Dissociation of reward anticipation and outcome with event-related fMRI

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Reward processing involves both appetitive and consummatory phases. We sought to examine whether reward anticipation *vs* outcomes would recruit different regions of ventral forebrain circuitry using event-related fMRI. Nine healthy volunteers participated in a monetary incentive delays task in which they either responded to a cued target for monetary reward, responded to a cued target for no reward, or did not respond to a cued target during scanning. Multiple regression analyses indicated that while anticipation of reward *vs* non-reward activated foci in the ventral striatum, reward *vs* non-reward outcomes activated foci in the ventromedial frontal cortex. These findings suggest that reward anticipation and outcomes may differentially recruit distinct regions that lie along the trajectory of ascending dopamine projections. *NeuroReport* 12:3683–3687 © 2001 Lippincott Williams & Wilkins.

Key words: Reward; Anticipation; Outcome; Nucleus accumbens; Ventromedial frontal cortex; fMRI; Human

INTRODUCTION

Ethologists have traditionally distinguished between appetitive and consummatory stages of reward processing [1,2]. In addition to occurring at different timepoints (i.e., reward anticipation *vs* outcome) and potentially involving qualitatively different affective phenomenology (i.e., high *vs* low arousal) [3], recent animal studies suggest that appetitive and consummatory stages of reward may recruit distinct neuroanatomical and neurochemical mechanisms [4]. While brain imaging studies have begun to demonstrate that tasks involving monetary reward can recruit both ventral striatal and frontal activity [5–10], it is unclear whether different parts of this circuitry are involved in distinct stages of reward processing in humans.

Primate electrophysiological studies suggest that ventral striatal regions such as the nucleus accumbens (NAcc) show neural activity as monkeys anticipate making a response for a reward, but the ventromedial (VMFC) and orbital frontal cortex (OFC) subsequently become active after the monkey has responded and receives the reward [11]. At present, only two fMRI studies have experimentally separated anticipatory from outcome phases of reward processing. In a study focusing exclusively on anticipation of monetary reward, we found that the NAcc showed reward-proportional activity during anticipation of increasing monetary rewards but not punishments. However, detectable activity was not observed in the VMFC or OFC during reward anticipation [3].

Concurrently, another group observed a similar pattern of ventral striatal activation in addition to VMFC and OFC activation during anticipation of monetary reward using a different task and analytic technique. They also reported that this pattern of activation did not change appreciably during receipt of reward outcomes [12].

Using event-related fMRI, we examined whether reward outcomes would recruit different brain regions than reward anticipation. Based on our prior findings, we predicted that the NAcc would be activated more by anticipation of responding for a reward than by anticipation of responding for no reward. Based on primate research, we also predicted that the VMFC or OFC would be more activated by presentation of reward outcomes than non-reward outcomes [11].

MATERIALS AND METHODS

Nine physically and psychiatrically healthy volunteers (seven women, right-handed, mean ($\pm$ s.d.) age 26.45 $\pm$ 5.85) participated in the study. Before entering the scanner, participants completed a practice version of the task and were shown the money that they could earn by performing the task successfully. Once in the scanner, anatomical and functional scans were collected. Participants engaged in a 5 min 24 s session of the monetary incentive delay (MID) task during functional scan acquisition [7]. All participants gave written informed consent, and the study was approved by the Institutional Review Board of the National Institute on Alcohol Abuse and Alcoholism.

MID task: The MID reward task session consisted of 54 6 s trials. During each trial, participants saw one of three colored squares (cue, 250 ms), then fixated on a cross-hair as they waited a variable interval (delay, 2000–2500 ms),

and finally responded to a white target square which appeared for a variable length of time (target, 160–260 ms) with a button press. Feedback (outcome, 1650 ms) which followed the target's disappearance notified participants whether they had won money during that trial and indicated their cumulative total at that point. fMRI volume acquisitions were time-locked to the offset of each cue and thus were acquired during anticipatory as well as during outcome periods [7].

Cues signaled potentially rewarded response ($n = 18$, yellow squares), an unrewarded response requirement ($n = 18$, blue squares), or no response requirement ($n = 18$, red squares). In the reward trials, participants won \$1.00 if they pressed a button during display of the subsequent target. Target durations were adjusted such that each participant would succeed on approximately 66% of his or her responses, based on reaction times obtained during the prescan practice session. In the non-rewarded response trials, participants did not win money for responding, but were still asked to rapidly press the button during display of the subsequent target. In the non-response trials, participants were asked to refrain from pressing the button during display of the subsequent target.

fMRI acquisition: Imaging was performed using a 1.5 T General Electric MRI scanner with a standard quadrature head coil. Sixteen contiguous sagittal 7 mm slices (in-plane resolution 3.75×3.75 mm) centered about the intra-hemispheric fissure were acquired, providing whole brain coverage, including subcortical regions of interest such as the NAcc, as well as the VMFC and rostral OFC. Only the posterior OFC (Brodmann's area (BA) 25) showed $>60\%$ signal dropout due to proximity to tissue boundaries. Functional scans were acquired using a T2*-sensitive gradient echo sequence that measured changes in blood oxygen level dependent (BOLD) contrast with parameters of repetition time (TR) = 2000 ms, echo time (TE) = 40 ms, flip = 90°, number of volumes = 162. Whole-brain structural scans were acquired using a T1-weighted spoiled grass pulse sequence (TR = 100 ms; TE = 7 ms, flip = 90°, $0.9375 \times 0.9375 \times 2$ mm voxels), which facilitated localization and co-registration of functional data.

fMRI analysis: Analyses focused on changes in BOLD contrast that occurred during anticipatory and outcome periods and were conducted using Analysis of Functional Neural Images (AFNI) software [13]. For preprocessing, voxel time series were interpolated to correct for non-simultaneous slice acquisition within each volume, corrected for three-dimensional motion, and slightly spatially smoothed (kernel FWHM = 4 mm). Visual inspection of motion correction estimates confirmed that no participant's head moved more than 1.5 mm in any dimension from one volume acquisition to the next and that no participant overtly vocalized in response to incentive outcomes.

Preprocessed timeseries data for each individual were analyzed with an orthogonal multiple regression model consisting of 12 regressors [14]. Two orthogonal regressors of interest contrasted: (1) anticipation of rewarded *vs* unrewarded response and (2) reward hit *vs* miss outcomes (reward trials only). Two orthogonal control regressors contrasted: (3) anticipation of response (both rewarded and unrewarded) *vs* anticipation of non-response and (4) outcomes on reward trials (both hit and miss) *vs* outcomes on other trials. Regressors of interest and control regressors were convolved with a gamma variate function modeling a prototypical hemodynamic response prior to inclusion in the regression model [15]. The remaining regressors modeled residual motion (six parameters) as well as a baseline and linear trend for the experimental session (two pararmeters).

Maps of t-statistics for the regressors of interest and control regressors were transformed into Z-scores, co-registered with structural maps, spatially normalized by warping to Talairach space, spatially smoothed (FWHM = 4 mm), and combined into a group map using a meta-analytic formula (average $Z \times \sqrt{(n)}$) [7]. Group maps were thresholded at an omnibus value of $p < 0.0001$. This threshold was based on a prior convention for multiple test correction in subcortical (i.e., NAcc, putamen, caudate, thalamus) and mesial cortical gray matter (i.e., OFC, VMFC, anterior cingulate, supplementary motor area, and primary motor cortex) regions in a representative brain ($\sim$500 voxels; $p < 0.05$, corrected) [7].

Activation foci (peak values) appearing in ventral striatal, ventral forebrain, and striatal motor control volumes of interest [16] that passed this threshold were used to construct three spherical volumes of interest (VOIs) of 4 mm diameter. Averaged BOLD contrast timeseries (calculated as percent change from overall intensity mean with linear trends removed) were extracted from these spherical VOIs for each trial type and for each individual. The averaged timeseries for NAcc, VMFC, and putamen VOIs were then analyzed with 4 (trial type, within) $\times$ 9 (epoch, within) repeated-measures ANOVA ($p < 0.05$) Average activation levels during anticipation and outcome periods were compared across trial types in each VOI at 6 s lags using Tukey's honestly significant difference paired comparisons ($p < 0.05$) [3,12].

RESULTS

Behavior: Participants achieved criterion or hit (i.e. received \$1.00) on an average of $61.0 \pm 14\%$ of the reward trials, approximating the targeted 66% hit rate, and on an average of $50.0 \pm 11\%$) of the non-rewarded response trials. Participants' average reaction time on rewarded hits (197.09 ± 23.13 ms) was slightly faster than their average reaction time on non-rewarded hits (213.11 ± 26.72 ms; $t(11) = 5.01$, $p < 0.001$).

Voxel-by-voxel analysis: The contrast of anticipation of responding for a reward *vs* no reward revealed a significant activation focus in the bilateral NAcc, as hypothesized. This contrast also revealed activation foci in the right anterior insula, bilateral caudate, left putamen, anterior thalamus right medial amygdala, mesial prefrontal cortex, supplementary motor area, left motor cortex, and right cerebellar vermis ($p < 0.0001$, uncorrected). This pattern replicated our prior findings (Table 1) [3].

Contrast of reward *vs* non-reward outcomes yielded a different pattern of activation foci including VMFC (Brodmann's Area 32/10), as hypothesized. This contrast also revealed foci in the right dorsal caudate, left frontal pole

Table 1. Group maximum Z-scores and Talairach Coordinates of activation foci ($p < 0.0001$, uncorrected; $n = 9$).

Area	Ant: Reward *vs* non-reward response		Ant: Response *vs* non-response		Out: $1.00 reward *vs* $50 reward		Out: all reward trials *vs* non-reward trials	
	Max Z	TC (R,A,S)	Max Z	TC (R,A,S)	Max Z	TC (R,A,S)	Max Z	TC (R,A,S)
R anterior insula (BA13)	4.41	33,17,−2						
L anterior insula (BA13)								
R NAcc	5.69	11,11,0						
L NAcc	4.95	−8,12,0						
R caudate	5.92	11,9,3			3.89	16,17,6		
L caudate	5.34	−9,5,4						
R putamen			5.15	24,6,2			−5.05	18,10,−3
L putamen	3.97	−20,1,−4	5.46	−21,−1,6				
Thalamus	6.29	3,−2,7	4.97	−8,−17,9			4.10	10,−7,13
R amygdala	4.86	16,−7,−7						
L amygdala								
Orbitofrontal cortex (BA10/32)					3.88	8,45,−13	−4.74	−4,43,−14
					4.40	6,38,−9		
L frontal pole (BA 10/32)					4.15	−3,51,8		
Anterior cingulate (BA24)								
Posterior cingulate (BA26/30)					4.25	3,−51,17		
Parietal cortex (BA7)					4.75	−4,−58,49	−4.90	−1,−30,52
Mesial prefrontal cortex (BA32)	3.95	5,41,12	6.00	3,5,44				
	4,73	3,11,43						
Supplementary motor area (BA6)	3.99	1,−1,48	7.27	−3,−4,50				
L motor cortex (BA4)	4.74	−40,−15,51	7,61	−36,−18,48				
Cerebellar vermis	4.67	3,−59,−5	6.24	4,−60,−9				

(BA 32/10), posterior cingulate, and parietal cortex ($p < 0.0001$, uncorrected).

Control regressor maps yielded distinct patterns of activation. The contrast of anticipation of all motor responses *vs* anticipation of no response revealed foci primarily in motor preparatory regions including bilateral putamen, ventrolateral thalamus, mesial prefrontal cortex, supplementary motor area, left motor cortex, and right cerebellar vermis [7]. The contrast of all reward trial outcomes (hit + miss) *vs* outcomes on other trials revealed an activation focus in the thalamus and deactivation foci in the VMFC (BA 32/10), right putamen, and parietal cortex ($p < 0.0001$, uncorrected).

Volume of interest analysis: Analysis of individual timeseries extracted from the right NAcc VOI yielded a significant interaction of trial type (4) × epoch (9) ($F(24,192) = 5.28$, $p < 0.00001$), indicating that some types of trials differed significantly over time. Planned comparisons for anticipation (lag = 6 s) revealed significantly greater NAcc activity during anticipation of reward response (on both hit and miss trials) *vs* anticipation of non-rewarded motor response ($p < 0.05$) or non-response ($p < 0.001$). Interestingly, planned comparisons of outcomes revealed significantly decreased NAcc activity during notification of non-reward (miss) but not reward (hit) outcomes relative to both types of control outcomes ($p < 0.05$; Fig. 1).

Analysis of VMFC VOI timeseries also indicated a significant interaction of trial type (4) × epoch (9) ($F(24,192) = 4.41$, $p < 0.05$). Planned comparisons for anticipation revealed no significant differences between any of the trial types. However, planned comparisons of outcomes again revealed decreased VMFC activity during notification of non-reward (miss) but not rewarded (hit) outcomes relative to both types of control outcomes ($p < 0.001$).

Analysis of the putamen VOI timeseries also yielded a significant interaction of trial type (4) × epoch (9) ($F(24,192) = 4.41$, $p < 0.00001$). Planned comparisons for anticipation revealed increased putamen activity during anticipation of reward (on both hit and miss trials) relative to anticipation of non-response ($p < 0.005$), but not relative to anticipation of non-rewarded response. As in other VOIs, planned comparisons of outcomes revealed decreased putamen activity during presentation of non-reward (miss) outcomes but not reward (hit) outcomes relative to both types of control outcomes ($p < 0.0005$).

DISCUSSION

By separately examining reward anticipation and outcomes with event-related fMRI, we found that the NAcc was primarily recruited by anticipation of monetary reward, that this activation subsided during delivery of rewarding outcomes, and further, that NAcc activity was suppressed when anticipated rewards were not obtained. Reward anticipation did not activate the VMFC, but omission of anticipated rewards did suppress VMFC activity. Deactivation of these regions during reward non-delivery is consistent with primate electrophysiological recordings showing decreased midbrain dopamine neural firing during reward omission [17].

Although participants had slightly faster reaction times when responding to reward *vs* control targets, several lines of evidence suggest that NAcc activity was more tightly linked to anticipation of reward than motor expectancy. First, a control regressor contrasting anticipation of all motor responses *vs* anticipation of non-response highlighted more lateral putamen foci but not the NAcc.

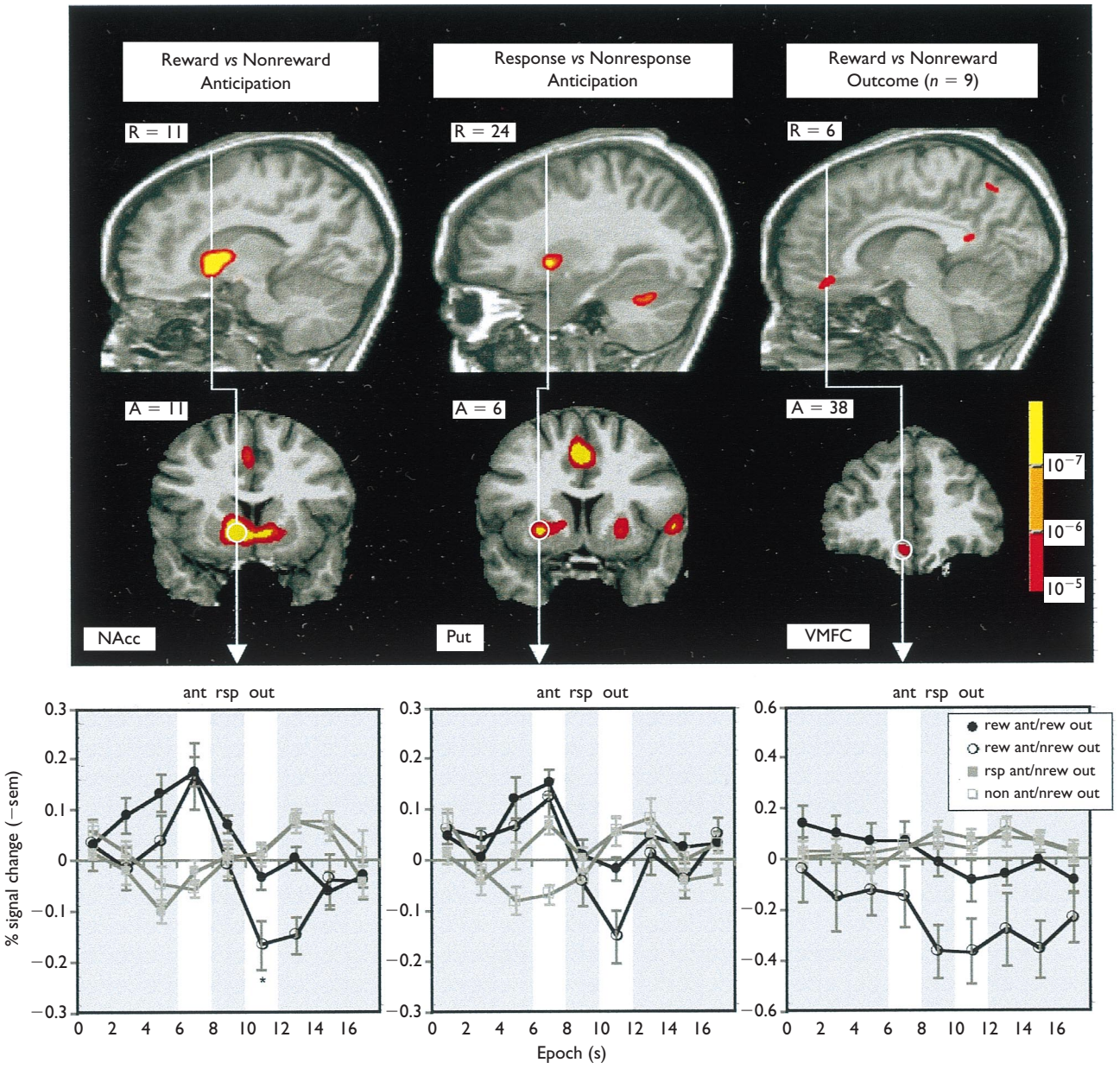

Fig. 1. Group activation maps for reward anticipation *vs* non-reward anticipation, response vs non-response anticipation, and reward *vs* non-reward outcome. Timecourse plots highlight these contrasts in NAcc, Put, and VMFC volumes of interest. R = right, A = anterior, NAcc = nucleus accumbens, Put = putamen, VMFC = ventromedial frontal cortex. *Significantly different from rsp ant/non-reward out and non-ant/non-reward out; † = significantly different from non-ant/non-reward out only ($p < 0.05$).

Second, timecourse analyses indicated that at the NAcc focus, anticipation of rewarded responses elicited significantly more activation than anticipation of non-rewarded responses, but at the putamen focus, anticipation of rewarded and non-rewarded responses elicited similar levels of activation. Third, in a separate study, we have demonstrated that anticipation of increasing monetary punishments, which might also reduce reaction time, does not significantly increase activity in the rostral NAcc [3]. Together, these results suggest that the rostral NAcc is more robustly recruited by reward anticipation than by anticipation of motor responding *per se*.

The presently observed neuroanatomical dissociation between reward anticipation and outcome stands in contrast to findings reported in the only other published study of this type [12]. Whereas other investigators have reported that reward expectancy and outcome both recruited NAcc, we observed NAcc activity primarily during reward anticipation. Further, while those investigators also reported that reward expectancy and outcome both recruited regions in

the VMFC, we observed the clearest evidence of VMFC recruitment during presentation of reward outcomes only. Differences in task design may account for some of these disparities. For instance, the MID task was developed to maximize affective and motivational aspects of reward processing by employing rapid presentation of stimuli (e.g. 2 s for anticipation and outcome periods) and invoking contingency (i.e. participants perceive that their performance determines their outcome) [7]. On the other hand, the task employed in the earlier report may invoke more cognitive and deliberative aspects of reward processing, since it involves slower presentation of stimuli (e.g. 6 s for anticipation and outcome periods) and no contingency (i.e. participants perceive that their outcomes are due to chance). Increased cognitive processing may be more likely to recruit cortical as well as subcortical components of reward circuitry. Interestingly, both studies produced evidence for deactivation in reward circuitry when expected rewards were not obtained. While these deactivations may seem unexpected from the perspective of the brain imaging literature, they can be predicted on the basis of primate electrophysiology research [11].

CONCLUSION

These findings suggest that ventral striatal and forebrain sites may be differentially recruited by reward anticipation *vs* outcome in humans [11], and that fMRI may provide investigators with a tool for neuroanatomically dissecting different stages of reward processing.

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