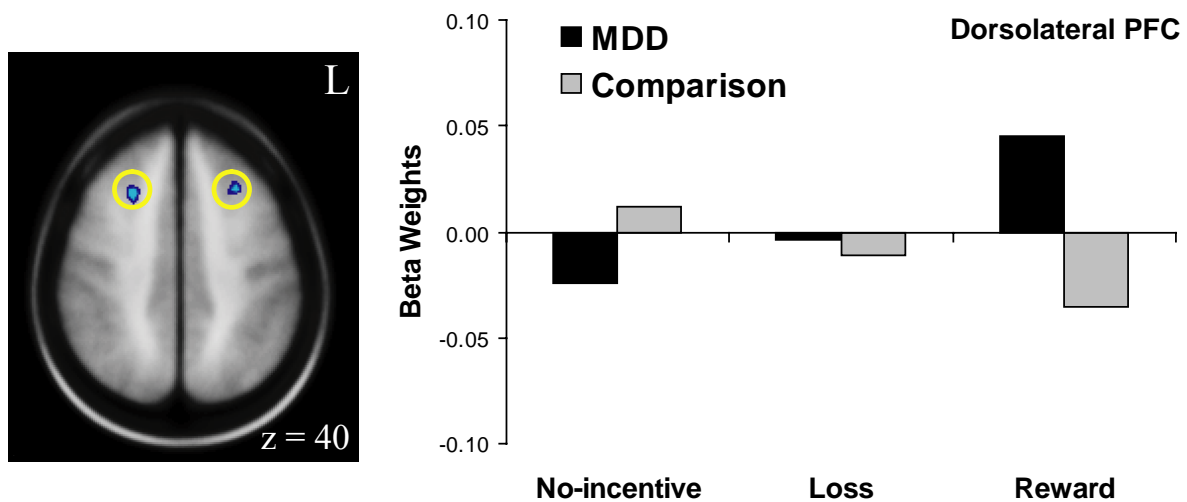


FIGURE S3. Secondary findings emerging from analyses investigating reward-related consummatory activation in MDD (N=26) and comparison (N=31) subjects.

Relative to comparison subjects, the MDD group showed relatively lower activation to gain feedback [Gain feedback – No-change feedback] in the dorsal anterior cingulate cortex (x=10, y=18, z=30). Follow-up analyses revealed group differences for reward feedback ( $p < 0.001$ ), but not penalty or no-change feedback. L = Left.

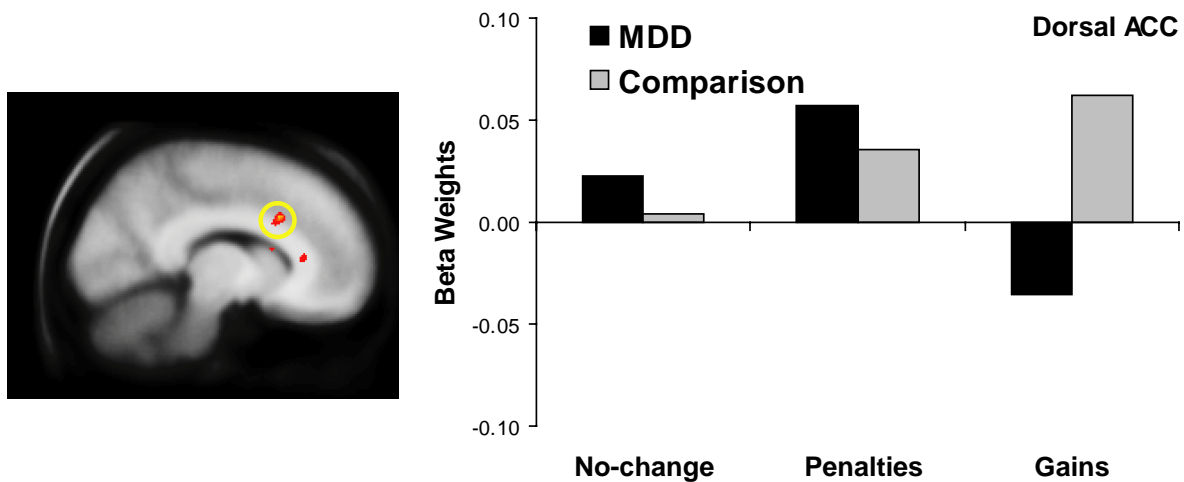


FIGURE S4. Secondary findings emerging from analyses investigating penalty-related anticipatory activation in MDD (N=26) and comparison (N=31) subjects.

Relative to comparison subjects, MDD subjects showed relatively higher activation to penalty cues [Loss cue – No-incentive cue] in the **(A)** left insula (x=-38, y=-7, z=-6), **(B)** right ventrolateral prefrontal cortex (PFC) (X=40, Y=44, Z=8), and **(C)** dorsal anterior cingulate cortex (ACC) (x=2, y=23, z=16). Follow-up analyses revealed that the insula finding was due to significantly lower activation to no-incentive cues in MDD relative to comparison subjects ( $p < 0.015$ ); for the right ventrolateral PFC and dorsal ACC regions, MDD subjects had significantly higher activation to both loss and reward cues ( $p < 0.05$ ). L = Left, A = Anterior.

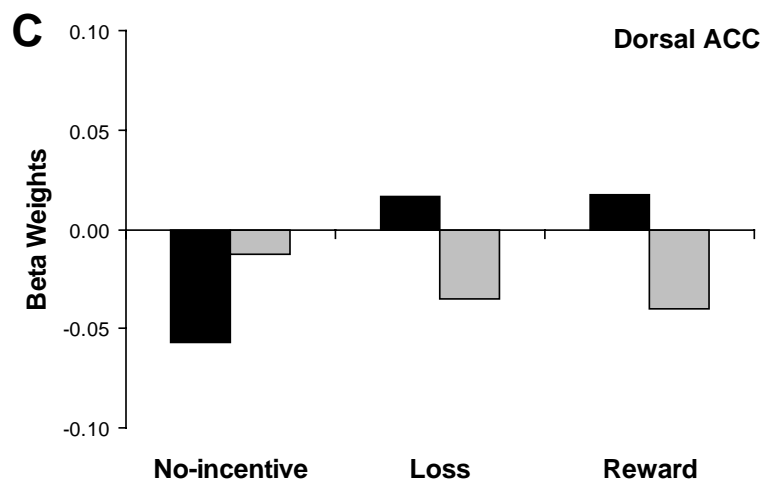
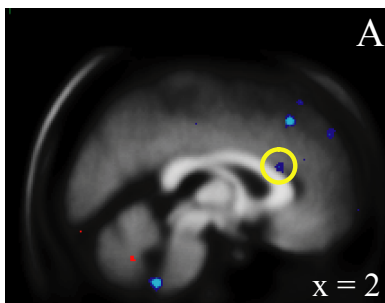
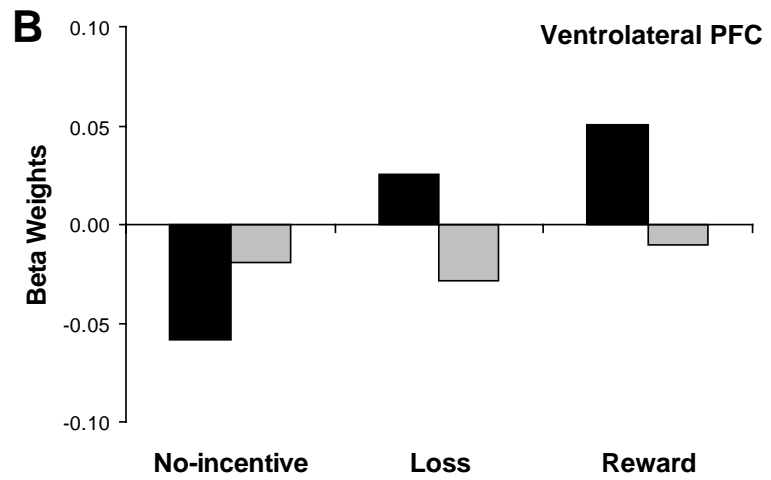
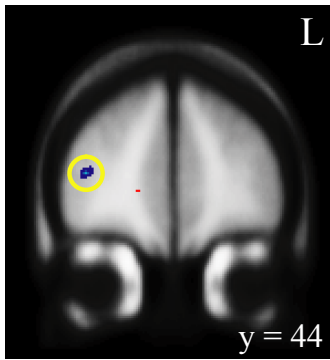
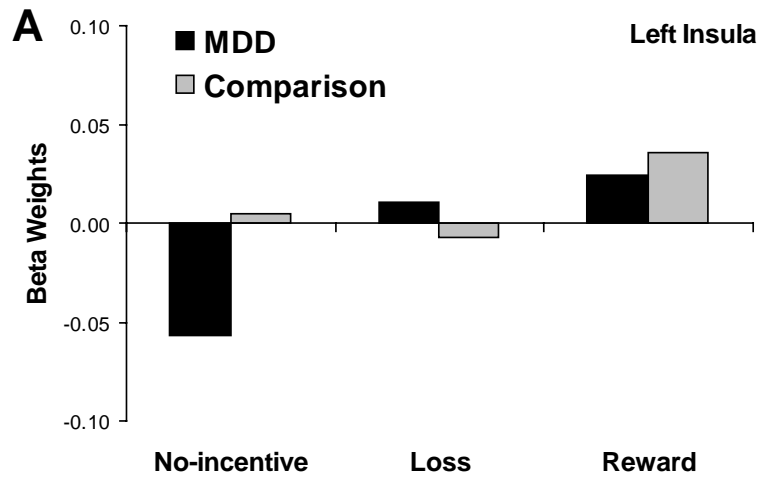
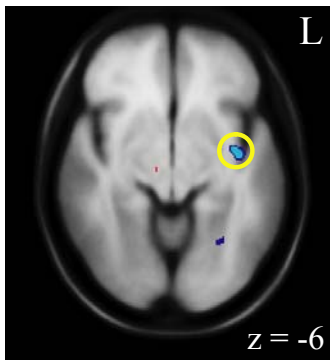


FIGURE S5. Secondary findings emerging from analyses investigating penalty-related consummatory activation in MDD (N=26) and comparison (N=31) subjects.

Relative to comparison subjects, MDD subjects showed significantly lower relative activation to penalty feedback [Penalty Feedback – No-change feedback] in the (A) right caudate ( $x=14$ ,  $y=23$ ,  $z=11$ ), and (B) left caudate ( $x=-8$ ,  $y=-2$ ,  $z=12$ ). Follow-up analyses revealed that the right caudate finding was due to a trend for higher activation to no-incentive cues for MDD relative to comparison subjects ( $p=0.074$ ); for the left caudate, follow-up analyses revealed that MDD subjects had decreased activation only to penalty feedback ( $p<0.013$ ). L = Left.

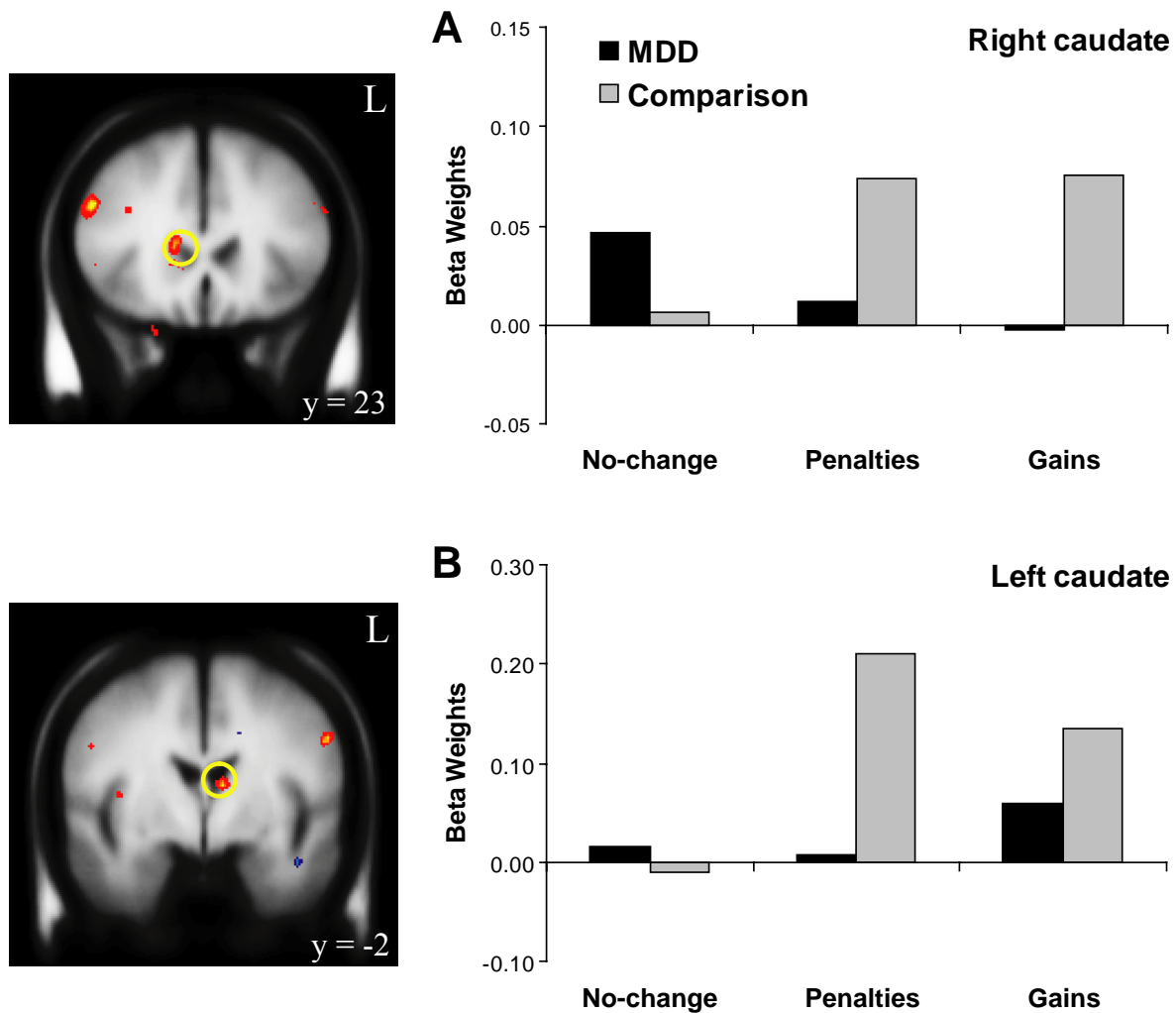


FIGURE S6. Examples of the automated labeling of the caudate in four representative MDD participants. For each participant, images on the left display high-resolution coronal and axial slices cutting passing through the caudate; images on the right show the same slices with the left caudate highlighted in green are.

