Motivation-dependent Responses in the Human Caudate Nucleus

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Motivation is a complex process that leads to completion or avoidance of a behavior. Past research strongly implicates the basal ganglia in a circuit integral for the control of motivation. Specifically, the human striatum has been shown to process reward information, differentiating between monetary rewards and punishments in recent neuroimaging experiments. It is unclear, however, how the dorsal striatum, particularly the caudate nucleus, responds to changes in the motivational context of a task. Using an event-related design, where participants were given positive and negative feedback upon guessing the value of an unknown card, we manipulated the motivational context of the task by dividing trials into periods of high incentive (where visual feedback indicated monetary rewards and punishments) and low incentive (where visual feedback indicated only accuracy). We found that activity in the caudate nucleus was strongly influenced by the different incentive periods. The hemodynamic response was characterized by a larger rise at the onset of trials and larger differences between positive and negative feedback during periods of high incentive. These results suggest that changes in motivation are capable of modulating basal ganglia activity, and further support an important role for the caudate nucleus in affective processing.

Keywords: basal ganglia, emotion, feedback, incentive, learning, punishment, reward, striatum, valence

Introduction

Behavior is often dependent on motivation. Changes in the motivational context surrounding the outcome of an action might enhance or reduce the frequency of the associated behavior. For example, a child may approach the behavior of doing homework differently if he is aware that praise and extra dessert will be received provided homework is finished before dinner. Although the addition of incentives to the performance of a behavior likely manipulates motivational processes, one must also consider the value of the incentive. Thus, the motivational context attached to the performance of an action or behavior is altered by both the anticipation and the value of the desired incentive. It is likely that areas of the brain responsible for mediating goal-directed behavior are influenced by changes in the motivational context of a behavior. One specific region whose activity may change in parallel with changes in the drive to perform a behavior is the basal ganglia, a structure previously implicated in processing reward information (Apicella *et al.*, 1991; Robbins and Everitt, 1992; Kawagoe *et al.*, 1998; Delgado *et al.*, 2000; Hollerman *et al.*, 2000; Knutson *et al.*, 2000; Schultz *et al.*, 2000; Berns *et al.*, 2001; Breiter *et al.*, 2001; Montague and Berns, 2002).

Recently, neuroimaging data have supported a role for the striatum, the input unit of the basal ganglia, in detecting the properties of a reward-related stimulus, such as valence and magnitude. Activity in the human striatum has been shown to respond to the expectation of a possible incentive (Breiter *et al.*, 2001; Knutson *et al.*, 2001a), further showing differential responses according to the incentive's valence (Delgado *et al.*, 2000) and magnitude (Breiter *et al.*, 2001; Delgado *et al.*, 2003), where the delivery of a monetary reward yields a larger signal than the presentation of a lesser monetary reward or punishment. Thus, research suggests that the striatum is capable of responding to reward-related stimuli and that it can differentiate between positive and negative incentives. Most of the human work, however, has highlighted the contributions of the ventral striatum to reward processing. There has been less focus on the responses of the human dorsal striatum to stimuli of positive and negative connotation. If the human dorsal striatum is involved in the brain's response to motivational changes in the environment, then the activity of a key striatum structure, such as the caudate nucleus, during performance of a behavioral task should be influenced by changes in the motivational context.

One investigation of how changes in motivation may affect activity in the dorsal striatum was reported by Kawagoe *et al.* (1998). In an elegant study, the authors recorded from neurons in the caudate nucleus of monkeys while they performed a memory-guided-saccade task in which motivational context was manipulated. Monkeys were trained to make a saccade to the location of a previously presented cue, but only one of four possible locations yielded a reward. The response of caudate neurons was dependent on the expectation of a possible reward, irrespective of location, thus showing that activity in the non-human primate dorsal striatum can be influenced by motivation.

The goal of the current study was to examine how changes in the motivational context of a task would affect activity in the caudate nucleus in humans. In a previous study, we found that during performance of a simple gambling paradigm the caudate nucleus showed a different pattern of activation for reward and punishment trials (Delgado *et al.*, 2000). We adapted the paradigm to include alternating periods of high and low motivational context, in which we varied the incentive to perform the task. Monetary rewards and punishments served as feedback during task periods of increased motivational context (high incentive condition), while non-monetary positive and negative feedback were given during task periods of low motivational context (low incentive condition). To assess the response of the caudate nucleus to variations in motivational context, we kept the motor and cognitive requirements of the task constant, but changed the motivational levels via the incentive value of the outcome. Predictions were made according to our previous experience with this task (Delgado

et al., 2000), where we observed an initial rise in hemodynamic response in the caudate nucleus at the onset of a trial, followed by a differential response to the actual incentive that was higher for positive than negative outcomes. Specifically, we predicted that the anticipation of the desired incentive (in this instance, the positive outcome) would be reflected by the initial rise in activity at the onset of a trial, and such activity would be higher during periods of high incentive. Further, we expected that the difference between the hemodynamic response to positive and negative outcomes should be larger during periods of high incentive versus periods of low incentive.

Methods

Nine right-handed volunteers participated in this study (five female, four male). Participants were students from the University of Pittsburgh (average age = 22.9, SD = 3.26). Participants were asked to fill out a small questionnaire to ensure that they were not abusive or excessive in their gambling behavior (i.e. have you played cards for money: not at all, less than once a week or once a week or more). The questionnaire was based on the South Oaks Gambling Screen (Lesieur and Blume, 1987) and no participants were disqualified based on their answers. All participants gave informed consent according to the Institutional Review Board at the University of Pittsburgh.

The paradigm involved a series of 180 interleaved trials, divided into 12 runs of 15 trials each. Each trial began with the presentation of a visually displayed card projected onto a screen (Fig. 1*a*). The card had an unknown value ranging from 1 to 9, and the participant was instructed to make a guess about the value of the card. A question mark appeared in the center of the card indicating that the participant had 2.5 s to guess if the card value was higher or lower than the number 5. Participants pressed the left or right button of a response unit to indicate their selection. After the choice-making period, a number appeared in the center of the card for 500 ms, followed by an arrow that was also displayed for another 500 ms. Each correct guess led to the presentation of a positive feedback. An incorrect guess was followed by negative feedback. The trials were blocked into alternating runs of monetary and non-monetary feedback trials (referred to as periods of high and low incentive). Prior to the onset of each run, participants were cued with the words 'money block' indicating that the trials in the upcoming run were all worth money (high incentive trials), or 'no-money block' indicating the trials in the upcoming run were not worth any money (low incentive trials). During the monetary runs, or periods of high incentive, a green positive feedback arrow pointing upwards indicated that the participant correctly guessed the card value and would receive a monetary gain of $4.00 or a 'reward'. A red negative feedback arrow pointing down indicated a monetary loss of $2.00, or a 'punishment'. If the outcome was a '5' then the participant was presented with neutral feedback (–), representing neither a loss nor a gain of money. During the non-monetary runs, or periods of low incentive, participants received positive or negative feedback after a response, but no money. The arrows in the low incentive trials pointed upward when the response was correct, and downward following an incorrect response. Both the upward and downward arrows were blue. Neutral feedback (–) represented neither a correct or incorrect response.

Participants were compensated $20.00 for volunteering, a value that represented the minimum possible gain as they were also told that whatever money they won during performance of the task was theirs to keep. Unbeknownst to the participants, the outcome of each trial was predetermined. Card values were selected only after the participant indicated their guess on each trial. Therefore, there were five types of trials that appeared 36 times per session (positive feedback during periods of high and low incentive, negative feedback during periods of high and low incentive, and neutral events). Trials where a response was not made on time were depicted by a pound sign (#) and were excluded from neuroimaging analysis. After the 3.5 s period between presentation of the response cue (question mark) and the feedback, there was an 11.5 s delay before the onset of the next trial. Each trial, therefore, lasted 15 s (Fig. 1*b*). Stimulus presentation and behavioral data acquisition were controlled by a Macintosh computer with PsyScope software (Macwhinney *et al.*, 1997).

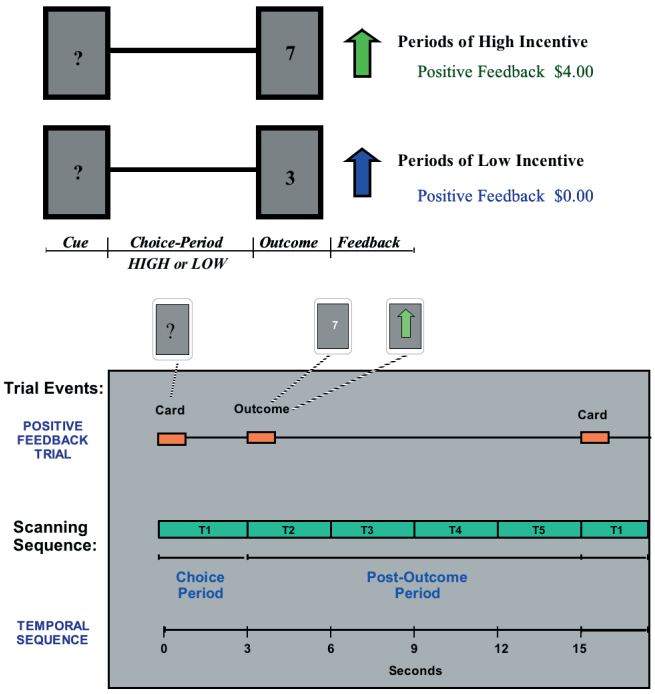

Figure 1. (*a*) Description of events in the card-guessing paradigm. At the onset of a trial, participants were presented with a cue (question mark) and asked to guess if the value of the card was higher or lower than 5. After the choice period (2.5 s), the value of the card (the outcome) was revealed (500 ms) and followed by the appropriate feedback (an up or down arrow presented for 500 ms). There was an 11.5 s delay before the onset of the next trial. Half of the trials were presented during periods of high incentive, where the feedback arrow was monetary, and participants received $4.00 per correct guess (green arrow) and were penalized $2.00 for incorrect guesses (red arrow). The other half of the trials were presented during periods of low incentive, where participants received non-monetary positive and negative feedback (blue arrows) according to their performance. (*b*) Temporal organization of a single trial in the card-guessing paradigm. Five scans of 3 s each were acquired during each 15 s trial (time points 1–5, referred to as T1–T5). Analysis was performed including all time points within a trial (T1–T5). Further investigations of the hemodynamic response occurred at the onset of the trial (the initial rise observed after presentation of the first trial cue, time periods T1–T2) and during the time period where differential responses between reward and punishment were previously observed using this paradigm (time period T4).

A conventional 1.5-T GE Signa whole-body scanner and standard RF coil were used to obtain 20 contiguous oblique-axial slices (3.75 × 3.75 × 3.8 mm voxels) parallel to the AC–PC line. Structural images were acquired in the same location as the functional images, using a standard T_1-weighted pulse sequence. Functional images were acquired using a 2-interleave spiral pulse sequence [T_R = 1500 ms, T_E = 34 ms, FOV = 24 cm, flip angle = 70° (Noll *et al.*, 1995)]. This T_2*-weighted pulse sequence allowed 20 slices to be acquired every 3 s. Images were reconstructed and corrected for motion with AIR (Woods *et al.*, 1992), smoothed using a three-dimensional Gaussian filter (4 mm FWHM) to account for small variations in signal due to movement and vascular effects, adjusted for scanner drift between runs with an additive baseline correction applied to each voxel-wise time course independently, and detrended with a simple linear regression to adjust for drift within runs. Structural images of each participant were co-registered to a common reference brain (Woods *et al.*, 1993). Both the statistical maps created in analysis and the reference brain were transformed to standard Talairach stereotaxic space (Talairach and Tournoux, 1988) using AFNI software (Cox, 1996). Functional images were then globally mean-normalized to minimize

differences in image intensity within a session and between participants, and smoothed using a three-dimensional Gaussian filter (4 mm FWHM) to account for between-subject anatomic differences.

A repeated-measures three-way ANOVA was performed on the entire set of co-registered data, with participants as a random factor. Within-subjects factors included type of trial (high and low incentive), type of feedback (positive and negative) and time (the five sequential 3 s scans in a trial of 15 s, referred to as T1–T5). Neutral trials were removed from analysis due to variability in both imaging data and participant's responses to such trials observed in our prior study (Delgado *et al.*, 2000). Our analyses were motivated by our experience with this task. Based upon prior findings (Delgado *et al.*, 2000), we began by examining overall task activation using voxelwise ANOVAs that examined the main effect of time (T1–T5). Regions of interest (ROIs) consisting of five or more contiguous voxels were selected, as a precaution against type 1 errors (Forman *et al.*, 1995). Inferences were made on regions defined by strength of effect ($P < 0.00001$) and size (five or more voxels). Further evaluation was done by analysis of event-related time-series data for each region of interest, which represent functional magnetic resonance imaging (fMRI) mean intensity value for each condition for time periods T1–T5.

Our primary, and *a priori* focus, was upon the pattern of response in the caudate. Thus, the results from the voxel-wise ANOVAs were used to isolate a left caudate ROI (peak at $x, y, z = -8, 8, 5$) and a right caudate ROI (peak at $x, y, z = 11, 7, 7$). We then looked at two phases of the hemodynamic response in these regions: (i) activation during the choice phase, as reflected in the initial rise from the onset of the trial (T1–T2) and (ii) activation during the outcome phase, particularly the time point where we have previously observed differential responses to feedback (T4). To examine the choice phase, activity in the caudate ROIs was assessed with a three-way ANOVA, with time (T1 or T2), period (high incentive or low incentive), and hemisphere (left or right) as factors. If changing the motivational context of the task influences activity in the caudate nucleus, we should observe an interaction between time and period, reflected by a higher initial rise at the onset of high incentive trials. The second comparison addressed whether differential responses to positive and negative feedback were affected by the motivational state. Activity in the caudate ROIs was examined at time period T4, the time at which we have previously observed the greatest differences between positive and negative feedback. We used a three-way ANOVA with feedback (positive or negative), period (high incentive or low incentive), and hemisphere (left or right) as factors. If changing the motivational context of a task affects the degree to which the feedback are differentiated at T4, then we should observe an interaction between feedback and period, reflected by clearer positive and negative feedback differences during high incentive trials. For our target area of interest, the caudate nucleus, the alpha level for the *a priori* contrasts was $P < 0.05$. Additionally, uncorrected planned contrasts (two paired *t*-tests, two-tailed) or *post hoc* tests (two paired *t*-tests, two-tailed) used a stricter alpha level of $P < 0.01$. All other regions identified in the task were also subjected to *post hoc* ANOVAs, although a stricter alpha level of $P < 0.01$ was used since these regions were not specified *a priori*.

Results

Behavioral Results

Participants were asked to make a response for each trial during the fMRI session, during both periods of high and low incentive. One tailed, paired *t*-tests suggested that participants missed more trials (e.g. failed to respond in time) during periods of low incentive [$t(8) = 4.37$, $P < 0.01$]. There was no evidence of a continued cognitive strategy as the distribution of 'high' and 'low' choices was random during both periods of high incentive [choices: 'high', mean ± SD = 44.89 ± 10.8; 'low', 45 ± 10.82; $t(8) = 0.15$, $P = 0.49$] and low incentive [choices: 'high', 43.11 ± 7.64; 'low', 46.44 ± 7.62; $t(8) = 0.66$, $P = 0.27$]. Participant's reaction times were collected for all trials and were variable across different periods [high incentive −658.29 ± 175.34; low incentive −646.34 ± 125.14; $t(8) = 0.38$, $P = 0.36$], although seven out of nine participants showed faster responses during periods of high incentive trials, as opposed to trials of low incentive, based on a Spearman rank correlation ($R = 0.82$, $P < 0.02$).

Neuroimaging Results

Regions activated during performance of the task (main effect of time, T1–T5) are listed in Table 1 [$F(4,32) = 11.00$, $P < 0.00001$]. They included brain areas that contribute to both sensory (i.e. visual cortex, somatosensory cortex) and affective (i.e. striatum) processes. The *a priori* ROI was the dorsal striatum, and as expected, a left (Fig. 2) and right (Fig. 3) caudate nucleus ROIs were identified in this contrast. The hemodynamic response showed two patterns that were further investigated: an initial rise at the onset of the trial and a differential response to positive and negative feedback.

Table 1
Areas showing a main effect of time

			Talairach coordinates		
Region of activation	Brodmann areas	Laterality	*x*	*y*	*z*
Increasing activity					
Precuneus	7/31	L	–3	–24	42
Cingulate gyrus	24	L	–1	–5	42
Inferior parietal gyrus	40	L	–43	–28	41
Inferior parietal gyrus	40	R	49	–46	40
Precentral gyrus	6	L	–39	–5	38
Medial frontal gyrus	32	R	8	20	37
Precuneus	7	L	–22	–59	34
Cuneus	19	R	9	–72	33
Inferior frontal gyrus	44/6	R	46	–5	32
Posterior cingulate gyrus	23/31	R	6	–27	27
Insula		L	–40	–5	16
Thalamus		R	18	–18	11
Thalamus		L	–9	–18	8
Inferior frontal gyrus	45	L	–27	21	8
Inferior frontal gyrus	45	R	35	23	8
Caudate nucleus		R	11	7	7
Caudate nucleus		L	–8	8	5
Middle temporal gyrus	21/37	L	–43	–47	9
Middle temporal gyrus	21	R	55	–41	5
Fusiform gyrus	18/19	L	–30	–82	–11
Fusiform gyrus	18/19	R	32	–85	–12
Orbitofrontal gyrus	11	R	24	49	–12
Decreasing activity					
Superior frontal gyrus	8	L	–6	43	42
Middle temporal gyrus	39	L	–41	–74	27
Insula		R	38	–20	15
Cingulate gyrus	24/32	L	–2	33	4

Activations reflect peaks found in ROIs of five or more contiguous voxels defined by this contrast [$F(4,32) = 11.00$, $P < 0.00001$]. Brodmann numeration is provided when applicable. The laterality of the activated ROIs is also provided where regions were located either in the right (R) or left (L) hemisphere. Finally, the stereotaxic coordinates of the peak of the activation are given according to Talairach space (Talairach and Tournoux, 1988).

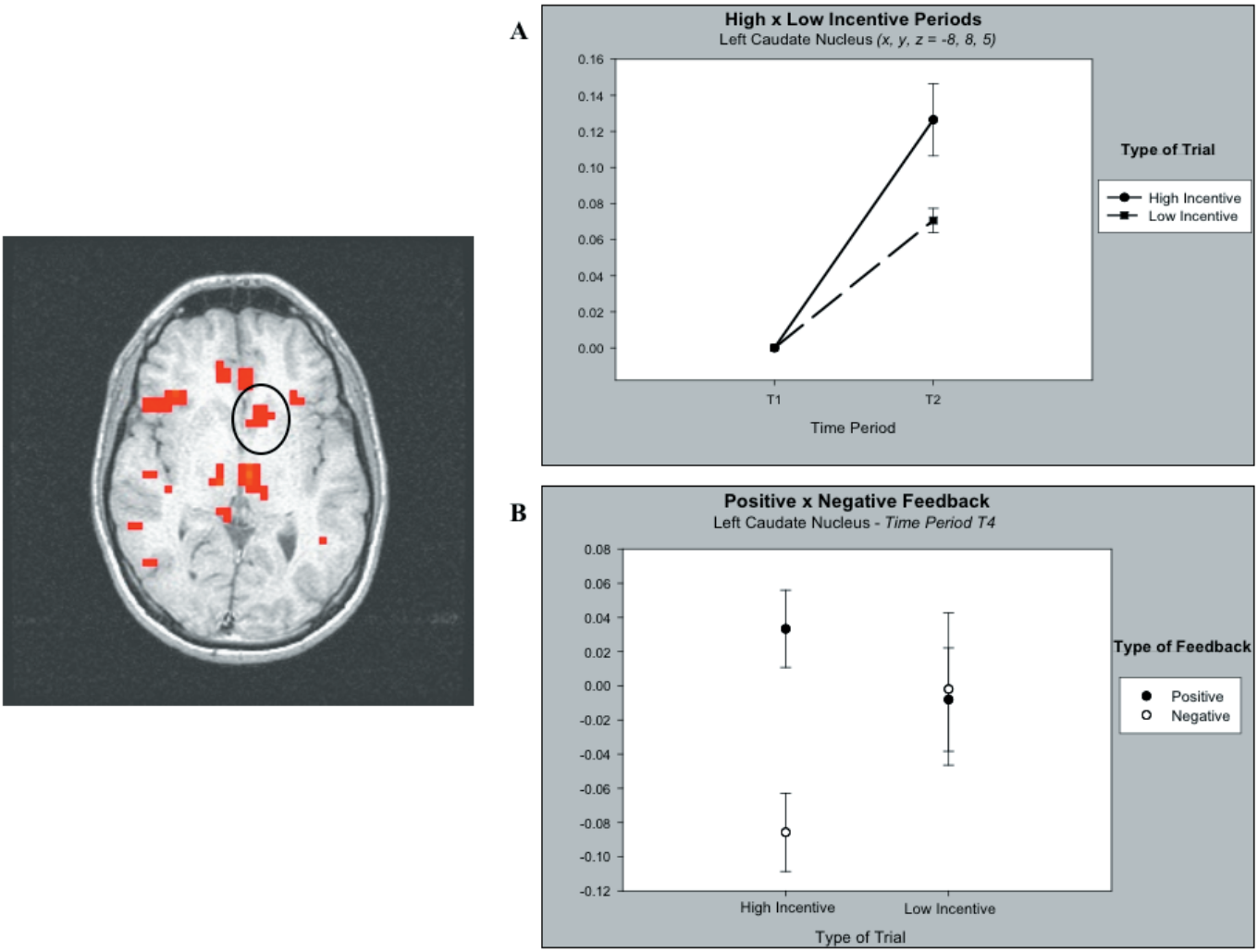

Figure 2. Activation of the left caudate nucleus defined in the main effect of time contrast (circled ROI: *x, y, z* = –8, 8, 5). (*a*) The initial rise at the onset of the trial (T1–T2) was larger during periods of high incentive, where the feedback was monetary, than under periods of low incentive, where the feedback was informative, but non-monetary. (*b*) Differential responses to positive and negative feedback during periods of high and low incentive in the left caudate nucleus at time period T4, where our previous studies have observed the largest differential responses between reward and punishment outcomes. In the current study, such differential responses were only observed during periods of high incentive. Standard error bars for all graphs displayed were calculated on a per participant basis across both time (T1–T5) and conditions (type of trial and type of feedback) using fMRI mean intensity values. These values were then standardized to per cent signal change differences and plotted.

The first observed pattern in the caudate hemodynamic response was an increase in activity at the onset of the trial that was significantly larger during periods of high incentive than periods of low incentive. This was indicated by a significant interaction between time and period (high versus low incentive) [$F(8,1) = 17.04$, $P < 0.003$]. There was also a significant interaction of hemisphere and time [$F(8,1) = 9.93$, $P < 0.01$], which merely reflect the fact that mean signal intensity was slightly higher in the right as compared to left caudate ROI. More importantly, the three-way interaction between time, period and hemisphere did not reach significance [$F(8,1) = 1.28$, $P = 0.29$], which suggests that the left and right caudate were influenced relatively similarly by the motivational manipulation (see also left and right caudate T1–T2 graphs, Figs 2 and 3). However, the null three-way ANOVA results should be treated with caution due to limited power, and some hemispheric differences may exist [two-tailed, exploratory *t*-test suggests a very weak trend: $t(8) = 1.99$, $P < 0.08$, uncorrected]. To further examine these effects, planned contrasts (two-tailed *t*-tests) independently examined the effect of time for the periods of high and low incentive. During periods of high incentive, a highly significant effect was observed [$t(8) = 6.01$, $P < 0.0003$, *uncorrected*], but it is also noteworthy that a less significant, but still reliably rise was observed during periods of low incentive [$t(8) = 3.35$, $P < 0.01$, *uncorrected*]. This difference between the two periods, where the behavioral requirements are constant but motivational levels are different, can also be seen in Figure 4, which portrays the hemodynamic response of positive feedback under periods of high and low incentive in the left caudate.

The assessment of the outcome phase focused upon time-period T4, the time at which we have previously observed robust differences between positive and negative feedback (Delgado *et al.*, 2000), that are further modulated by the magnitude of the outcome (e.g. a $4.00 versus a $0.40 reward; Delgado *et al.*, 2003). The ANOVA revealed a main effect of period [$F(8,1) = 7.31$, $P < 0.03$], which reflects the fact that the MR signal intensity is higher overall for periods of high versus

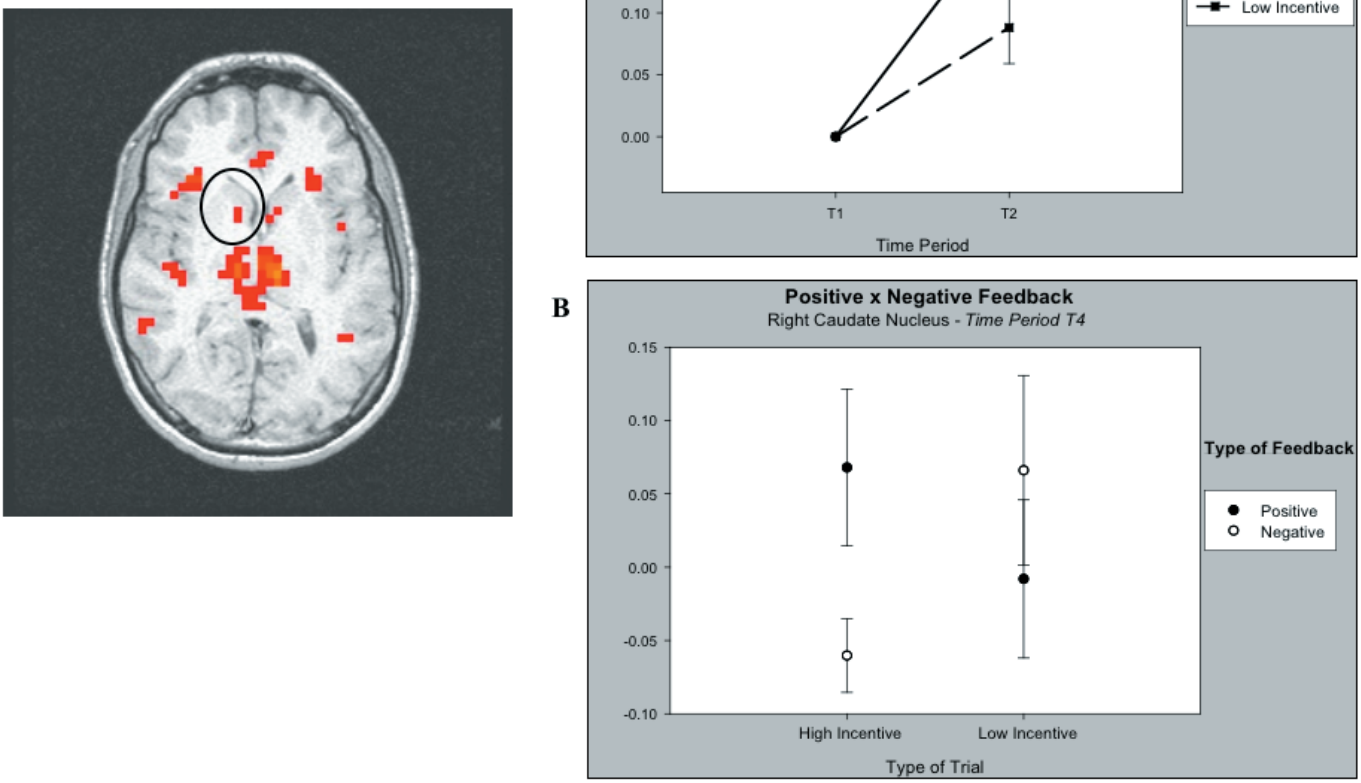

Figure 3. Activation of the right caudate nucleus defined in the main effect of time contrast (circled ROI: *x, y, z* = 11, 7, 7). (*a*) As it was observed in the left caudate nucleus, the initial rise at the onset of the trial (T1–T2) in the right caudate nucleus was larger during periods of high incentive, where the feedback was monetary, than under periods of low incentive, where the feedback was informative, but non-monetary. (*b*) Differential responses to positive and negative feedback during periods of high and low incentive in the right caudate nucleus at time period T4, where our previous studies have observed the largest differential responses between reward and punishment outcomes, were also observed. Standard error bars for all graphs displayed were calculated on a per participant basis across both time (T1–T5) and conditions (type of trial and type of feedback) using fMRI mean intensity values. These values were then standardized to per cent signal change differences and plotted.

low incentive (a finding that is consistent with the fact that the signal rises to a higher level during the onset of high incentive trials). The *a priori* focus was upon the interaction between period and feedback; a weak trend was found to support the hypothesis that the size of the positive versus negative feedback difference would be modulated by the attentional state. The interaction of feedback (correct versus incorrect) and period (high versus low incentive) failed to reach significance [$F(8,1) = 3.63$, $P = 0.09$]. This might at first seem to raise concerns about the reliability of our prior findings; to address this issue, we conducted a *post hoc* two-tailed *t*-test on the correct versus incorrect feedback trials (data from time period T4) during periods of high incentive only, and found a highly significant effect of feedback [$t(8) = 3.33$, $P < 0.01$, *uncorrected*]. A similar contrast during periods of low incentive revealed an insignificant effect of feedback [$t(8) = 0.09$, $P = 0.935$, *uncorrected*], as expected given the observed trend towards an interaction between period and feedback.

Besides the striatal focus of interest, other brain regions were activated during performance of the task (main effect of time, T1–T5 – Table 1). Although our *a priori* region of interest was the striatum, we performed exploratory analysis on these other regions. Specifically we applied *post hoc* ANOVAs that used the same factors as those employed in our analysis of the striatum with the exception that hemisphere was not included when the ROI was unilateral. We report significant results for our two *a priori* interactions of interest (time × period in the choice phase, and feedback × period in the outcome phase) using a more strict alpha of $P < 0.01$; however, due to the *post hoc* nature of these exploratory analyses, these results should be considered preliminary. No regions showed an interaction between time and period in the choice phase. One region showed a significant interaction between feedback and period during the outcome phase, observed in the cingulate cortex [$F(8,1) = 19.9$, $P < 0.01$]. Higher signals were observed for the negative feedback in the

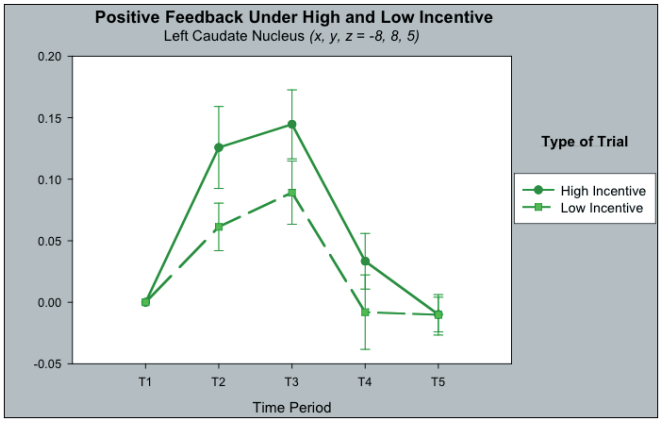

Figure 4. Hemodynamic response of the left caudate nucleus to trials where a positive feedback was received under periods of high and low incentive. Participants are presented with the cue (question mark) at the onset of the trial and asked to guess the value of the card. The feedback is revealed 3 s later. When the feedback was positive (monetary reward for periods of high incentive and non-monetary positive feedback for periods of low incentive), the activity of trials during periods of high incentive had a larger initial rise from onset and overall larger response than the activity of trials during periods of low incentive.

low incentive periods, perhaps in accordance with a role for the cingulate cortex in error processing (Ullsperger and van Cramon, 2003).

Discussion

The goal of this experiment was to investigate the hemodynamic response of the dorsal striatum when the motivational context of a task was manipulated. Brain activity was measured during performance of a gambling paradigm previously shown to engage striatal activity. Participants were asked to guess the value of an unknown card and were given feedback on their performance. The feedback was at times financial (monetary gains or losses), or just informative (non-monetary positive and negative feedback). Thus, while the task's behavioral requirements were kept constant, the task's motivational context was manipulated across periods of monetary and non-monetary trials. A dorsal striatum region of interest, specifically located in the caudate nucleus, showed two characteristics. First, an observed initial rise at the onset of a trial was larger when the incentive was higher (during periods of high incentive). Second, after delivery of the feedback, the difference between positive and negative feedback during periods of high incentive tended to be larger than the difference between positive and negative feedback during periods of low incentive. Taken together, both observations suggest that motivational changes in task context influence activity in the human caudate nucleus, further implicating the striatum in motivated behaviors.

It is important to be mindful, however, of the many physiological and psychological processes that can be altered when discussing motivational changes. Arousal, uncertainty and expectation are examples of motivational processes and it is difficult to disengage one from the other; thus, when we refer to changes in the motivational context of a task, it includes potential modulation related to all the aforementioned processes. Motivation itself can be broadly defined as a modulating influence on the direction of behavior (Shizgal, 1999). Both internal (i.e. hormonal changes) and external (i.e. environmental changes) factors can impact motivation, and thus, shape behavior. The addition of an incentive to an action, for example, will lead to an anticipation for the desired incentive and undoubtedly motivate someone to perform such action. Thus, a brain structure such as the caudate nucleus that typically responds to a task where feedback is received (Elliott *et al.*, 1998b), may respond even more if the motivational context of the task is changed and a more valuable feedback or incentive is presented.

The striatum has been implicated not only in processing task-related feedback but also in processing reward-related information by a variety of studies and is therefore a strong candidate to also process and monitor motivational information. Neurons in both dorsal and ventral striatum have been found to respond to the expectation and delivery of a primary reward (Hikosaka *et al.*, 1989; Apicella *et al.*, 1991, 1992; Schultz *et al.*, 1992), to conditioned stimuli that predict a reward (Hollerman and Schultz, 1998; Hollerman *et al.*, 2000), and to different types of reward, showing a preference ranking system (Hassani *et al.*, 2001). Similarly, activation in the striatum has been reported in neuroimaging paradigms during delivery of rewards (Delgado *et al.*, 2000; Breiter *et al.*, 2001; Delgado *et al.*, 2003), conditioned stimuli that predict a reward (Berns *et al.*, 2001; Pagnoni *et al.*, 2002; McClure *et al.*, 2003; O'Doherty *et al.*, 2003) and even during the anticipation of primary (O'Doherty *et al.*, 2002) and secondary rewards (Elliott *et al.*, 2000; Knutson *et al.*, 2000, 2001a,b; Breiter *et al.*, 2001). However, few neuroimaging studies have focused specifically on the role of the human caudate nucleus in motivation and reward, despite the various neurophysiological evidence suggesting a link between the non-human primate caudate nucleus and motivated, goal directed behavior (Hikosaka *et al.*, 1989; Apicella *et al.*, 1991; Kawagoe *et al.*, 1998; Hollerman *et al.*, 2000; Hassani *et al.*, 2001; Lauwereyns *et al.*, 2002). The card-guessing paradigm used in this experiment has previously been shown to activate the caudate nucleus during task performance, showing differential responses according to feedback valence (Delgado *et al.*, 2000) and magnitude (Delgado *et al.*, 2003).

A variety of neuroimaging tasks have indirectly targeted motivation by inducing manipulations of feedback, where the amount or valence was varied. For example, in one study, striatal activation was found for trials in which a cue indicated if a reward or non-reward should be anticipated (Knutson *et al.*, 2000). Although it is clear from such designs that motivation is influencing striatal activity, the results are blurred since the cues served as predictors of reward. The paradigm used in the current study involved the same cue across trials to indicate that an outcome was following, but not the valence of the outcome. Participants were aware only that an impending feedback was to be presented upon response during all trials, and that the incentive to correctly respond to the trial was higher during periods of high incentive (to gain a monetary reward or avoid a monetary punishment). Therefore, any observed differences in the rise of activity should reflect differences in motivational properties rather than the valence or magnitude of the stimuli. The initial rise in activity at the onset was significantly higher in trials presented during the periods of high incentive rather than those trials presented in the periods of low incentive. This finding indicates that changing the motivational context of the task influenced activity in the caudate nucleus. Although the initial rise is significantly larger during periods of high incentive, it is worth noting that a rise in activity was still

observed during periods of low incentive. This is in accordance with studies by Elliott *et al.* (1998b) that found activity in the caudate nucleus during blocks of a cognitive task where participants received non-monetary feedback, compared with blocks where feedback was absent. Since the rise is present in both high and low incentive periods, it might be reflecting an array of motivational processes. For example, the initial rise might reflect anticipatory feelings caused by the uncertainty of the outcome. This possibility is supported by observed neuronal response in the striatum in response to stimuli that predict a reward (Schultz *et al.*, 1998; Hollerman *et al.*, 2000; Schultz, 2000). In the case of our paradigm, the question mark at the onset of the trial may serve as a predictor of a possible reward, leading to more activity when the potential feedback is more desirable. Indeed, a recent study found that dopamine neurons, which project to the striatum, respond to uncertainty in accordance with the probability of an eventual outcome (Fiorillo *et al.*, 2003). The initial rise may also be reflecting some preparatory motor response, as participants were asked to make right-handed responses promptly after presentation of the cue, although this is less likely since the initial rise was observed in both left and right caudate nucleus.

A second component of the observed response of the caudate nucleus is the activation pattern that follows the delivery of positive and negative feedback. Previously, we demonstrated that activity in the caudate nucleus shows a differential response between reward and punishment trials ~6–9 s after delivery of the feedback (Delgado *et al.*, 2000, 2003). During this same time window, we evaluated the relative difference between correct and incorrect trials for both periods of high and low incentive. As expected, the difference between feedback trials was higher during periods of high incentive (though the interaction between feedback and period was only significant at trend levels). These findings suggest that the affective salience of a feedback (monetary versus non-monetary) can influence the blood-flow response, although, due to statistical significance, further studies are necessary to support this claim.

One difficulty in interpreting the differences between high and low incentive periods after the delivery of the feedback is that we cannot distinguish between the effects of motivational state and the magnitude of the feedback received. We have shown that the caudate nucleus is sensitive to the magnitude of monetary feedback, with larger differences between reward and punishment observed with $4 rewards and $2 punishments than $0.40 rewards and $0.20 punishments (Delgado *et al.*, 2003). Thus, the insignificant difference between correct and incorrect trials during periods of low incentive may represent an extension of these prior results, since at some point feedback of very low magnitude (such as non-monetary feedback) may produce such small responses to the feedback that significant differences between reward and punishment trials can no longer be observed.

Alternatively, it is possible that the response to a particular reward or punishment is influenced by the context in which it is received. For instance, if a few trials with monetary feedback were embedded in a period of low incentive, insignificant differences between these monetary reward and punishment trials might now be found (although the confound between motivation and reward magnitude would now be replaced with a confound between expectancy and reward value). Along similar lines, it is possible that positive and negative feedback differences in low incentive periods might be more prominent if these trials occurred in a scanning session that did not include high incentive, monetary reward and punishment trials. However, the results of other studies, which have also failed to find differences between positive and negative non-monetary feedback in overall activation of the caudate nucleus (Elliott *et al.*, 1998a,b), argue against this interpretation.

Finally, it is important to discuss the lack of ventral striatum activation in this study. Activation in other neuroimaging studies have highlighted the contributions of the ventral striatum to reward processing (Breiter *et al.*, 1997; Elliott *et al.*, 2000; Berns *et al.*, 2001; Breiter *et al.*, 2001; Knutson *et al.*, 2001a; Montague and Berns, 2002; O'Doherty *et al.*, 2002, 2003), concurrent with animal literature (Apicella *et al.*, 1991; Koob, 1992; Robbins and Everitt, 1992, 1996; Koob, 1996; Berridge and Robinson, 1998; Shidara *et al.*, 1998; Di Chiara *et al.*, 1999; Rolls, 1999; Cardinal *et al.*, 2002). This study primarily focuses on the dorsal striatum, which as previously discussed is also involved in reward-related processing, for a variety of reasons. First, it seems to be the region where the most robust activity is seen when using the current paradigm (Delgado *et al.*, 2000, 2003). Perhaps features of this paradigm are more successful in recruiting dorsal than ventral activation, such as feedback presentation or the fact that the outcome is contingent on an action (making a choice at the presentation of the cue). Second, perhaps technical issues regarding either signal dropout in more ventral areas of the brain (maybe amplified by the oblique-axial acquisition of functional slices, which may have attenuated signals from basal forebrain regions), in conjunction with the low number of samples per participants (and conservative ANOVA threshold) may have obscured that region. Although, activation in the ventral striatum was observed in our first study (Delgado *et al.*, 2000), twice the number of trials per participant were present and the mean intensity signal was higher for more dorsal than ventral areas of the brain, suggesting some signal drop out. Third, a growing number of studies are finding that the dorsal striatum is important in motivational processes as previously discussed. One recent positron emission tomography (PET) study, for example, looked at dopamine binding in food-deprived participants following food stimulation (i.e. when hungry participants were exposed to food items) and found increases in extracellular dopamine associated with dorsal, but not ventral striatum, and these increases were further correlated with self-reports of 'desire' for the food item (Volkow *et al.*, 2002).

Overall, our results support the idea that the dorsal striatum, and in particular the caudate nucleus, has an important role in processing reward-related information. The response of the caudate nucleus can be fractionated into pre- and post-outcome effects. An initial rise in activation is present pre-outcome during both periods of high and low incentive, but post-outcome differences between feedback valence were only detected during periods of high incentive associated with the delivery of monetary rewards and punishments. The results and ideas put forth in this study further implicate the caudate nucleus as a structure integral in mediating motivated or goal-directed behaviors.

Notes

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