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Modulation of Caudate Activity by Action Contingency

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Summary

Research has increasingly implicated the striatum in the processing of reward-related information in both animals and humans. However, it is unclear whether human striatal activation is driven solely by the hedonic properties of rewards or whether such activation is reliant on other factors, such as anticipation of upcoming reward or performance of an action to earn a reward. We used event-related functional magnetic resonance imaging to investigate hemodynamic responses to monetary rewards and punishments in three experiments that made use of an oddball paradigm. We presented reward and punishment displays randomly in time, following an anticipatory cue, or following a button press response. Robust and differential activation of the caudate nucleus occurred only when a perception of contingency existed between the button press response and the outcome. This finding suggests that the caudate is involved in reinforcement of action potentially leading to reward, rather than in processing reward per se.

Introduction

The subjective experience of receiving a reward or punishment is complex. Not only do rewards induce feelings of pleasure, but they also serve as positive reinforcers of behavior (Schultz et al., 1998). Therefore, the brain must be sensitive to the hedonic nature of rewards while also associating behavior with the outcomes it produces. Previous research in both animals (Hikosaka et al., 1989; Schultz et al., 1998) and humans (Delgado et al., 2000; Elliott et al., 2000; Knutson et al., 2000) has shown that the striatum is important for processing reward-related information. Yet activity in the human striatum has primarily been observed during tasks in which rewards and punishments were contingent upon a cognitive decision or a motor response. It is not clear whether the resulting striatal response is driven solely by the existence of a reward or punishment, or whether other aspects of the task contribute to or are necessary for the occurrence of such a response.

Our first goal was to determine whether the striatum would respond to feedback indicating monetary rewards and punishments that were simply presented at pseudorandom intervals. While an array of functional magnetic resonance imaging (fMRI) studies have found that secondary reinforcers such as money can activate reward-related brain regions (Breiter et al., 2001; Delgado et al., 2000, 2003; Elliott et al., 2000; Knutson et al., 2000, 2001a, 2001b; O'Doherty et al., 2001), these studies have not examined the extent to which the dorsal and ventral striatum are activated in response to displays indicating monetary rewards and punishments presented unpredictably in time. However, there is evidence that randomly presented primary rewards elicit striatal activation. Electrophysiological recording studies in monkeys have shown that unpredicted primary rewards cause activity of dopaminergic neurons in the substantia nigra and ventral tegmental area (Schultz et al., 1997), and these neurons project to dorsal and ventral striatum, respectively (Haber and Fudge, 1997). In addition, an fMRI study using human subjects found an enhancement of activity in the ventral striatum when primary liquid rewards were presented in an unpredictable, rather than a predictable, manner (Berns et al., 2001). Activity in dorsal striatum, however, was not reported in this experiment.

To understand how the striatum reacts to unpredictable rewards and punishments, we used an oddball paradigm in which a meaningless standard habituating stimulus (a purple square) was repeatedly presented, interrupted with infrequent oddball stimuli indicating monetary gain or loss (Figure 1). This design allowed us to present reward and punishment displays at varying intervals. Oddball paradigms have been used extensively in ERP experiments (Courchesne et al., 1975; Johnson, 1986; Sutton et al., 1965) and more recently in fMRI experiments (Kiehl and Liddle, 2003; McCarthy et al., 1997; Menon et al., 1997; Strange et al., 2000). With this type of paradigm, the repeating standard stimulus presentations serve as a baseline, against which activity elicited by the oddballs can be compared.

In our first experiment, each of our oddball stimuli could be one of three items: a green upward arrow, indicating a monetary reward, a red downward arrow, indicating a monetary loss, or a sideways blue arrow, indicating a neutral trial. These oddball stimuli were presented pseudorandomly once every 10.5–19.5 s. This variable intertrial interval minimized time-locked anticipation of when the reward or punishment would occur. Subjects were instructed to press a button upon seeing any of the arrows. Subjects knew that this response did not affect the outcome, since this action occurred after the onset of the reward or punishment display.

Our second goal was to determine whether time-locked anticipation of the reward or punishment would drive a striatal response. Anticipation of an upcoming reward has previously been shown to affect activity in reward-related brain regions. When conditioned stimuli predict an upcoming reward, the firing of dopamine neurons occurs after the reward-predicting stimulus, rather than after the reward itself (Schultz et al., 1997). Human fMRI experiments have shown both dorsal and ventral

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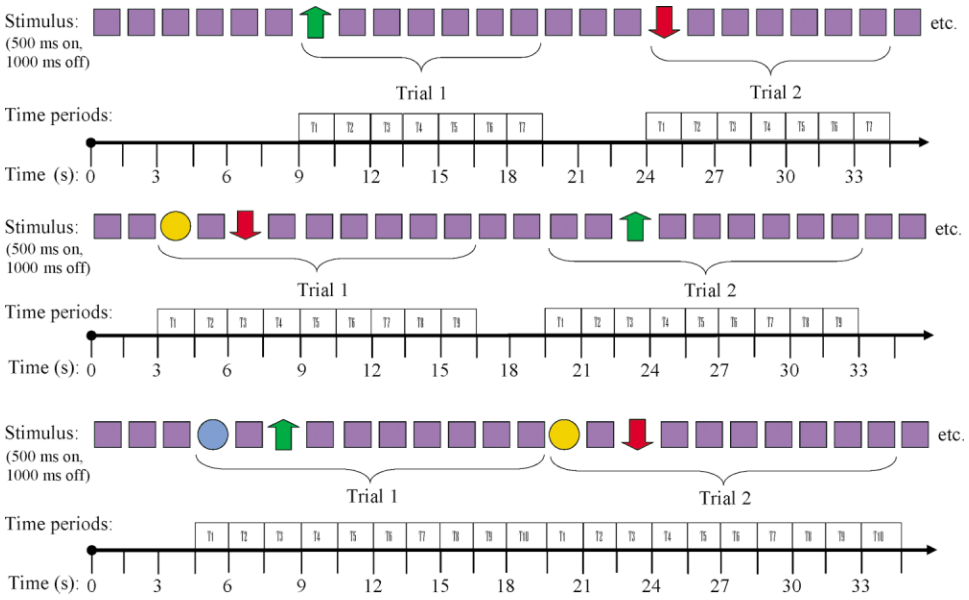

Figure 1. Experimental Design

Top: In Experiment 1, a habituating stimulus (a purple square) was displayed once every 1500 ms for a duration of 500 ms, interrupted psuedorandomly every 10.5–19.5 s with an oddball stimulus, which was an upward green arrow, a downward red arrow, or a sideways blue arrow. The green arrow indicated a reward of $1.50, the red arrow indicated a punishment of $0.75, and the blue arrow indicated no money won or lost. Subjects were instructed to push the index finger button on the response glove upon seeing each arrow. Functional images were acquired every 1.5 s, and for each trial, the first seven of these 1.5 s time periods (beginning with the onset of the oddball stimulus) were analyzed.

Middle: The task for Experiment 2 proceeded much as in Experiment 1, but was modified such that for half the trials, an anticipatory cue (a yellow circle) preceded the oddball stimulus by 3.0 s. This circle provided no information about the outcome valence. Neutral trials were not included in this experiment. Subjects were again instructed to push the index finger button upon seeing each arrow. For each trial, the first nine 1.5 s time periods, beginning 3.0 s before the onset of the arrow stimuli (i.e., at the onset of the anticipatory cue, when present), were analyzed.

Bottom: For Experiment 3, all arrows were preceded by an anticipatory cue 3 s before the onset of the arrow stimulus. For half of the trials, the cue was a blue circle, and subjects were instructed to push the thumb button upon seeing this cue. For the other half of the trials, the cue was a yellow circle, and subjects were instructed to choose between pushing the first and second finger buttons and were told that their button presses determined the valence of the outcome. In actuality, the outcome valence was predetermined. For each trial, the first ten 1.5 s time periods (beginning with the onset of the anticipatory cue) were analyzed.

striatal activity during anticipation of reward (Breiter et al., 2001; Knutson et al., 2001a; O'Doherty et al., 2003). To more fully compare activation caused by anticipated and unanticipated monetary rewards, we performed a second experiment. Trials like those in Experiment 1, in which rewards and punishments were not predicted, were intermingled with trials in which an anticipatory cue (a yellow circle) preceded the reward or punishment by 3 s (Figure 1). Subjects did not respond to the cue, but responded to the arrows, as in Experiment 1.

Finally, we explored a third possibility, that striatal activity may be modulated by the perceived connection between action and outcome. Studies in both monkeys and humans suggest that this perception might be especially important for driving activity in the dorsal striatum. Electrophysiological recordings in monkeys in the caudate nucleus, a key structure in the dorsal striatum, suggest that its activity may be dependent on the anticipated consequence of the monkey's performance (Hikosaka et al., 1989; Kawagoe et al., 1998; Lauwereyns et al., 2002a, 2002b; Rolls, 1999; Schultz et al., 2000). Caudate neurons show selective activation for trials in which a monkey's movement will result in a reward, as opposed to trials in which the monkey is cued that a reward will not be delivered but must make the movement to continue the experiment (Schultz et al., 2000). In other studies done in monkeys, caudate neurons fired in anticipation of a cue or target requiring a visual saccade only when saccades to the neurons' preferred location would be rewarded (Lauwereyns et al., 2002b; Takikawa et al., 2002). Human fMRI tasks have also found the caudate nucleus to be active during reward-related tasks in which subjects believed that their performance determined the outcome. For example, bilateral caudate activity was found in gambling-like tasks in which subjects thought that their button presses determined whether they won or lost money (Delgado et al., 2000, 2003; Elliott et al., 2000). Similarly, Knutson and colleagues (2001b) found bilateral caudate and ventral striatal activity when subjects anticipated a monetary reward that would occur if they successfully hit a button during the display of a briefly presented target. While these tasks did not dissociate the perception of contingency between action and outcome from other aspects of the tasks, they stand in contrast to other experiments in which monetary rewards and punishments were not linked to subjects' actions, and dorsal striatal activity was not reported (Breiter et al., 2001).

A third experiment was performed to examine this issue directly, again by taking advantage of the oddball

Table 1. Behavioral Data: Reaction Times across Conditions and Experiments

	Number of Errors (Mean ± SD)	Reaction Time (ms; Mean ± SD)
Experiment 1[a]		
Reward	4 ± 9	565 ± 215
Punishment	5 ± 10	588 ± 199
Neutral	3 ± 8	606 ± 207
Experiment 2[b]		
Cued reward	1 ± 1	338 ± 120
Cued punishment	2 ± 3	348 ± 130
Uncued reward	1 ± 3	484 ± 80
Uncued punishment	1 ± 2	499 ± 76
Experiment 3		
Choice	2 ± 2	775 ± 173
No-choice	1 ± 1	726 ± 117

[a] Due to a data logging error, behavioral data were not collected for five of the subjects. In addition, the data shown here includes behavioral data from one subject who missed 66 of the 144 trials (each of the other subjects made fewer than 5 errors). While this is most likely due to responses only registering intermittently, these trials have been omitted from the fMRI analysis, as were any no-response trials from the other subjects.

[b] Behavioral data from one subject were not collected due to a data logging error.

paradigm. In this version of the task, we compared activity resulting from action-contingent and noncontingent rewards and punishments. An anticipatory cue preceded each reward or punishment by 3 s, and subjects responded to the cue rather than to the arrow that followed it. The cue was one of two types, which were pseudorandomly intermixed. A light blue circle indicated that the subjects should respond by hitting the thumb button on the response glove; they were told that in this condition they had no control over which type of arrow would follow the cue. However, when the cue was a yellow circle, subjects were told to guess whether the first or second finger key was the "right answer," and that whether they won or lost money on these trials would depend on whether they guessed correctly. Unbeknownst to the subjects, the outcomes were actually predetermined. In this way, we were able to selectively manipulate perceived contingency between action and outcome, while keeping other aspects of the task constant.

Results

Behavioral Data

Error and reaction time data from subjects' button press responses are shown in Table 1. No-response errors were kept to a minimum by informing subjects that if they failed to respond on any given trial, they would automatically lose $1.00. Error rates were generally low, indicating that the subjects were attending to the task in each experiment. A one-way ANOVA on the data from Experiment 1 revealed that the reaction times were significantly different across conditions (reward, punishment, and neutral) [$F(2,10) = 7.5$, $p < 0.05$], with post hoc two-tailed t tests revealing faster responses to reward than neutral displays [$t(5) = 3.4$, $p < 0.05$]. For Experiment 2, a two-way ANOVA, with cue condition and valence (reward versus punishment) as factors, showed no significant valence differences in reaction time but did reveal that responses to cued trials were faster than to uncued trials [$F(1,11) = 33.0$, $p < 0.05$]. A two-tailed t test on the data for the choice versus no-choice conditions in Experiment 3 found no significant difference. Since the subjects responded prior to seeing the outcome in Experiment 3, differences between valence conditions were not examined.

To see whether subjects' subjective experiences were different in the choice versus the no-choice conditions in Experiment 3, a brief Likert-scale questionnaire was administered at the end of the experiment. Table 2 summarizes the responses from the questionnaire. Although the outcomes were fixed and pseudorandomly ordered for both choice and no-choice conditions, subjects rated their sense of control significantly higher in the choice condition than in the no-choice condition [$t(8) = 4.4$, $p < 0.05$, two-tailed]. Their degree of certainty that there was a pattern to correct answers was also higher for the choice than no-choice conditions [$t(8) = 3.4$, $p < 0.05$, two-tailed]. While subjects rated how much they cared about winning and losing money as higher in the choice condition than the no-choice condition, this trend was not significant [$t(8) = 2.1$, $p < 0.1$, two-tailed].

Functional Imaging Data

Signal Change in the Caudate Nucleus

Based on previous fMRI experiments (Delgado et al., 2000, 2003), we had an a priori interest in the response of the caudate nucleus across our three experiments. Therefore, for each experiment, we performed an ANOVA on the voxels corresponding to the Talairach coordinates for the peak activation reported in the left and right caudate nucleus in previously published work from our laboratory (Delgado et al., 2000). These coordinates were ($x = -12$, $y = 15$, $z = 7$) for the left caudate nucleus and ($x = 11$, $y = 16$, $z = 7$) for the right caudate nucleus (Talairach and Tournoux, 1988). While the size of our individual voxels is $3.75 \times 3.75 \times 3.8$ mm^3, the size of the analyzed area is actually somewhat greater than this due to the smoothing of the functional image data (Cohen et al., 2002). This analysis allowed us to take advantage of methodological and technical similarities (e.g., analysis pathway, scanner) with our previous work to predict where activation might occur, while using a very conservative approach to assess significance in each experiment. For all three experiments, valence and time period were within-subjects factors; additionally, cue condition was a within-subjects factor for Experiment 2 (cued versus uncued) and Experiment 3 (choice versus no-choice). As shown in Figure 1, for Experiment 1 the time periods used were the first seven 1.5 s time periods of each trial (T1–T7), beginning with the arrow stimulus; for Experiment 2, the first nine 1.5 s time periods of each trial were used (T1–T9), beginning 3 s before the arrow stimuli (for cued trials, this corresponds to when the cue occurred); and for Experiment 3, the first ten 1.5 s periods of each trial were used (T1–T10), beginning with the cue. The time courses for the three experiments are shown in Figure 2. Specifically, the ANOVAs

Table 2. Summary of Experiment 3 Questionnaire Ratings

Question[a]	Rating[b] (Mean ± SD)
Did you care more about winning/losing money for the **blue** or the **yellow** cue trials? (1 = cared much more during **blue** cue trials; 7 = cared much more during **yellow** cue trials)	5 ± 2
How much control did you feel you had over whether you won or lost money for the **yellow** cue trials? (1 = no control; 7 = complete control)	4 ± 1
How much control did you feel you had over whether you won or lost money for the **blue** cue trials? (1 = no control; 7 = complete control)	2 ± 2
Do you think there was a pattern to the "winning" answers for the **yellow** cue trials? (1 = no, I think it was just random; 7 = yes, I definitely think there was a pattern)	5 ± 2
Do you think there was a pattern to the "winning" answers for the **blue** cue trials? (1 = no, I think it was just random; 7 = yes, I definitely think there was a pattern)	3 ± 1

[a] Blue cue trials, no-choice trials; yellow cue trials, choice trials.
[b] Ratings are on a 7 point scale; 2 subjects did not complete the questionnaire, so results are based on ratings from the other 9 subjects.

revealed no significant main effects or interactions for Experiments 1 and 2 at a threshold of $p < 0.01$. Robust activation was found only in Experiment 3 [main effect of time, $F(9,90) = 5.22$, $p < 0.00001$ for left caudate; $F(9,90) = 7.96$, $p < 0.0000001$ for right caudate], and within this experiment, only for the choice condition [cue × time interaction, $F(9,90) = 6.57$, $p < 0.000001$ for left caudate; $F(9,90) = 4.77$, $p < 0.0001$ for right caudate]. This suggests that the caudate nucleus is only strongly recruited when there is a perceived contingency between the subject's actions and the outcome.

As Figure 3 shows, the time course patterns for the choice condition differ between reward and punishment outcomes. After an anticipatory rise between the cue and the outcome, the response peaks and then rapidly decreases below baseline for punishment trials, while there is a more sustained response for reward trials. This follows the pattern observed in a gambling-like paradigm with perceptually distinct but conceptually similar task demands and similar timing parameters between response choices and displays (Delgado et al., 2000, 2003). As in these papers, the largest and most reliable difference between reward and punishment responses occurs 6 s after the presentation of the reward or punishment outcome (time period T7). A two-tailed paired t test performed on the choice condition data at T7 (6.0–7.5 s after outcome presentation) showed that reward activity was significantly greater than the punishment activity for both left [$t(10) = 3.1$, $p < 0.05$] and right [$t(10) = 4.2$, $p < 0.01$] caudate.

Results from Voxel-Wise ANOVAs

In addition to analyzing the caudate activation across experiments, we also performed voxel-wise repeated measures ANOVAs on each of the three functional imaging data sets to confirm that this more typical approach yields findings in the striatum that are consistent

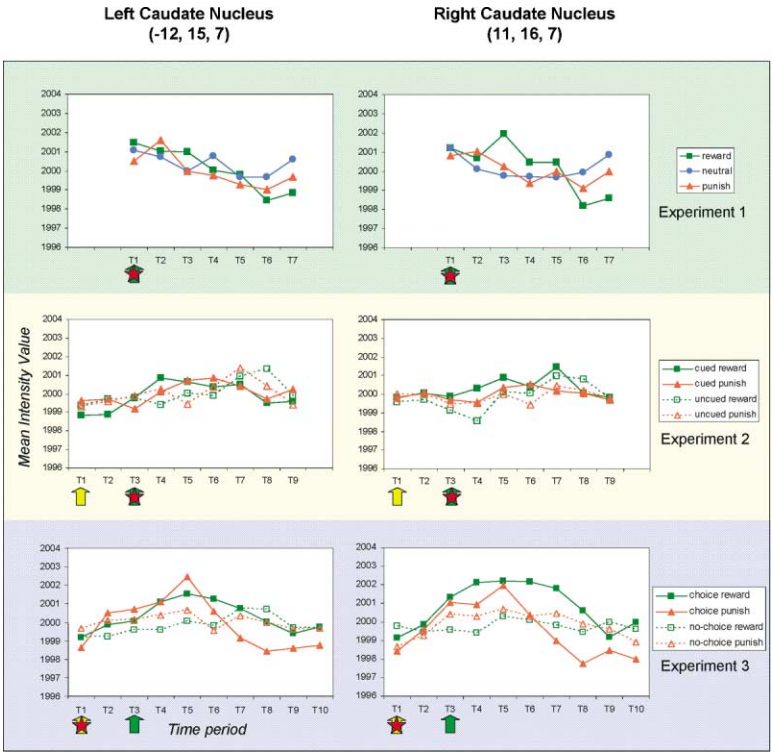

Figure 2. Activation in the Caudate Nucleus across the Three Experiments

Throughout, each time period (T1, T2, etc.) represents 1.5 s. The green arrows indicate the time period at which the outcome was revealed. The yellow arrows indicate the time period at which an anticipatory cue was displayed, for those trials when one was present. The red stars indicate the time period at which the subjects made a button press response.

Top: Activation in the left and right caudate nucleus, defined by reported peak activation Talairach coordinates (Delgado, et al., 2000). In Experiment 1, robust activity was not observed for any of the conditions (reward, punishment, and neutral).

Middle: In Experiment 2, robust activity occurred neither for cued nor uncued conditions.

Bottom: In Experiment 3, robust activity occurred for the choice but not the no-choice condition. Activity for the reward and punishment conditions differed significantly at time period T7 (6.0–7.5 s after the onset of the reward or punishment stimulus) for the choice condition for both left and right caudate.

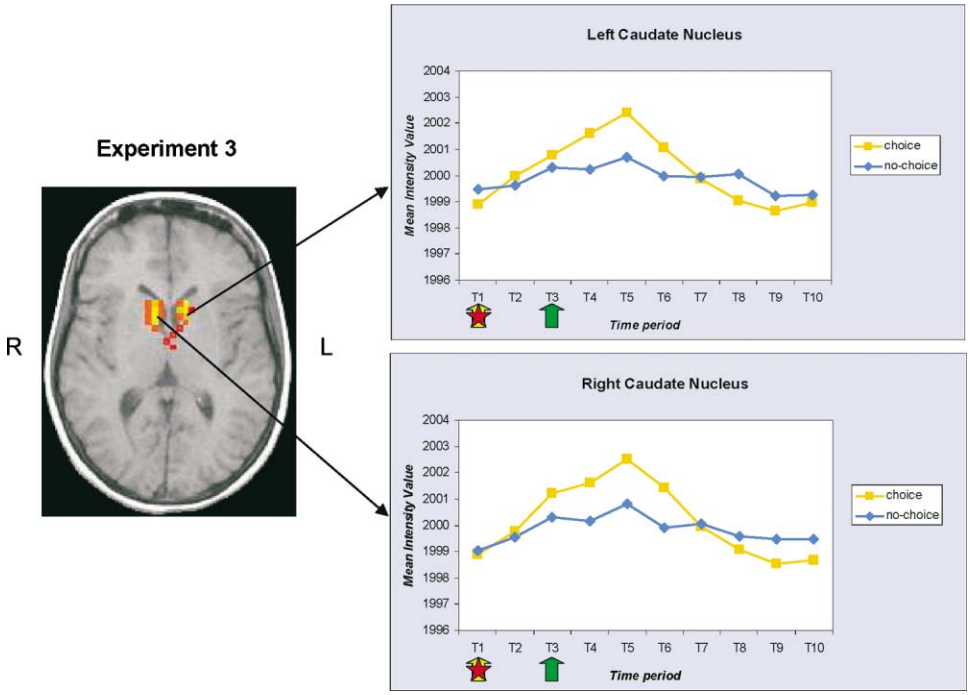

Figure 3. Activity in Caudate Voxels Showing a Cue Condition × Time Interaction in Experiment 3

Each time period (T1–T10) represents 1.5 s. Green arrows indicate the time period at which the outcome was revealed. The yellow arrows indicate the time period at which an anticipatory cue was displayed, for those trials when one was present. The red stars indicate the time period at which the subjects made a button press response.

Left: Both the left and right caudate nucleus voxel clusters display a cue condition (choice versus no-choice) by time interaction at $p < 0.0001$ in Experiment 3.

Right: Time courses of the caudate voxel clusters reveal that activity is significantly greater for the choice condition than the no-choice condition for both left and right caudate nucleus.

with our a priori VOI analysis, and to identify voxel clusters that are modulated by affective stimuli without requiring assumptions about where those regions would be. As in the a priori VOI analysis, the ANOVAs used subject as a random factor, and time period, valence, and cue (except for Experiment 1) as within-subjects factors. The time periods used in these analyses were the same as those described in the previous section. These ANOVAs do not require assumptions about the shape of the hemodynamic response.

Striatal Activation. Striatal activation clusters identified using the voxel-wise ANOVAs for each experiment, with a contiguity threshold of four voxels, are shown in Table 3. In further support of the observation that the caudate nucleus was more strongly activated when subjects thought that their responses determined the outcome, caudate activation clusters showing a cue condition by time interaction were identified bilaterally for the data from Experiment 3 [$F(9,90) > 4.35$, $p < 0.0001$] (Figure 3). The Talairach coordinates with the maximal F-value for each activation cluster were ($x = -12$, $y = 11$, $z = 8$) and ($x = 9$, $y = 16$, $z = 4$), which are each only about one voxel away from the caudate coordinates used in our a priori analysis. As can be seen from the time courses in Figure 3, these clusters were strongly activated for the choice condition but showed only a very weak response for the no-choice condition.

Additionally, in Experiment 3, the left caudate nucleus showed a valence condition (reward versus punishment) × time interaction [$F(9,90) > 4.35$, $p < 0.0001$] and both left and right caudate showed a main effect of time [$F(9,90) > 4.35$, $p < 0.0001$], while no caudate voxels showed these effects in Experiments 1 and 2 (Table 3). These results reinforce the findings from the a priori caudate analysis.

The absence of a significant valence by time effect in the nucleus accumbens is worth noting, since this area is a key projection site of dopaminergic neurons and is a major region in the brain's reward circuit (Koob, 1992). Signal dropout, due to the proximity of this region to air and fluid cavities, may be one factor in interpreting our null result. To systematically assess the degree of dropout across our three studies, we compared overall mean intensity in the nucleus accumbens [Talairach coordinates: ($x = -12$, $y = 8$, $z = -8$) and ($x = 12$, $y = 8$, $z = -8$); cf. Zink et al., 2003] to the voxels used in our a priori analysis of caudate activation for each of our studies. The nucleus accumbens to caudate intensity ratio was 0.42 for Experiment 1, 0.46 for Experiment 2, and 0.52 for Experiment 3. This indicates that there was a similar degree of dropout in this area in each of our experiments. However, our relative dropout does appear to be greater than in a previous study from our lab in which there was a significant valence by time effect in the ventral striatum using a 2-shot spiral scanning sequence (Delgado et al., 2000). In that data set, the ratio of intensity in the ventral striatal ROI compared to an ROI found in the caudate nucleus was 0.81.

Table 3. Striatal Clusters of Activation

	Experiment 1		Experiment 2		Experiment 3	
	Region of Activation	Talairach Coordinates (x, y, z)	Region of Activation	Talairach Coordinates (x, y, z)	Region of Activation	Talairach Coordinates (x, y, z)
Main effect of time	putamen (L)	−20, −3, 8	putamen (L)	−20, 1, −4	caudate nucleus (L)	**−12, 12, 4**
					caudate nucleus (R)	8, 0, 12
Valence × time interaction	-		-		caudate nucleus (L)	**−16, 12, 4**
					putamen (R)	17, 8, −1
Cue type × time interaction	N/A		putamen (R)	12, −3, 14	caudate nucleus/anterior thalamus (L)	**−12, 11, 8**
					caudate nucleus (R)	9, 16, 4

Note: Talairach coordinates in bold are within 2 voxels of the coordinates used in the a priori analysis of caudate activation. All activation clusters were identified at a significance threshold of $p < 0.0001$ and a contiguity threshold of four voxels.

Additional Brain Regions Showing a Cue Type by Time Interaction in Experiment 3. A montage displaying voxel clusters showing a cue type by time interaction in Experiment 3, at a significance threshold of $p < 0.0001$ and a contiguity threshold of 4 voxels, is depicted in Figure 4. In addition to the caudate bilaterally, the anterior cingulate gyrus ($x = -3$, $y = 30$, $z = 40$), the right superior frontal gyrus ($x = 31$, $y = 52$, $z = 16$), and the right middle frontal gyrus ($x = 28$, $y = 44$, $z = 0$) showed greater activation in the choice condition than the no-choice condition. The cuneus ($x = 5$, $y = -76$, $z = 28$) and the left middle temporal gyrus ($x = -50$, $y = -50$, $z = -4$) showed less activation in the choice condition than in the no-choice condition. Other than in the caudate nucleus, none of the voxels from these activation clusters also showed significant valence by time effects at a threshold of $p < 0.0001$ in this experiment, indicating that activation in these regions may reflect non-reward-related differences between the two conditions, such as additional executive control necessary to perform the task in the choice condition.

Brain Regions Showing a Valence by Time Interaction. To find regions that showed differential responses to reward and punishment feedback across experiments, we used an overlap function to isolate voxels that showed a valence by time interaction at a threshold of $p < 0.0001$ in all three experiments. Neutral trials were excluded in the ANOVA for Experiment 1 since there were no neutral trials in the other two experiments. The voxels where a significant valence by time interaction was found in each of the experiments are shown in Figure 5.

Only one region showing a valence by time interaction in all three experiments was identified using this overlap analysis, a right lingual cluster that covered 5 voxels (Figure 6). The Talairach coordinates for the peak F-value (averaged across the three experiments) are ($x = 12$, $y = -69$, $z = 4$). As can be seen from the time courses in Figure 6, when there is no cue (as in Experiment 1, and the uncued condition for Experiment 2), the hemodynamic response to punishment is very weak, while there is a much larger response to reward. When a cue is present (as in Experiment 3 and the cued condition for Experiment 2) there is a rise at the onset of the cue, followed by a differentiation of response following the

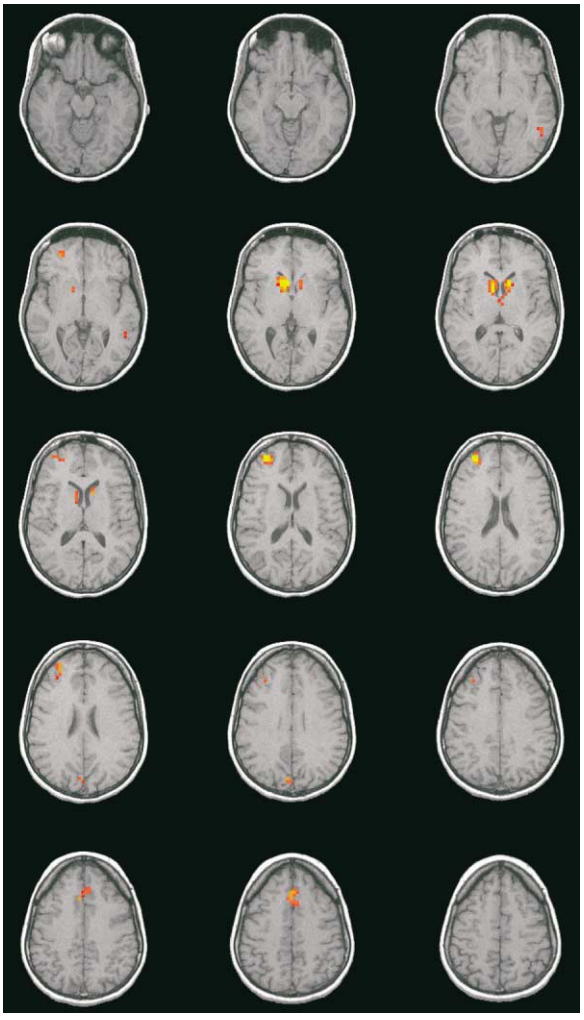

Figure 4. Brain Regions Showing a Cue Type by Time Interaction in Experiment 3

Voxel clusters displaying a cue type by time interaction in Experiment 3 are shown ($p < 0.0001$; contiguity threshold of 4 voxels). Each activation cluster shown, except for the cuneus and the left middle temporal gyrus, displays a greater response in the choice condition than in the no-choice condition.

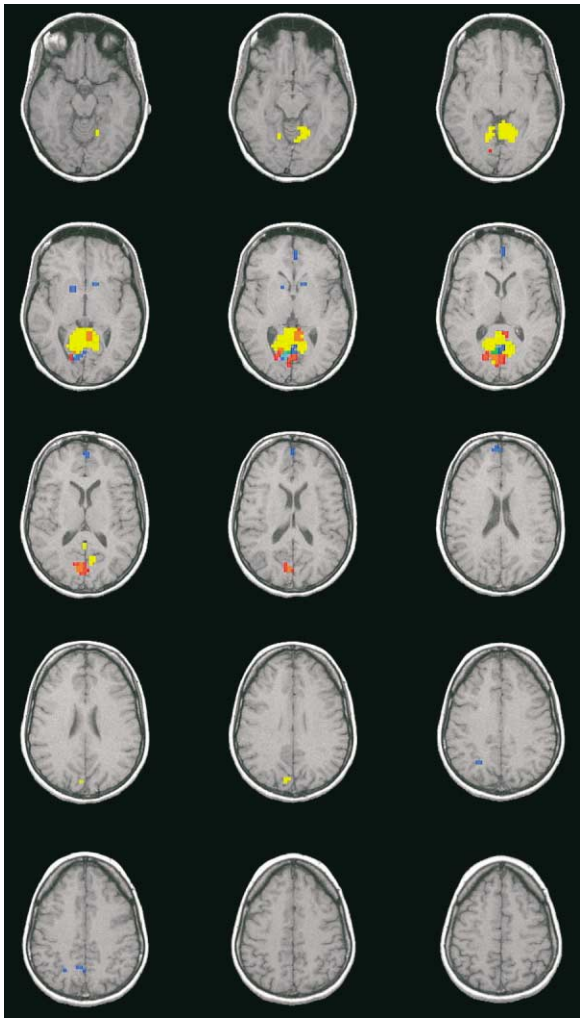

Figure 5. Brain Regions Showing a Valence by Time Interaction in Each Experiment

Regions displaying a valence × time period interaction are shown, color-coded by experiment ($p < 0.0001$). Colors reflect a significant effect in the following experiments: red = 1 only; yellow = 2 only; blue = 3 only; orange = 1 and 2; violet = 1 and 3; green = 2 and 3; cyan = 1, 2, and 3. The only voxels showing a significant valence by time period interaction across all three experiments are in the right lingual gyrus. All voxel clusters shown display greater activation for reward than for punishment.

outcome display. Namely, the response to punishment falls back to baseline while the response to reward is more sustained. Unlike the response in the caudate nucleus, the response in the lingual gyrus does not differentiate based on whether there is a perceived contingency between the subject's responses and the outcome.

Discussion

The main goal of these experiments was to ascertain which aspects of affective stimuli drive activity in the human striatum. A major finding of this work is that the caudate nucleus was robustly activated only when the subjects thought that their button presses determined whether they won or lost money; neither pseudorandomly presented rewards and punishments nor time-locked anticipation of the rewards and punishments was enough to drive such a response. It should be noted that in all three experiments, subjects were told that a failure to make a response would result in a monetary fine, so in a sense, the reward was dependent on making a response in all cases. However, in the first two experiments presented here, responding to the oddball stimuli presented no difficulty to the subjects, as evidenced by their low error rates. Thus there was a very low probability of not getting a reward due to failure to respond appropriately. In contrast, in Experiment 3, responding "appropriately" was much more difficult; in the choice condition, only 50% of the time did the subjects guess "correctly" and win money. This is not to say that decision-making is the key component in driving caudate activation. Caudate activation has also been elicited in paradigms requiring rapid target detection in order to get a reward or avoid a punishment (Knutson et al., 2000, 2001a, 2001b). While these paradigms have surface similarities to the no-choice condition in Experiment 3 (a single button is pressed upon seeing a target, followed by a feedback display indicating a monetary outcome), there is an important difference: in the rapid target detection tasks, the outcome is dependent upon speed of response, whereas in the no-choice condition in Experiment 3, there is no connection between the speed of response and the outcome. This difference is reflected in the imaging results from the two tasks: caudate activity was elicited in the rapid target detection tasks, but not in the no-choice condition in Experiment 3.

It seems, then, that the caudate nucleus is not activated by all instrumental tasks (i.e., tasks involving behavioral reinforcement), but instead only by those tasks in which there exists both a perceived connection between action and outcome and some uncertainty about whether the action will lead to the desired outcome. This idea is supported by electrophysiological work done in monkeys. Specifically, caudate neurons' activity related to saccades to a rewarded location is diminished when all saccade locations are rewarded (Takikawa et al., 2002). Future studies in both animals and humans could aim to more narrowly define the key components of tasks with action-dependent outcomes that elicit striatal activation, such as the uncertainty or increased motivation inherent in these tasks. The questionnaires that subjects in Experiment 3 filled out may provide some insight into this issue. They indicate that caudate activation was correlated with subjective ratings of control and the impression that there was a pattern to the winning answers: both were higher for the choice than the no-choice condition. It may be that these subjective impressions of a task matter more in determining the strength of caudate activation than whether the task involves instrumental conditioning or Pavlovian (i.e., classical) conditioning, in which stimulus-reward associations are built up through pairing of a conditioned stimulus with an unconditioned rewarding stimulus.

The findings presented here should help to reconcile differences in caudate activity observed in prior studies. In studies in which the subjects' decisions (Delgado et al., 2000, 2003; Elliott et al., 2000) or reaction time (Knutson et al., 2000, 2001a, 2001b) determined the out-

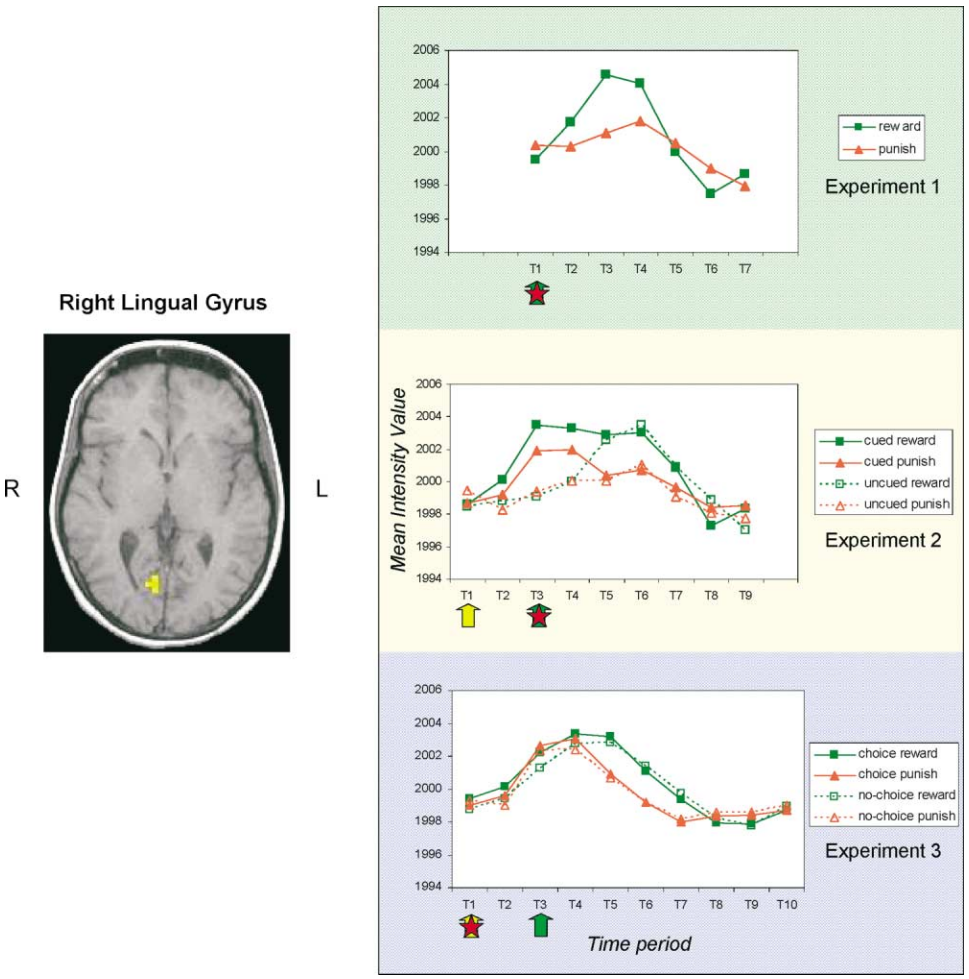

Figure 6. Activity in the Lingual Gyrus across All Three Experiments

Left: The right lingual gyrus shows an interaction of valence × time at $p < 0.0001$ in all three experiments. Voxels that met this significance threshold in all three experiments are shown.

Right: The time courses of the activation in the right lingual gyrus region shown on the left are graphed for each experiment. All show a greater response to reward than punishment. The yellow arrows indicate the time period at which an anticipatory cue was displayed, for those trials when one was present. The red stars indicate the time period at which the subjects made a button press response. Anticipatory activation is shown for the conditions in which an anticipatory cue was present: for the cued condition in Experiment 2 and for both conditions in Experiment 3. This activity then differentiates once the outcome is revealed, indicated by the green arrows.

come, caudate activation has been reported. In studies in which the subjects' responses did not determine the outcome (Berns et al., 2001; Breiter et al., 2001; McClure et al., 2003; O'Doherty et al., 2003) or in which, as in the first two experiments presented here, only a noneffortful response was necessary to get a reward (Elliott et al., 2003), activation in the caudate was not reported. Therefore, the caudate appears to be sensitive to reinforcement of action, rather than to rewards per se. That is, caudate activation seems to reflect the "goodness" of actions by differentiating between positive and negative consequences. This sort of valuation of action can then be used to bias future behavior (Montague and Berns, 2002).

The sensitivity of the caudate to the contingency between action and outcome puts it in a prime position to aid in learning. More specifically, the signal from the caudate associating an action with either a positive or negative outcome could be used to either reinforce or weaken the action (Barto, 1995). In the experiments presented here, the outcome of each trial was actually fixed, so learning was impossible. However, other studies have shown that the caudate does indeed play an important role in learning. For example, one study found that the preferred direction of monkeys' caudate neurons changed as a function of rewarded direction of eye movement (Kawagoe et al., 1998). In addition, inactivation of the caudate and anterior putamen decreases monkeys' ability to learn new motor sequences (Hikosaka, 2002). In humans, the dorsal striatum has been found to be important in habit learning tasks with feedback (Packard and Knowlton, 2002).

While this work has focused on caudate activation, other striatal regions have also been found to be involved in processing reward-related information, including the ventral striatum and putamen (Berns et al., 2001;

Delgado et al., 2000, 2003; Elliott et al., 2000, 2003; Knutson et al., 2001a, 2001b; McClure et al., 2003; O'Doherty et al., 2003; Pagnoni et al., 2002). The nucleus accumbens, a key projection site of dopaminergic neurons, lies within the ventral striatum and is a major region in the brain's reward circuit (Koob, 1992). Yet we did not find significant activation in the nucleus accumbens in this work. Our functional data set had more signal dropout in this area than it did in more dorsal areas of the brain, which leaves open the possibility that we did not detect activity in this region that was nevertheless occurring. A human fMRI study showed that the nucleus accumbens is more responsive to unpredictable, as opposed to predictable, juice rewards (Berns et al., 2001); thus, one might have especially expected to find such activation in our first experiment, in which the rewards and punishments were presented pseudorandomly. However, there are several methodological differences between the present and prior work that could explain this discrepancy. The study conducted by Berns et al. (2001) had only one 5 min run in each condition, to insure maximal unpredictability. It may be that over time, subjects in our experiment found the rewards and punishments more and more predictable as they became accustomed to the range of time between each oddball event. It is also possible that primary rewards such as juice may more strongly activate the nucleus accumbens, whereas more abstract, behaviorally dependent secondary rewards, such as winning money for a correct response, may more selectively recruit the caudate nucleus.

A functional dissociation between dorsal and ventral striatum has been suggested by a recent fMRI experiment, in which infrequent distracter stimuli elicited significant activation in the caudate nucleus only when the stimuli were behaviorally relevant, in that they potentially required a response, but activation in the nucleus accumbens was not dependent on behavioral relevance (Zink et al., 2003). A functional dissociation between ventral and dorsal striatum is also supported by research on rat striatum. For example, it has been proposed that the dorsal striatum mediates consummatory aspects of reward-related behavior, while the ventral striatum has more influence on appetitive aspects of behavior (Robbins and Everitt, 1992). More recently, dopamine release in the dorsal striatum has been found to increase during drug-seeking behavior contingently linked with a cocaine-associated conditioned stimulus, but not when the conditioned stimulus presentation was not contingent upon the rats' lever presses (Ito et al., 2002); however, the reverse pattern occurred in the nucleus accumbens, with the noncontingent presentations increasing dopamine release, but not the contingent presentations (Ito et al., 2000).

While we expected to find reward-related activity in the striatum, we unexpectedly found that the lingual gyrus showed a differential response to reward and punishment in all three experiments. This finding could simply reflect a visual epiphenomenon, in that the lingual gyrus may be responding to differences in color between the green arrow indicating reward versus the red arrow indicating punishment, or differences in direction of the arrows. At the very least, then, the differential activity in the lingual gyrus indicates that subjects were processing differences in the visual stimuli in all of the experiments; in other words, the lack of caudate activation for Experiments 1 and 2 cannot be attributed to subjects' failure to monitor the incoming stimuli. However, reward-dependent activity in the lingual gyrus has also been reported in several other experiments (Delgado et al., 2003; Elliott et al., 2003). These prior findings may also represent the influence of visual differences in the feedback displays. However, the possibility also exists that lingual activation may reflect retrieval of the reward-dependent meaning of the visual display. Indeed, the lingual gyrus has been shown to be activated during visual cue processing associated with high states of arousal, as characterized by skin conductance responses (Critchley et al., 2000; Lane et al., 1999; Patterson et al., 2002). In addition, the lingual gyrus increases in activity during recognition of previously studied emotionally salient images (Taylor et al., 1998) and words studied in an emotionally negative context (Maratos et al., 2001).

In summary, we performed three experiments using an oddball paradigm to dissociate various factors that might drive reward-dependent activity in the dorsal striatum. We showed robust activity in the caudate nucleus only when subjects believed that their button presses determined whether they won or lost money. This finding not only reconciles previous seemingly conflicting findings in the caudate nucleus, but also suggests that compared to other striatal regions, the way the caudate processes reward-related information may be unique in that it is dependent upon an action-reward contingency. While the task used in this work did not require subjects to gamble their own money, the choice condition in the third experiment can be likened to a gambling situation in which a person performs an action that results in either monetary gain or loss. Perhaps it is no coincidence that real-life gambling situations require action: a lever must be pulled on a slot machine, a coating rubbed off a lottery ticket, etc. In a sense, every action is a gamble, potentially leading to a positive or negative consequence. An awareness that the caudate may play a distinctive role in processing action-contingent reward-related information furthers our understanding of the mechanisms by which humans interpret and learn about the consequences of their actions.

Experimental Procedures

Subjects

Thirty-eight healthy, right-handed volunteers participated in these experiments; 12 of these volunteers participated in Experiment 1, 13 participated in Experiment 2, and 13 participated in Experiment 3. Due to excessive head motion for two of the subjects and equipment malfunction for a third, data from three subjects were not used in the analyses, leaving 11 subjects with analyzable data in Experiment 1 (8 female, 3 male, mean age 22 $\pm$ 3 SD), 13 in Experiment 2 (7 female, 6 male, mean age 23 $\pm$ 3 SD), and 11 in Experiment 3 (4 female, 7 male, mean age 23 $\pm$ 4 SD). All subjects filled out a brief questionnaire based on the South Oaks Gambling Screen (Lesieur and Blume, 1987) to insure that no subject was excessive in gambling behavior. All subjects gave informed consent according to the Institutional Review Board at the University of Pittsburgh.

Experimental Task

An "oddball" task was used in which a standard habituating stimulus (a purple square) was presented once every 1500 ms for a duration of

500 ms, interrupted with infrequent "oddball" stimuli. These oddball stimuli could be a green upward arrow, a red downward arrow, or, in Experiment 1 only, a blue sideways arrow. The subjects were informed that each time the green upward arrow appeared, they had won $1.50, while each time a red downward arrow appeared, they had lost $0.75. The blue sideways arrow indicated a neutral trial, in which the subject neither won nor lost money. For the first two experiments, the subjects' task was simply to press the first finger button on a response glove each time they saw either type of arrow. Since the button press occurred after the reward-relevant stimulus was presented, the subjects knew that their response did not affect the trial outcome. However, to make sure that they consistently responded on each trial, they were told that they would be fined $1.00 for every arrow they failed to respond to. Trials on which the subject did not respond were not included in the analysis. While lying in the scanner, subjects viewed stimuli projected onto a mirror. Stimuli were presented and behavioral data were acquired using Psyscope software on a Macintosh computer (MacWhinney et al., 1997).

For Experiment 1, each session consisted of 7–12 runs of 12 trials each, for a total of 84–144 trials per subject. Trial type order was pseudorandom, with the constraints that overall the numbers of reward, punishment, and neutral trials were equal, and that no more than 3 events of a given trial type could occur in a row. Oddballs occurred once every 10.5–19.5 s.

In Experiment 2, a yellow circle appeared 3 s before the arrow stimulus on half of the trials, serving as an anticipatory cue indicating when the arrow would appear. The cue did not provide any information about the valence of the upcoming arrow, and no response was made to it. In addition, there were no neutral trials in this experiment. Each session consisted of 12 runs of 11 trials each, for a total of 132 trials. Trial length ranged from 13.5–19.5 s. Trials in which a subject did not respond or responded to both the cue and the arrow were not included in the analysis. Trial type order was again pseudorandom, with the constraints that overall the number of trials in the four conditions (cued reward, uncued reward, cued punishment, uncued punishment) were equal, and that no more than 3 events of a given trial type could occur in a row.

In Experiment 3, a cue appeared 3 s before the arrow on each trial, and the subjects responded when the cue appeared, rather than when the arrow appeared. For half of the trials, this cue was a light blue circle, and for the other half, a yellow circle. Subjects were instructed to simply press the thumb key on the response glove upon seeing a blue circle. They were told that in this condition (the "no-choice" condition) they had no control over which type of arrow would be presented. In contrast, the subjects were instructed that when they saw the yellow circle, they should choose between responding by pressing the first-finger key or second-finger key on the response glove (the "choice" condition). They were told that if they "guessed the correct button" they would win and see the upward green arrow, while if they guessed incorrectly, they would lose and see the red downward arrow. In this way, the perception of contingency between action and outcome was manipulated. In reality, the trials were fixed such that half of the trials were reward trials and half were punishment. For all trials in which no response was made, a screen with three white dashes was shown instead of the arrow stimulus. To insure that subjects would respond consistently, they were told that if they did not respond on a given trial, they would lose $1.00. No-response errors were excluded from the analyses.

Each session consisted of 12 runs of 11 trials each, for a total of 132 trials. Trial length ranged from 13.5 to 21.0 s. Trials were ordered pseudorandomly, with the constraints that there were equal numbers of the four conditions (choice reward, no-choice reward, choice punishment, no-choice punishment), and that no more than 3 events of a given trial type could occur in a row. As in the other experiments, the subjects earned $50 by the end of the experiment. At the end of the experiment, subjects filled out a brief Likert-scale questionnaire asking their impressions of the task, including whether they felt they had more control when responding to the yellow circle or to the blue circle, whether they cared more about winning and losing money when responding to the yellow circle or to the blue circle, and whether they thought there was a pattern to the "correct" responses in each condition.

Data Acquisition

Subjects were scanned using a conventional 1.5 Tesla GE Signa whole-body scanner and standard radio frequency coil. Structural images were collected using a standard T1-weighted pulse sequence, in 36 contiguous slices ($3.75 \times 3.75 \times 3.8$ mm voxels) parallel to the AC-PC line. Oblique axial functional images were collected at the location of the middle twenty of the structural slices, using a one-shot spiral pulse sequence (TR = 1500 ms, TE = 35 ms, FOV = 24 cm, flip angle = 70°).

Data Analysis

The NeuroImaging Software package (NIS 3.5), developed at the University of Pittsburgh and Princeton University, was used to analyze the fMRI data, along with the graphical computing environment, Functional Imaging Software Widgets (fiswidgets; Fissell et al., 2003). Images were reconstructed and corrected for subject motion with Automated Image Registration (AIR 3.08; Woods et al., 1992). Runs in which motion exceeded 3 mm or 3° in any direction were not used in analysis. The images were detrended to adjust for scanner drift within runs. The structural images of each subject were stripped to remove the skull and coregistered to a common reference brain, chosen from among the subjects (Woods et al., 1993). Functional images were transformed into the same common space, normalized by a mean scaling of each image to match global mean image intensities across subjects, and smoothed using a three-dimensional Gaussian filter (8 mm FWHM) to account for anatomical differences between subjects. This set of data was then analyzed statistically. To visualize the data, the AFNI software program was used (Cox, 1996); this program was also used to warp the data into Talairach space (Talairach and Tournoux, 1988).

For each experiment a repeated-measures ANOVA was performed on the coregistered functional data in the two voxels representing peak activation reported in the left and right caudate nucleus in previously published work from our laboratory (Delgado et al., 2000). The Talairach coordinates corresponding to these voxels are ($x = 12$, $y = 15$, $z = 7$) and ($x = -11$, $y = 16$, $z = 7$). For Experiment 1, subject was a random factor and trial valence (reward, punishment, or neutral) and time (1.5 s time periods, T1–T7) were within-subjects factors. Note that although trial length varied, only the first 10.5 s of each trial (beginning with the presentation of the arrow) were analyzed. For Experiment 2, the ANOVA had subject as a random factor and cue condition (uncued or cued), trial valence (reward or punishment), and time (1.5 s time periods, T1–T9) as within-subjects factors. For this experiment, the first 13.5 s of each trial were analyzed, beginning with the time period 3 s before the presentation of the arrow. This is when the cue appeared for trials in which a cue was present. For Experiment 3, the ANOVA was performed with subject as a random factor and cue condition (choice or no-choice), trial valence (reward or punishment), and time (1.5 s time periods, T1–T10) as within-subjects factors. The first 15 s of each trial were analyzed, beginning with the time period when the cue stimulus appeared, 3 s before the arrow stimulus appeared.

Additionally, a voxel-wise repeated-measures ANOVA was performed on all the coregistered data for each experiment, with the same factors as in the a priori analysis of the caudate voxels. For Experiment 1, a second ANOVA was performed excluding neutral trials, for more direct comparison with the other two experiments. Activation clusters were defined as regions with four or more contiguous voxels showing a significant effect; this contiguity threshold serves as a precaution against type 1 errors (Forman et al., 1995). The time courses from such clusters located in the striatum were plotted and analyzed. A conjunction analysis was performed to isolate voxels showing a valence by time interaction at a significance threshold of $p < 0.001$ in all three experiments; in this analysis, the Experiment 1 ANOVA excluding neutral trials was used. The time course from the resulting conjunction voxels was also plotted and analyzed.

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