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Valence and salience contribute to nucleus accumbens activation

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Abstract

Different accounts of nucleus accumbens (NAcc) function have emphasized its role in representing either valence or salience during incentive anticipation. In an event-related FMRI experiment, we independently manipulated valence and salience by cuing participants to anticipate certain and uncertain monetary gains and losses. NAcc activation correlated with both valence and salience. On trials with certain outcomes, NAcc activation increased for anticipated gains and decreased for anticipated losses. On trials with uncertain outcomes, NAcc activation increased for both anticipated gains and losses but did not differ between them. These findings suggest that NAcc activation separately represents both valence and salience, consistent with its hypothesized role in appetitive motivation.

Introduction

A central goal of affective neuroscience is to understand how the brain generates emotional experience. Emotional states differ in many ways, but one of the most fundamental is valence, or how positive or negative an emotion feels (Russell, 1980; Wundt, 1896). Distinguishing between positive and negative has fundamental implications for both subjective experience and behavior. Positive emotions are linked to approach, while negative emotions are linked to avoidance (Schneirla, 1959). Despite the importance of this dimension, identifying neural correlates of valence with human brain imaging techniques has remained a challenge.

Several decades of comparative research on reward processing have identified a mesolimbic network that responds to anticipated or received positive incentives (Olds and Milner, 1954), and recent neuroimaging research suggests that these findings generalize to humans (Knutson and Cooper, 2005; Montague and Berns, 2002; O'Doherty, 2004). This research has implicated the midbrain (Schultz, 1998) and its projection areas in the ventral striatum (especially the nucleus accumbens [NAcc]; Knutson et al., 2001), dorsal striatum (Delgado et al., 2004; Zald et al., 2004), orbitofrontal cortex (Rolls, 2004), and other areas of mesial prefrontal cortex (Knutson et al., 2003; Ramnani et al., 2004), in anticipating or receiving rewards from money to attractive pictures to pleasant tastes. This network has been characterized as a "reward pathway" that responds to subjectively positive stimuli.

In both animal and human research, the NAcc in particular has been linked to anticipation of positive incentives (Ikemoto and Panksepp, 1999; Knutson et al., 2001). Dopamine infusion into this structure unconditionally elicits appetitive behavior (Ikemoto and Panksepp, 1999), and dopamine is released in it prior to delivery of primary or pharmacological rewards (Garris et al., 1999). The NAcc is a small structure nestled in the ventral parts of the striatum; it is not

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anatomically or cytoarchitectonically well-defined in humans, nor is it explicitly identified in commonly used brain atlases (i.e., Talairach and Tournoux, 1988), but neuroimaging researchers have devised anatomical boundaries for studies of humans (Breiter et al., 1997). According to these specifications, an increasing number of studies have demonstrated NAcc activation in humans in anticipation of monetary and other rewards (Knutson and Cooper, 2005). Two theories have emerged to account for this activation.

One account suggests that the positive valence of anticipated rewards drives NAcc activation and that NAcc activation is key to distinguishing positive from negative valence (Ikemoto and Panksepp, 1999; Knutson et al., 2001; Schultz et al., 2000). Positive cues are those that predict fitness-increasing outcomes for an organism; a cue's positive valence increases with reward magnitude, reward probability, or a particular motivational state (e.g., the sight of an oasis while thirsty). This account draws on imaging studies in humans that demonstrate increasing NAcc activation with increasing magnitude of anticipated rewards (Breiter et al., 2001; Knutson et al., 2001) and increasing self-reported positive arousal (Drevets et al., 2001), as well as decreasing NAcc activation with painful stimulation or increasing potential losses (Becerra et al., 2004; Tom et al., 2007). The valence account has historical roots in brain stimulation studies in rats (Olds and Milner, 1954), identifying electrical stimulation of the subcortex near the septum as a powerful positive reinforcer. More recently, this valence account has been revived by electrophysiological work in nonhuman primates linking reward anticipation to activation of midbrain dopamine neurons (Schultz et al., 1997; Tobler et al., 2005), some of which project to the NAcc. Computational models inspired by learning theory (Daw and Doya, 2006; Montague et al., 1996; Montague et al., 2006) have drawn on this data to suggest dopaminergic inputs to the NAcc represent a predictive learning signal that can guide behavior toward rewards. The valence account makes the key predictions that anticipatory NAcc activation will correlate with positive emotional experience and so will predict approach behavior (Knutson et al., 2007).

However, a second account suggests that the salience of an incentive cue, not its valence, drives NAcc activation, and thus that NAcc activation does not necessarily distinguish positive from negative. We define salience behaviorally: a salient cue is one that increases the chance an organism will need to make an important behavioral response in the near future. Crucially, this action might involve either approach or withdrawal; cues predicting danger or a need for escape will hold as much (if not more) salience as cues predicting reward. According to this account, the NAcc promotes attention towards important or unexpected events, rather than promoting approach behavior (Berridge & Robinson, 1998; Redgrave et al., 1999). Cue salience might increase with absolute incentive magnitude (good or bad), incentive uncertainty, or the contingency of the response (i.e., how important an organism's response is to the outcome). The salience account references evidence that NAcc activation increases with behavioral demands or interference (Tricomi et al., 2004; Zink et al., 2004; Zink et al., 2006), in response to novel nonrewarded events (Zink et al., 2003), or in anticipation of painful stimulation (Berridge and Robinson, 1998; Jensen et al., 2003). At least two studies have reported NAcc activation correlated with salience prediction error models of conditioning for painful stimuli that included decreases during unpredicted avoidance of painful stimuli (Jensen et al., 2007; Seymour et al., 2004). The salience account, like the valence account, pertains primarily to anticipation. Incentive outcomes (especially unpredicted) may recruit attention or arousal, but they do not necessarily require further action. Existing studies have yielded conflicting evidence as to whether all salient outcomes increase NAcc activation (e.g., O'Doherty et al., 2003; Pagnoni et al., 2002). In the case of anticipation, however, the salience account clearly makes predictions in contrast to the valence account. Specifically, the salience account predicts that NAcc activation will correlate with orienting and subjective arousal, but not preferentially with positive experience or approach behavior.

Earlier studies have not independently varied both valence and salience in the same incentive modality, creating an opportunity to test these opposing predictions in a single experiment. This study aimed to compare these accounts by independently varying valence and salience in the context of a monetary incentive delay task (Knutson et al., 2001) and by comparing anticipatory NAcc activation across different conditions. While earlier studies have often focused only on gains, we used both gain and loss to manipulate valence, and varied the certainty of the outcome to manipulate salience. We also examined the connection between NAcc activation and subjective experience by including self-reported affect probes in real time for a subset of the task trials.

This design enabled us to contrast specific conflicting predictions. Both valence and salience accounts predict increased NAcc activation during anticipation of uncertain (i.e., salient) gains and unchanged or decreased activation during anticipation of certain (i.e., nonsalient) losses. However, the valence account predicts increased NAcc activation during anticipation of certain gains but the salience account does not. Additionally, the salience account predicts increased NAcc activation during anticipation of uncertain losses but the valence account does not.

Given prior experimental support for both valence and salience accounts, we also considered the possibility that NAcc activation may correlate with multiple factors. Several recent studies found that midbrain dopamine neurons and ventral striatal activation represent different reward features during anticipation of a single reward (Dreher et al., 2006; Fiorillo et al., 2003; Knutson et al., 2005; Preuschoff et al., 2006). In these studies, early dopamine firing or NAcc activation increased with anticipated reward magnitude or probability, but continued dopamine firing or NAcc activation during anticipation increased with reward variance. These findings suggest that any single-factor theory of the NAcc's role may not fully account for its activation. We therefore predicted that NAcc activation might increase during anticipation of both certain gains and uncertain gains and losses.

Materials and methods

Participants

Twelve right-handed healthy volunteers (6 women; ages 19-25) participated. Participants had no history of neurological or psychiatric disorder and gave informed consent for a protocol approved by the Institutional Review Board of the Stanford University School of Medicine. Participants were screened for excessive head motion in the scanner (> 1 mm across sequential acquisitions) and none were excluded based on this criterion.

Experimental Design and Task

We used a variant of the monetary incentive delay (MID) task previously used by Knutson et al. (2001; 2003) to elicit NAcc activation in response to cues for monetary gain and loss (Figure 1). In each trial in the MID task, participants first see a shape cue (2000 ms) that indicates the trial condition. The cue disappears for a delay (2000-2500 ms, randomized), and then a visual target (a triangle) appears on the screen briefly (variable around 350 ms). Participants attempt to "hit" the target by pressing a button on a button box while the target is on-screen. After another delay (1300-1800 ms), participants receive feedback about how much money they earned on that trial and how much total money they have earned (2000 ms). The design allows the analysis of neural activity specific to anticipation, by examining the delay after participants have seen the cue but before the target appears. We used an automated adaptive timing algorithm that adjusted target speed for neutral and incentive trials separately to maintain a hit rate of approximately 66% for neutral and incentive trials over the experiment. Slower participants thus encountered slower targets, and faster participants encountered faster targets.

Initial target duration for all participants and trial conditions was 250 ms. Mean target duration over all participants and trials was 350.2 ms (*SEM* 39.9 ms).

Participants' potential gain or loss on each trial was determined by trial condition, each indicated by a different cue. In this variant, cues signaled six conditions: two levels of uncertainty ("uncertain" and "certain", signaled respectively with horizontal and vertical lines within the cue) crossed with three levels of incentive (gain, neutral, and loss, signaled respectively by circles, diamonds, and squares). In the three uncertain conditions, the amount of money a participant earned depended on whether they hit the target. In uncertain-gain trials, the participant made $3 on a hit, but made $0 (i.e., stayed the same) on a miss. In uncertain-neutral trials, the participant made $0 on both hits and misses. In uncertain-loss trials, the participant made $0 on a hit, but lost $3 on a miss.

In the three certain conditions, the amount of money a participant earned did not depend on his or her response speed. These three conditions again varied by incentive. In certain-gain trials, participants made $3 on both hits and misses. In certain-neutral trials, like uncertain-neutral trials, participants made $0 on both hits and misses. In certain-loss trials, participants lost $3 on both hits and misses. Participants were instructed to respond rapidly on all trials, regardless of whether they involved uncertain or certain outcomes.

Feedback for all incentive trials included a valence signal, so a miss on an uncertain-gain trial received "+$0.00" feedback, while a hit on an uncertain-loss trial received "-$0.00" feedback, and a hit on a certain-loss trial received "-$3.00" feedback. Feedback for neutral trials was always signaled neutrally, with "$0.00" (thus, participants could not distinguish hits from misses in neutral trials).

Participants were also asked to rate their affect during trials. Every trial contained an "affect probe" (8000 ms) asking participants to rate how they felt at that moment on two dimensions: arousal and positivity, each with a 5-point Likert scale (Russell, 1980). Participants used a five-button box to respond. The arousal scale ran from *not aroused* to *very aroused*, while the positivity scale ran from *negative* to *positive*. The side of each positivity anchor was counterbalanced across participants.

Affect probes were used at two different points in trials over the experiment. In one run, participants rated their affect during the anticipatory delay, after they had seen the cue and knew the trial condition, but before the target appeared. In this run ("anticipation-probe"), the affect probe was preceded and followed by delays (2000-2500 ms, randomized) after the cue but before the target. In the other run ("outcome-probe"), participants rated their affect after the outcome was displayed. In this run, the affect probe was preceded by outcome feedback and followed by a delay (2000 ms) before the next trial began. Total trial time was 18 s for all trials in both runs. Participants were informed before each run which probe placement they would encounter on that run, and the run order was counterbalanced across participants.

Each of the six trial conditions was presented eight times in individually randomized order during each of two runs, for a total task time of 28.8 min (14.4 min / run). Before scanning, participants were instructed about the incentives for each cue, as well as the meaning of each dimension of the affect probes. They performed a short (10 min) training version of the task, including all trial conditions with both affect-probe placements. They were also shown the cash they could win. Participants were not told about the adaptive timing algorithm, nor were they told how many trials of each condition they would face.

After the experiment, all participants were tested to make sure they understood the meaning of each cue. Participants were paid $40 for participating in addition to their task winnings; total payment ranged from $49 to $84 (mean $65.42, *SEM* $2.99). No participant reported knowing

the pattern by which target speed varied or reported using any response strategy that differed by trial condition, and we found no evidence that participants optimized their strategy for the adaptive threshold (Supplemental Results).

Imaging

Participants were scanned with a General Electric 3 Tesla Signa scanner using a custom head coil. Head movement was minimized with a bite bar and foam padding. Stimuli were projected on a mirror mounted on the head coil using E-Prime 1.1 on a Compaq Presario computer. For each participant 880 functional images (440 per run) with 28 contiguous 4-mm-thick axial slices were collected using a T2*-sensitive spiral in/out pulse sequence (TR = 2000 ms, TE = 40 ms, flip = 90°, 3.44 × 3.44-mm inplane resolution) to minimize susceptibility dropout in ventral frontal and medial temporal brain regions (Glover and Law, 2001; Preston et al., 2004). We also acquired high-resolution and in-plane structural scans (high-resolution: T1-weighted spoiled-grass, TR = 100 ms, TE = 7 ms, flip = 90°) to aid in normalizing and visualizing the data. The first 7 images of each run were discarded to avoid magnetic equilibration effects.

Data Analysis

Behavioral analyses were performed with SPSS 14.0 for Windows. Significant contrasts were identified at $p < 0.05$ using a repeated-measures general linear model, testing for a linear main effect of certainty, linear and quadratic main effects of valence, a linear interaction, and the effect of salience (a linear × quadratic interaction contrasting uncertain-gain and uncertain-loss trials against all others). T-tests were used to investigate significant main effects and interactions (standardizing correlation coefficients with Fisher's Z). Diagnostics were applied to ensure approximate normality of test-statistic distribution; reaction times were transformed with the natural logarithm function to account for their skew.

Functional images were preprocessed and modeled with SPM2. Images were corrected for slice timing and realigned, and then in-plane and high-resolution anatomical images were coregistered to the mean functional image and normalized to the ICBM152 template brain. The functional images were then normalized with the in-plane parameters, interpolated to 2 × 2 × 2-mm voxels, and smoothed with a 4-mm FWHM Gaussian filter. A high-pass filter (cutoff 100 s) was applied within runs to remove low-frequency noise.

Each participant's effects were analyzed with the general linear model using an event-related design. We constructed a model for each participant that included separate regressors for cue, arousal probe, positivity probe, and feedback events. We then constructed three individualized regressors for each participant to model first-order parametric modulations of the cue effect by valence, salience, and their interaction. The valence regressor represented modulation by the expected monetary gain or loss of each condition. It was weighted with 1 at certain-gain cue onsets and -1 at certain-loss cue onsets; at uncertain-gain and uncertain-loss cue onsets it was weighted with each participant's individual expected value for those conditions relative to the certain outcomes, calculated using the participant's individual hit rates. (Analyses using 0.66 and -0.33 for every participant's uncertain expected values did not significantly change results.) The valence regressor was weighted with 0 at all other timepoints (including all neutral trials). The salience regressor represented modulation by salient events. It was weighted with 1 at uncertain-gain and uncertain-loss cue onsets and 0 at all other timepoints (including all certain trials and all neutral trials). The interaction regressor represented an interaction term for which the effect of valence was greater in certain trials than in uncertain trials. For certain-gain and certain-loss trials, it was weighted with 1 and -1 (as above); for uncertain-gain and uncertain-loss trials, it was weighted with each participant's individually-calculated relative expected value (as above) multiplied by -1.

To account for potential trial-by-trial differences in motor preparation or effort, we also included a first-order parametric modulator of the cue effect weighted at each cue onset with that trial's reaction time. All seven regressors of interest and the reaction-time regressor were convolved with a standard hemodynamic response function (Cox, 1996). Six regressors modeling residual effects of head motion and a constant term were also included in each model. Least-squares estimation was used to create whole-brain statistic images for each regressor for each participant. The regression coefficient images were then tested with one-sample t-tests over all participants to create group statistic maps for each parametric effect. These maps were thresholded voxelwise at $p < 0.001$ and with an extent threshold of 10 voxels, which provided protection against overall Type I error at $p < 0.001$ according to Monte Carlo simulations with AlphaSim (Ward, 2002). Peak activations are reported in ICBM coordinates.

Due to our specific hypotheses about NAcc activation, we also performed a volume-of-interest (VOI) analysis in this region. Individualized left and right NAcc coordinates were located in each participant's high-resolution structural images (Supplementary Methods). Spherical VOIs (8-mm diameter) were centered on those coordinates to ensure equal volumes of tissue were sampled from each participant. Timecourses of percent signal change relative to the experiment mean were extracted from each participant's VOIs, trimmed for outliers, linearly detrended and high-pass filtered (with a cutoff of 100 s). Timecourses locked to the onset of each trial condition were then calculated and averaged across the group. We analyzed the first 6 timepoints (0 - 10 s) of each condition's timecourse with a $6 \times 6 \times 2$ repeated-measures general linear model with timepoint, condition, and hemisphere as within-participant factors, using the Huynh-Feldt correction for nonsphericity (denoted as $p_{H\text{-}F}$). T-tests were used to investigate significant effects (standardizing correlation coefficients with Fisher's Z).

Because our predictions focused on incentive anticipation rather than outcomes, and to ensure adequate statistical power, we only analyzed anticipatory activity in each trial. However, in the anticipation-probe run, anticipation was substantially disrupted and lengthened by the affect probes. To avoid confounding activation due to incentive anticipation with activation due to responding to the affect probes (Phan et al., 2004), only the outcome-probe runs were included in the whole-brain and VOI results.

Results

Behavioral

Participants responded on almost all trials; mean response rate was 93.3% (*SEM* 1.4%). There were no main effects or linear interactions of certainty or valence on response rate, but there was a significant effect of salience ($F(1,11) = 5.75$, $p < 0.05$). Paired t-tests revealed that uncertain-gain and uncertain-loss trials had significantly higher response rates than all other trials (Table 1). No other trial types differed. In all conditions, however, average response rates exceeded 90%, and no participant responded to fewer than 86.5% of trials, suggesting participants generally followed instructions to respond on all trials.

The adaptive timing algorithm ensured the average hit rate was at the 66% target ($M = 65.7\%$, *SEM* 1.0%). This algorithm did not control each condition's hit rate separately for different conditions and thus did not eliminate all between-condition differences. Valence had no main effect on hit rate, nor did the linear interaction of factors, but there were significant effects of certainty (linear: $F(1, 11) = 6.52$, $p < 0.05$) and salience ($F(1,11) = 8.25$, $p < 0.05$). Paired contrasts revealed these effects were due to increased hit rates in uncertain-gain and uncertain-loss trials (Table 1).

Reaction times were similar but not identical to hit rates (because hit rates were under adaptive control). For reaction time, there were no effects of certainty, the linear interaction, or salience,

but valence did have an effect (quadratic: $F(1, 11) = 10.09$, $p < 0.01$). Paired tests revealed this effect was driven by slower responses to certain-neutral trials (Table 1).

We examined self-reported arousal and positivity during anticipation in the anticipation-probe trials (Figure 2). Because our hypotheses focused on anticipation, we did not analyze outcome-related affect. Arousal and positivity were not on average correlated within participants ($t(11) = 0.54$, *ns*), suggesting participants were able to independently rate these dimensions. Arousal was significantly affected by both certainty ($F(1, 11) = 10.19$, $p < 0.01$) and a quadratic effect of valence ($F(1, 11) = 13.33$), as well by salience ($F(1, 11) = 7.95$, $p < 0.05$). Participants were more aroused by certain-gain than certain-neutral trials ($t(11) = 2.41$, $p < 0.05$) and showed a trend towards greater arousal for certain-loss than certain-neutral trials ($t(11) = 2.01$, $p = 0.07$). Arousal did not differ between certain-gain and certain-loss trials ($t(11) = 1.39$, *ns*). Participants were more aroused by both uncertain-gain and uncertain-loss trials than uncertain-neutral trials (gain > neutral: $t(11) = 4.15$, $p < 0.01$; loss > neutral: $t(11) = 3.39$, $p < 0.01$), but arousal did not differ between uncertain-gain and uncertain-loss trials ($t(11) = 1.60$, *ns*). Participants were more aroused by uncertain-gain than certain-gain trials ($t(11) = 2.60$, $p < 0.05$) and more aroused by uncertain-loss than certain-loss trials ($t(11) = 3.46$, $p < 0.01$).

For positivity, there was no main effect of certainty, quadratic effect of valence, or effect of salience, but there was a linear effect of valence ($F(1, 11) = 25.32$, $p < 0.01$) and a significant linear interaction ($F(1,11) = 16.81$, $p < 0.01$). Participants felt more positive in certain-gain than certain-neutral trials ($t(11) = 4.26$, $p < 0.01$) and in certain-neutral than certain-loss trials ($t(11) = 3.26$, $p < 0.01$). The same pattern was true in uncertain trials: participants felt more positive in uncertain-gain than uncertain-neutral trials ($t(11) = 2.29$, $p < 0.05$), and more positive in uncertain-neutral than uncertain-loss trials ($t(11) = 4.40$, $p < 0.01$). Certain-gain trials were more positive than uncertain-gain trials ($t(11) = 2.36$, $p < 0.05$), but uncertain-loss trials were more positive than certain-loss trials ($t(11) = 2.54$, $p < 0.05$).

To summarize, relative to neutral trials, participants were especially aroused in uncertain-gain and uncertain-loss trials and somewhat aroused in certain-gain and certain-loss trials. By contrast, participants felt most positive in certain-gain trials and less so for uncertain-gain trials, followed by neutral trials, then uncertain-loss trials, then certain-loss trials.

Whole-Brain Analyses

Although this study focused on NAcc activation, we also performed exploratory whole-brain analyses. Response to the cue was modulated in several areas by valence, salience, and their interaction (see Supplemental Material for tables of activations and additional figures).

Maps of the valence effect revealed areas where response to the cue was increased by increasing valence of the trial condition (Figure S1). The largest and most significant cluster was in the anterior cingulate and mesial prefrontal cortex (Brodmann areas 32 and 24). Other significant clusters were in precuneus, thalamus, middle and inferior frontal gyri (Brodmann areas 10 and 46), orbitofrontal cortex (Brodmann area 11), inferior and superior parietal lobules (Brodmann areas 40 and 7), premotor cortex, cerebellum, and claustrum / insular cortex. No significant clusters had responses that were decreased by increasing valence.

A different pattern emerged in maps of the salience effect (Figure S1), which revealed areas where response to the cue was greater for salient trials (uncertain-gain and uncertain-loss) than for less-salient trials (uncertain-neutral and all certain trials). The largest clusters were in bilateral caudate and globus pallidus, extending into the amygdala on the left and thalamus bilaterally. Other significant clusters included posterior cingulate bordering precuneus (Brodmann area 31), inferior parietal lobule (Brodmann area 40), mesial prefrontal cortex (Brodmann area 10), superior and middle frontal gyri (Brodmann areas 10 and 8), middle

temporal gyrus (Brodmann area 21), precuneus and cuneus, insula / inferior frontal gyrus (Brodmann areas 13 and 9), and parahippocampal gyrus (Brodmann area 37). No significant clusters were more active for nonsalient than for salient trials.

Finally, maps of the interaction of valence and salience revealed only a single cluster where the effect of valence was larger in certain trials than in uncertain trials (Figure 3): in the ventral striatum (x / y / z = -6 / 6 / -4 mm). No significant clusters were active for the opposite interaction.

Volume-of-interest (VOI) analyses

In order to test our specific hypotheses about NAcc activation, we examined average percent signal change timecourses for each condition from individually-localized VOIs in both left and right NAcc. Laterality had no significant main effect ($F(1, 11) = 0.35$, *ns*) and did not significantly interact with any other factor, so we recalculated average timecourses for bilateral NAcc and used them in all further analyses (Figure S2). There was a significant main effect of condition ($F(5, 55) = 6.47$, $p_{H\text{-}F} < 0.01$) and a trend towards a main effect of time ($F(5, 55) = 3.49$, $p_{H\text{-}F} < 0.06$). The predicted interaction between timepoint and condition was significant ($F(25, 275) = 3.44$, $p_{H\text{-}F} < 0.01$), suggesting different conditions differentially affected the hemodynamic response over time.

We examined the interaction with paired t-tests at 4 s following cue onset, when cue-related hemodynamic activity would be expected to peak (Figure 4). Activation was greater for certain-gain than either certain-neutral or certain-loss trials (gain > neutral: $t(11) = 2.42$, $p < 0.05$; gain > loss: $t(11) = 3.19$, $p < 0.01$). Certain-loss trials did not differ from certain-neutral trials ($t(11) = 1.74$, *ns*). However, activation was greater in both uncertain-gain and uncertain-loss trials than in uncertain-neutral trials (gain > neutral: $t(11) = 3.12$, $p < 0.01$; loss > neutral: $t(11) = 3.14$, $p < 0.01$). NAcc activation did not differ between uncertain-gain and uncertain-loss trials ($t(11) = 0.13$, *ns*).

Across certainty levels, uncertain-loss and uncertain-gain trials had significantly more activation than certain-loss trials (uncertain-loss > certain-loss, $t(11) = 3.36$, $p < 0.01$; uncertain-gain > certain-loss, $t(11) = 3.73$, $p < 0.01$), but neither uncertain-loss nor uncertain-gain trials differed from certain-gain (uncertain-loss > certain-gain, $t(11) = 0.77$, *ns*; uncertain-gain > certain-gain, $t(11) = 0.75$, *ns*), nor did uncertain-neutral differ from certain-neutral ($t(11) = 1.40$, *ns*).

To investigate whether differences in NAcc activation between conditions could be explained by variations in effort or motor preparation, we correlated each participant's trial-by-trial log-transformed reaction time with their NAcc activity 4 s following cue onset for each trial. The average correlation was not significant ($t(11) = -1.13$, *ns*), and only one participant's individual correlation trended towards significance (most significant: $r(46) = -0.28$, $p < 0.06$).

In summary, NAcc activation varied with both valence and salience. When outcomes were certain, NAcc activation was higher for gain trials than for loss trials. However, when outcomes were uncertain, NAcc activation was higher for both gain and loss trials than for neutral trials.

Discussion

Combining event-related FMRI with a novel variant of the monetary incentive delay (MID) task (Knutson et al., 2001), we directly compared valence and salience accounts of NAcc activation. We found that both the valence and salience of anticipated incentives correlated with NAcc activation, and further found a significant interaction between these factors. When outcomes were certain and salience was low, NAcc activation increased for anticipated gain

and decreased for anticipated loss. However, when outcomes were uncertain and salience was high, NAcc activation increased for both anticipated gain and loss.

Whole-brain analyses fit the findings of prior research. Salience activated a network of brain areas involved in arousal, attention, and uncertainty processing, including precuneus, parietal cortex, thalamus, amygdala, and insula (Huettel et al., 2005; Simmons et al., 2004). Salient trials also activated bilateral dorsal striatum, including caudate and globus pallidus, consistent with earlier studies investigating areas that support salience or contingency detection (Tricomi et al., 2004; Zink et al., 2006). By contrast, increasing valence activated a network of brain regions linked to reward representations, including mesial prefrontal cortex (Knutson et al., 2005), orbitofrontal cortex (O'Doherty et al., 2001; Rolls, 2004), and inferior parietal cortex (Ernst et al., 2004; Glimcher et al., 2005). Only the ventral striatum, however, was significantly activated by the interaction of valence and salience, consistent with a unique role for this area in reward anticipation.

This study extends prior research by, for the first time, independently varying valence from negative to positive and salience from low to high within the same incentive modality. Independently manipulating these two factors allowed us to separately examine each factor's influence on NAcc activation. Earlier studies that have focused on valence, using monetary incentives or aversive shock, have not independently varied salience (Abler et al., 2006; Breiter et al., 2001; Jensen et al., 2007; Knutson et al., 2001; Tobler et al., 2007; Tom et al., 2007), while studies that have varied salience have not independently varied valence across gains and losses (Bjork and Hommer, 2006; Jensen et al., 2003; Tricomi et al., 2004; Zink et al., 2006).

For the first time, we also used a real-time measure of the subjective impact of our incentive manipulations. These affect probes confirmed that participants were able to rate their arousal and positivity as uncorrelated factors. Varying outcome uncertainty had a significant impact on arousal (a possible index of salience, e.g., Zink et al., 2004) but not positivity, while varying incentives between gains and losses had a significant impact on positivity but not arousal. This real-time method might not be without cost; although we examined neural activity only during trials without anticipatory affect probes, introspecting about emotions might be enough to influence affect or brain activation throughout the experiment. However, investigators who used continuous online ratings in an FMRI study to probe affect during film clips reported no effect of rating on either self-reported affect or brain areas associated with the affective response to films (Hutcherson et al, 2005; although the NAcc was not one of these). The areas they and others (e.g., Phan et al., 2004; Taylor et al., 2003) have found to be associated with rating emotion (anterior cingulate, insula, and parietal cortex) were not the direct focus of this study, but further investigation of how online probes affect reward-related paradigms is needed.

The novel design of this study enabled a direct comparison of valence and salience accounts of NAcc activation--but neither account fully predicted the observed pattern of activation. The salience account suggests that NAcc activation should not differentiate between certain-gain and certain-loss trials, which were equally non-salient. They were equally arousing, and participants responded to them equally as often and as quickly, suggesting the conditions did not differentially recruit attention or motor preparation. Yet NAcc activation significantly distinguished between certain gain and loss, increasing prior to certain gains and decreasing prior to certain losses.

On the other hand, the valence account suggests that the NAcc activation should differentiate between uncertain-gain and uncertain-loss trials, since the former had positive expected value and elicited more positive affect. Yet NAcc activation did not distinguish between these trial types in this paradigm. Further, the valence account predicts that the NAcc should be more active for certain-gain than uncertain-gain or uncertain-loss trials, based on expected value and

positive affect. Instead, NAcc activation did not distinguish between these conditions, despite obvious differences in their expected rewards.

Participants responded and hit more often in salient trials than non-salient trials, raising the possibility of a strategic difference between salient and non-salient. Salience is a stimulus-related feature that might be separate from, for example, effort induced by salience (Niv, 2007). We attempted to control for the effects of reaction time, as an index of effort; reaction times were included in the whole-brain regression models, did not correlate with NAcc timecourses, and did not change systematically over time (Supplemental Results). However, both the salience and valence accounts also make key predictions within salience levels that were not confirmed by the data. Certain-gain and certain-loss trials had identical salience and were matched in terms of elicited behavior, yet they induced significantly different NAcc activation, which the salience account cannot explain. On the other hand, uncertain-gain and uncertain-loss trials had differing valences and were matched in behavior, yet they were not significantly distinguished by NAcc activation, which the valence account cannot explain.

Single-component accounts invoking valence or salience do not fully explain NAcc activation in this paradigm. Since variation in either valence or salience correlates with NAcc activation, the data instead suggest that NAcc function may be better characterized with a two-component account involving both valence and salience. Several recent neuroimaging findings allude to a two-component account (Bjork and Hommer, 2006; Dreher et al., 2006; Knutson et al., 2005; Preuschoff et al., 2006; Tobler et al., 2007; Yacubian et al., 2006). Knutson et al. (2005) and Yacubian et al. (2006) varied anticipated reward magnitude and probability separately and found that NAcc activation represented magnitude independently of probability. Because these studies used a limited range of probability, the salience of the anticipated rewards may not have been as controlled as in the current paradigm. Bjork and Hommer (2006) scanned participants in a reward-anticipation paradigm involving both certain and uncertain-gain trials, some of which required a motor response. Ventral striatal areas were active both for certain rewards requiring a motor response and for an interaction of uncertainty and response, when valence and salience were both high. Dreher et al. (2006) varied reward probability in trials with longer anticipatory delays, and found that while early activation in the midbrain correlated with reward probability, ventral striatal activity during reward anticipation was greatest when rewards were maximally uncertain. Preuschoff et al. (2006) varied reward probability across several levels (rather than merely certain or uncertain) and found that early ventral striatal activation correlated best with increasing reward probability, but later ventral striatal activation correlated best with maximal uncertainty. Tobler et al. (2007) found that ventral striatal activation increased with both reward probability and magnitude. Although they found that ventral striatal activation for certain gains was greater than activation for uncertain gains, their design did not permit separate analysis of gain anticipation versus outcome or allow comparisons across different levels of motor demands.

These studies did not include loss anticipation overall, but all found that NAcc activation varied independently as a function of changes in anticipated reward valence or uncertainty. The current data are consistent with these findings and extend them into the domain of loss anticipation. NAcc activation correlated with valence when uncertainty was low, while NAcc activation correlated with primarily with uncertainty when uncertainty was high.

Valence and salience processing may additionally show distinct temporal profiles in the NAcc. Dreher et al. (2006) and Preuschoff et al. (2006) suggested that phasic, cue-related NAcc activation reflects the expected value of a reward, while tonic activation during anticipation reflects reward uncertainty. Electrophysiologists studying nonhuman primates responding to juice cues have found a similar pattern in midbrain dopamine neuron firing (Fiorillo et al., 2003). Although our study's design was not optimized to separate early from late anticipatory

activation, we conducted post hoc analyses to examine whether the pattern of NAcc activation changed over time (Supplemental Results, Figure S3). At 4 s after cue onset, when cue-related hemodynamic activity would be expected to peak, NAcc activation was similarly elevated for both uncertain-gain and certain-gain trials. By 6 s after cue onset, however, when delay-related activity would be expected to peak, NAcc activation was more elevated for uncertain gain and loss trials than for all certain trials. (These later peaks were earlier than would be expected for hemodynamic activity related to the motor response, which occurred an average of 4.6 sec after the cue.) This pattern is consistent with a two-component account where valence-related activity at the cue signaled the presence of a potential reward and salience-related tonic activity continued to elevate NAcc activation for uncertain, but not certain, trials during anticipation.

The simplest two-component account suggests that NAcc activation codes for both valence and salience separately, perhaps separated in time. But other two-component accounts are possible. One such account is expected value (e.g., Tobler et al., 2007), in which NAcc activation reflects the product of reward magnitude (correlated with valence) and probability (which has a quadratic relationship with salience). The current data do not support this account, since certain-gain and uncertain-gain trials have substantially larger expected values than uncertain-loss, but NAcc activation does not distinguish among them (and during anticipation, certain-gain activation is the lowest of the three).

A second account is the positive arousal (PA) account (Knutson et al., 2001), in which NAcc activation reflects a combination of arousal and positivity proposed to constitute an underlying dimension of emotional experience (Watson et al., 1999). Earlier studies using only uncertain trials found correlations between NAcc activation during gain anticipation and retrospective reports of PA (Bjork et al., 2004; Knutson et al., 2001). We calculated average online PA for each participant to compare it with NAcc activation (Supplemental Results, Figure S4). The current data do not fully support this account, since PA was significantly larger for uncertain-gain than uncertain-loss trials, but the NAcc does not distinguish between them. In other respects, however, the PA account matches NAcc activation more closely than either the valence or salience accounts, and thus the conditions under which PA might explain NAcc function deserve further investigation.

A third account proposes different incentive processing for gains and for losses. Economic behavior and brain activation both respond to incentive magnitude differently depending on whether the incentive is a gain or a loss relative to a reference point (De Martino et al., 2006; Friedman and Savage, 1948; Kahneman and Tversky, 1979; Tom et al., 2007). Tom et al. (2007) recently found NAcc responses to mixed gambles decreased more steeply with loss magnitude than they increased with gain magnitude. Although their design did not permit separate analysis of anticipation or of salience, their findings might suggest a valence account with different response slopes between gains and losses. The current findings do not fully support such an account, since a valence account within gains alone would predict greater activation for certain-gain than uncertain-gain trials, while the current data demonstrate early NAcc activation does not distinguish the two (and later activation is greater for uncertain-gain trials). Potential strategic differences between certain and uncertain might well confound this comparison, however, and so we cannot rule out accounts with separate processing of gains and losses that take some aspect of salience or strategy into account. All of these accounts deserve further investigation with more specific paradigms.

The current data is thus most consistent with a simple two-component account that predicts anticipatory NAcc activation reflects changes in either valence or salience. The nature of the broad factors of “valence” and “salience,” though, remain to be fully clarified. We defined salience as a cued increase in the need for an important action, which we operationalized by manipulating reward certainty. Many cue features can increase salience, including outcome

variance or uncertainty, outcome contingency, and subjective attention, all of which have been proposed to be specifically reflected in activation of various parts of the striatum. This paradigm was not intended to disentangle these features, and so these salience-related features all varied between uncertain and certain trials. Different effects of valence on NAcc activation within salience levels, however, suggests that recruitment of this region reflects at least two incentive features. Further studies will be needed to parse the concept of "salience" into a finer-grained set of features, and investigate how they may be separately represented in various parts of the striatum and elsewhere.

Questions also remain about how NAcc activation might reflect valence. NAcc activation in this study distinguished between anticipated gains and losses in certain but not uncertain trials. Both of these findings should be qualified by the small number of trials our design provided (eight per condition). The low percent signal change in the certain conditions especially calls for replication, although it is consistent with evidence for the valence account. The lack of distinction between uncertain-gain and uncertain-loss trials is less consistent with previous findings. Several studies using the MID task (e.g., Bjork et al., 2004; Guyer et al., 2006; Knutson et al., 2001; Knutson et al., 2003; Knutson et al., 2005) have found greater NAcc activation for uncertain gain than loss (but not all; Juckel et al., 2006). The current paradigm used smaller incentives ($3.00 vs. $5.00), which might be too small to elicit this difference. Accordingly, replications of the MID task have found the difference for large but not small incentives (i.e., $5.00, but not $1.00). Alternatively, this study's novel mixture of certain and uncertain trials may have induced a framing effect in which participants considered both the chance to obtain gains and the chance to avoid losses in uncertain trials to be rewarding relative to certain losses (Ikemoto and Panksepp, 1999; Nieuwenhuis et al., 2005). Consistent with this possibility, participants' positivity ratings were more negative for certain-loss than uncertain-loss trials and distinguished between gain and loss better in certain than uncertain trials. The current design did not allow analysis of outcomes, which might better distinguish these explanations. The framing account, however, predicts that NAcc activation reflects valence differently depending on other available incentives. The firing of monkey midbrain dopamine neurons appears susceptible to framing effects (Tobler et al., 2005), but further human research will be necessary to determine whether NAcc activation shows such effects.

Conclusion

These findings are consistent with a two-component account in which anticipatory NAcc activation reflects both valence and salience. Valence and salience each partially account for NAcc activation during incentive processing, but neither provides a complete account. Further, findings from this and other studies are consistent with the possibility of a temporal separation between processing of valence and salience. If NAcc activation is proportional to a spatiotemporal summation of local postsynaptic activity (Knutson and Gibbs, 2007; Logothetis and Wandell, 2004), the current findings may reflect a combination of valence and salience signals in the NAcc that occur at different timescales. A two-component account is consistent with recent experimental results, and may help to unify conflicting findings from studies of incentive processing. A critical future direction will involve using information about where incentive features are processed to understand how the brain integrates these features to guide behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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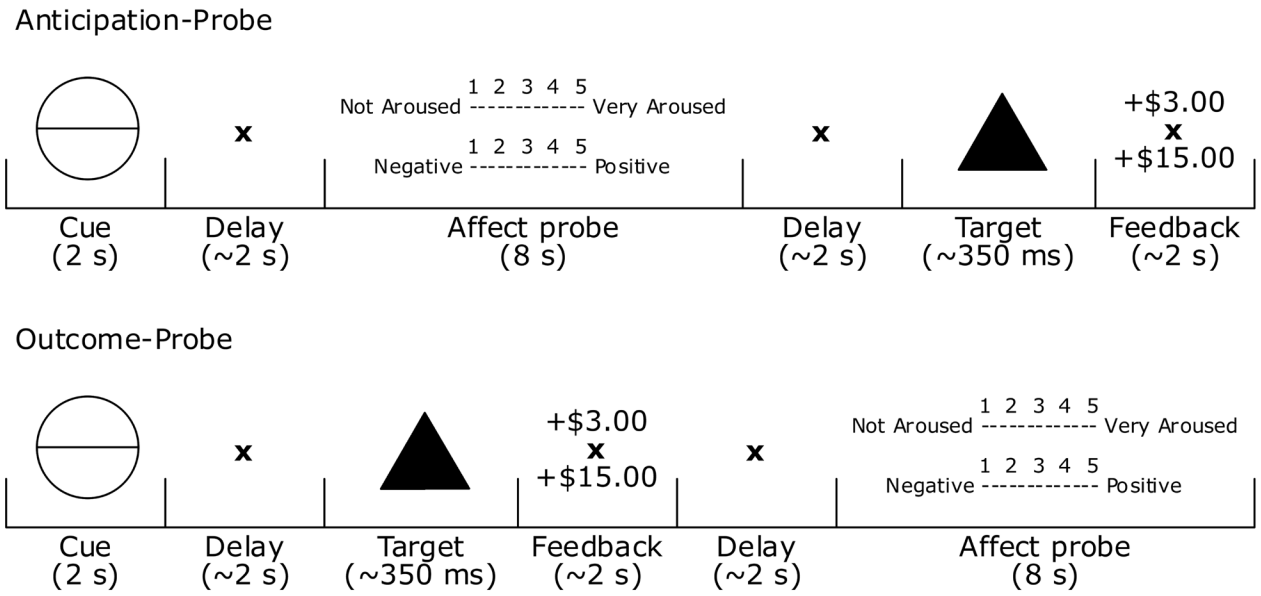

Figure 1.
Trial structures. Anticipation-probe and outcome-probe trials were used in separate runs for each participant. The two trial structures differed only in placement of the affect probe phase. Trial conditions within a run were distinguished by different cue shapes. Outcome amounts were given both for the current trial and the current total earned.

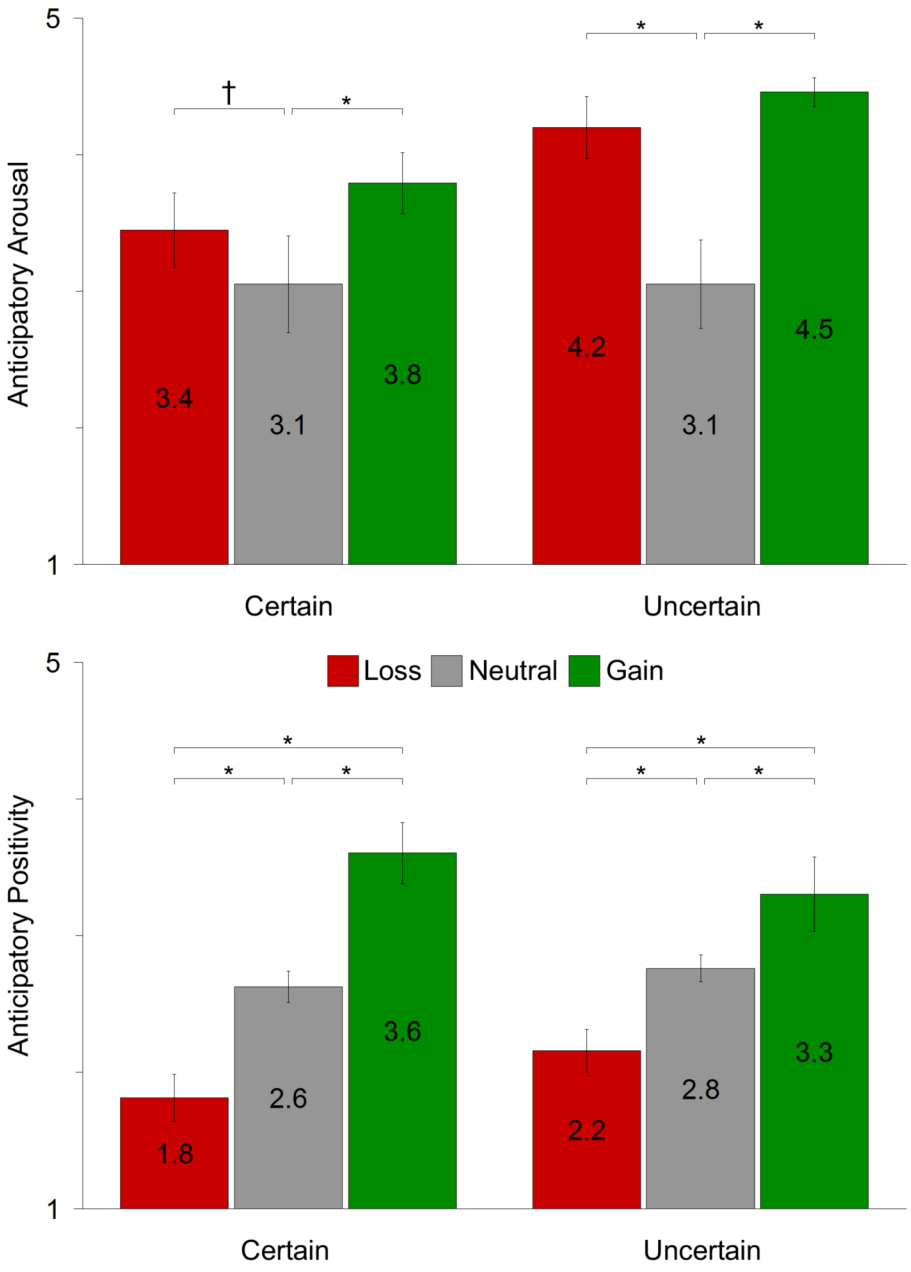

Figure 2.
Anticipatory affect. Bars represent mean self-reported arousal (upper panel) and positivity (lower panel) during anticipation. Error bars represent standard errors across participants. Participants responded on each trial to 5-point Likert scales for both arousal and positivity. †$p < 0.1$. *$p < 0.05$.

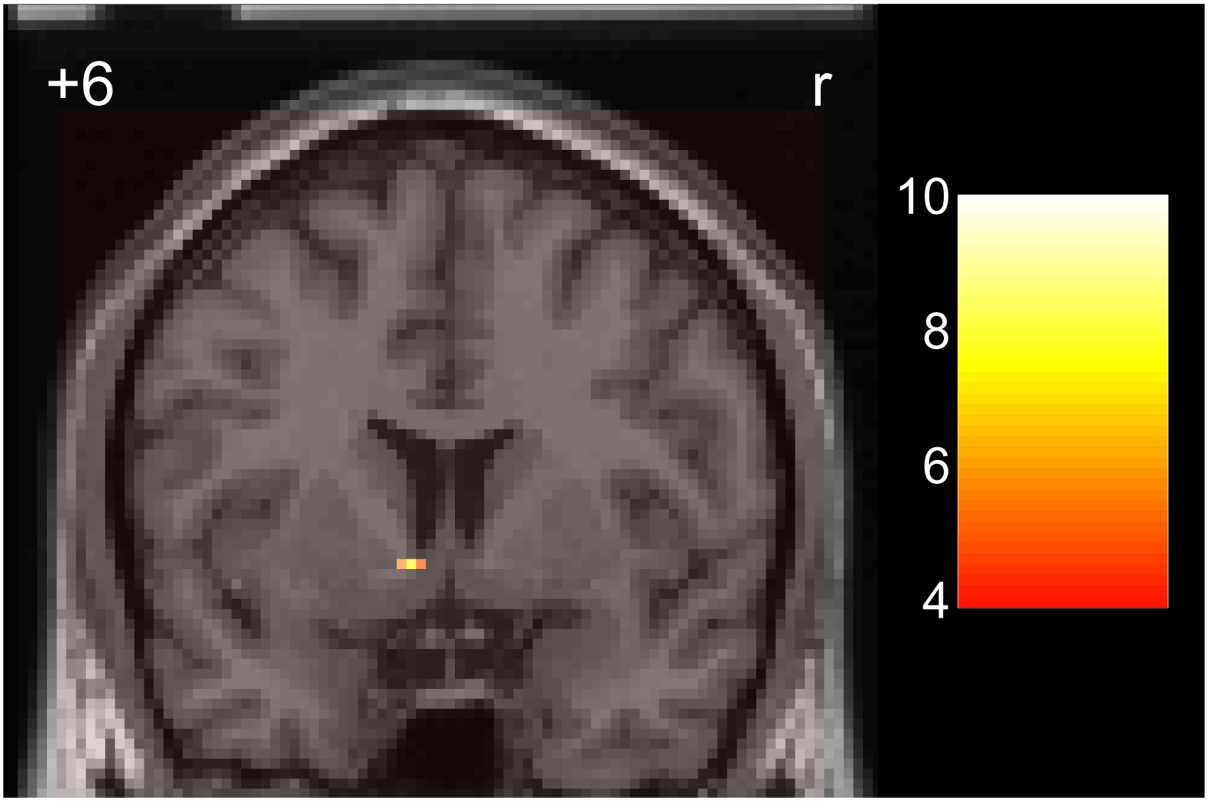

Figure 3.
Average cue response modulation. The activated cluster indicates regions in which activation to the cue was modulated by an interaction of expected value and salience (x / y / z = -6 / 6 / -4 mm). The map was thresholded voxelwise at $p < 0.001$ and with a cluster threshold > 10 voxels (corresponding to a whole-brain threshold of $p < 0.001$). R indicates right. Voxel color indicates t-statistic according to the legend.

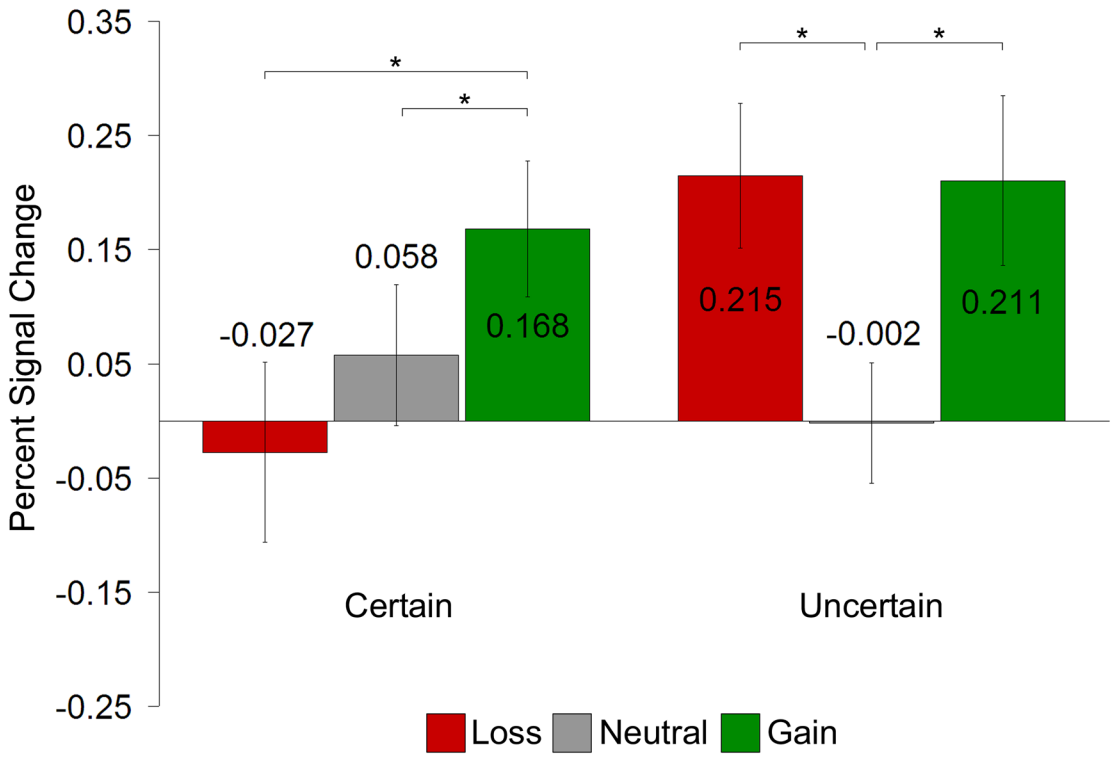

Figure 4.
Percent signal change in nucleus accumbens. Bars represent mean percent signal change in bilateral nucleus accumbens (NAcc) at 4 s following cue onset. Error bars represent standard errors across participants. *$p < 0.05$.

Table 1

Behavioral responses by condition

Condition	Response rate (*SEM*)	Hit rate (*SEM*)	Reaction time (*SEM*)
Certain-loss	91.7_{a} (3.0)	58.9_{x} (3.3)	$305.92_{i,j}$ (26.78)
Certain-neutral	91.7_{a} (2.7)	$61.5_{x,y}$ (3.0)	360.73_{j} (37.77)
Certain-gain	94.3_{a} (1.6)	$60.4_{x,y}$ (4.4)	320.31_{i} (25.65)
Uncertain-loss	97.4_{b} (1.8)	$72.9_{y,z}$ (3.6)	272.57_{i} (18.96)
Uncertain-neutral	90.6_{a} (2.5)	$64.1_{x,y}$ (4.2)	$318.23_{i,j}$ (27.97)
Uncertain-gain	97.4_{b} (1.4)	76.6_{z} (2.4)	282.64_{i} (23.15)

Note. Data is percentage of trials on which any response was made (response rate), or on which the target was hit (hit rate), or reaction time in ms. Data points within a column which share subscripts do not differ at $p < 0.05$ (two-tailed). Reaction times were log-transformed for statistical comparison; original reaction times are reported here for clarity.