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A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI

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Abstract

The function of the mesial prefrontal cortex (MPFC: including Brodman areas 10/12/32) remains an enigma. Current theories suggest a role in representing internal information, including emotional introspection, autonomic control, and a "default state" of semantic processing. Recent evidence also suggests that parts of this region may also play a role in processing reward outcomes. In this study, we investigated the possibility that a region of the MPFC would be preferentially recruited by monetary reward outcomes using a parametric monetary incentive delay (MID) task. Twelve healthy volunteers participated in functional magnetic resonance scans while playing the MID task. Group analyses indicated that while the ventral striatum was recruited by anticipation of monetary reward, a region of the MPFC instead responded to rewarding monetary outcomes. Specifically, volume-of-interest analyses indicated that when volunteers received $5.00 after anticipating a $5.00 win, MPFC activity increased, whereas when volunteers did not receive $5.00 after anticipating a $5.00 win, MPFC activity decreased, relative to outcomes with no incentive value. These findings suggest that in the context of processing monetary rewards, a region of the MPFC preferentially tracks rewarding outcomes.

Keywords: Reward; Human; Functional magnetic resonance imaging (FMRI); Nucleus accumbens (NAcc); Ventral striatum; Mesial prefrontal cortex (MPFC); Anticipation; Outcome; Money

Introduction

The rapid development of human neuroimaging techniques has led to an explosion of interest in the psychological functions of the prefrontal cortex. The lateral prefrontal cortex seems specialized for representing external information (Courtney et al., 1998), with hemispheric specialization for image-based (right) versus analytical (left) information (McDermott et al., 1999), vertical specialization for object-based (ventral) versus spatial (dorsal) information (Haxby et al., 2000), and rostrocaudal specialization for abstract (rostral) versus concrete (caudal) information (Christoff et al., 2001). However, the functions of the mesial wall of the prefrontal cortex have been characterized as playing a more prominent role in the representation of various types of internal information (Panksepp, 1998), including autonomic control (Critchley et al., 2000), emotional introspection (Lane et al., 1997), and a "default" state of semantic processing (Binder et al., 1999; Gusnard et al., 2001; Raichle et al., 2001). This functional distinction parallels the traditional neuroanatomical view that lateral aspects of cortex represent sensorimotor information while more medial aspects represent visceral information (Panksepp, 1998).

Consistent with the postulated role of the mesial prefrontal cortex (MPFC) in representing internal information, researchers have documented activation of this region during presentation of rewarding stimuli such as attractive faces (Aharon et al., 2001) and pleasant music (Blood et al., 1999). Money represents an experimentally tractable reward stimulus in humans, since it is (1) motivationally salient and valued by most people, (2) reversible and thus comparable

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across rewarding and aversive circumstances, and (3) scalable and thus comparable across different amounts (Knutson et al., 2000). Accordingly, several brain imaging studies have documented MPFC activation in the context of monetarily rewarding tasks (Bush et al., 2002; Delgado et al., 2000; Elliott et al., 2000b; Knutson et al., 2000; O'Doherty et al., 2001; Pochon et al., 2002; Thut et al., 1997). However, reward processing involves multiple stages, which were not separately examined in these studies.

Thanks to recent enhancements in the temporal and spatial resolution of event-related FMRI, investigators can now functionally "dissect" different stages of reward processing. In line with suggestions from the animal literature (Berridge and Robinson, 1998; Schultz et al., 2000), recent event-related studies have provided some preliminary support for functional neuroanatomical distinctions between appetitive and consummatory reward processes (Breiter et al., 2001; Knutson et al., 2001b). Specifically, anticipation of monetarily rewarding but not aversive outcomes preferentially activates the ventral striatum in a manner that scales with the amount of anticipated reward (Knutson et al., 2001a). However, receipt of monetary rewards instead recruits the MPFC (Knutson et al., 2001b). This functional dissociation between appetitive and consummatory processes is not restricted to monetary rewards, since anticipation of a rewarding (i.e., sweet) taste elicits both ventral striatal and prefrontal activity, whereas actual receipt of the rewarding taste elicits activity only in the prefrontal cortex (O'Doherty et al., 2002). Given the current evidence, it is not clear whether these regions of the MPFC respond preferentially to rewarding outcomes, or simply to all motivationally salient outcomes, including aversive outcomes (Lane et al., 1998). More specifically, studies utilizing monetary incentives to date have not included greater than one level of monetarily rewarding incentive along with neutral and aversive control conditions.

Here, using rapid event-related FMRI, we examined the hypothesis that a region of MPFC may preferentially track monetarily rewarding outcomes. In an earlier report, we found deactivation of a region of MPFC when people did not obtain expected rewards (Knutson et al., 2001b). Using larger incentives, we now predicted not only that this region would show *decreased* activation when anticipated rewards are not obtained, but also *increased* activation when anticipated rewards are obtained. We also predicted that if the activity of this region preferentially encodes monetarily rewarding outcomes, it should not respond similarly during the receipt of monetarily aversive outcomes.

Materials and method

Twelve physically and psychiatrically healthy volunteers (six women, right-handed, mean age 31) participated in the study. Before entering the scanner, volunteers completed a practice version of the task lasting 10 min, for which they did not receive payment. This practice task both minimized later learning effects and provided an estimate of each individual's reaction time for standardizing task difficulty in the scanner. Volunteers were also shown the money that they could earn by performing the task successfully in the scanner. All volunteers correctly believed that they would receive cash at the end of the experiment. Once in the scanner, anatomical and functional scans were collected. Volunteers engaged in two 10-min sessions of the monetary incentive delay (MID) task during functional scan acquisition. Following each session, volunteers retrospectively rated how they felt when they saw each of the seven cues on 4-point Likert scales indexing cue-elicited affective valence (e.g., "happy" and "unhappy"). All volunteers gave written informed consent, and the study was approved by the Institutional Review Board of the National Institute on Alcohol Abuse and Alcoholism.

Monetary incentive delay task

Each of the two MID task sessions consisted of 72 6-s trials, yielding a total of 144 trials. During each trial, participants saw one of seven cue shapes (cue; 250 ms), fixated on a crosshair as they waited a variable interval (delay; 2000–2500 ms), and then responded to a solid white target square which appeared for a variable length of time (target; 160–260 ms) with a button press. Feedback (feedback; 1650 ms) which followed the target's disappearance notified participants whether they had won or lost money during that trial and indicated their cumulative total at that point. On incentive trials, volunteers could win or avoid losing money by pressing the button during target presentation. Task difficulty, based on reaction times collected during the practice session prior to scanning, was set such that each volunteer should succeed on approximately 66% of his or her target responses. FMRI volume acquisitions were time-locked to the offset of each cue as well as the onset of feedback presentation and thus were acquired during anticipatory delay periods as well as feedback presentation periods (see Fig. 1).

Cues signaled potentially rewarding outcomes ($n = 54$, denoted by open circles), potentially aversive outcomes ($n = 54$; denoted by open squares), or no monetary outcome ($n = 36$; denoted by open triangles). Reward cues signaled the possibility of winning either \$0.20 ($n = 18$; a circle with one horizontal line), \$1.00 ($n = 18$; a circle with two horizontal lines), or \$5.00 ($n = 18$; a circle with three horizontal lines). Similarly, aversive cues signaled the possibility of losing either \$0.20 ($n = 18$; a square with one horizontal line), \$1.00 ($n = 18$; a square with two horizontal lines), or \$5.00 ($n = 18$; a square with three horizontal lines) (Knutson et al., 2001a). Prior studies revealed that switching the cue-incentive associations (circles with potential reward and squares with potential punishment) or using different types of cues (colored squares) did not appreciably alter patterns of brain response during reward anticipation

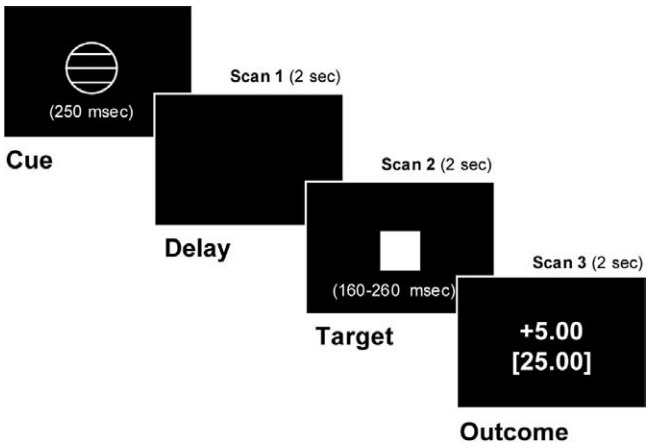

Fig. 1. Task structure for a representative trial.

(Knutson et al., 2001b). Trial types were pseudo-randomly ordered within each session.

fMRI acquisition

Imaging was performed using a 1.5-T General Electric MRI scanner and a standard quadrature head coil. Twenty-two 3.8-mm-thick slices (in-plane resolution 3.75 × 3.75 mm) centered about the intrahemispheric fissure were sagittally acquired with no interslice gap. This plane of acquisition and voxel size provided adequate resolution of subcortical regions of interest, such as the NAcc and amygdala, as well as of the anterior orbital frontal cortex, although the subgenual cortex showed baseline signal dropout in some subjects due to proximity to tissue boundaries. Functional scans were acquired using a T2*-sensitive gradient echo sequence with parameters of repetition time (TR) = 2000 ms, echo time (TE) = 40 ms, flip = 90°, number of volumes = 432. Structural scans were acquired using a T1-weighted spoiled grass sequence (TR = 100 ms; TE = 7 ms, flip = 90°), which facilitated localization and coregistration of functional data.

fMRI analysis

Analyses focused both on changes in blood oxygen-level-dependent (BOLD) contrast that occurred during anticipatory delay periods and also on changes in BOLD contrast that occurred during outcome periods. All analyses were conducted using Analysis of Functional Neural Images (AFNI) software (Cox, 1996). For preprocessing, voxel time series were interpolated to correct for nonsimultaneous slice acquisition within each volume (using sinc interpolation and the rightmost slice as a reference), concatenated across both task sessions, and then corrected for three-dimensional motion (using the third volume of the first session as a reference). 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.

Preprocessed time series data for each individual were analyzed with multiple regression (Neter et al., 1996), which allowed covariance of "nuisance" variables related to head motion and scanning session, in order to optimally localize functionally relevant foci of interest. Thus, the regression model consisted of a set of six orthogonal regressors of interest, six regressors describing residual motion, and six regressors modeling baseline, linear, and quadratic trends for each of the two experimental sessions. The regressors of interest contrasted: (1) anticipation versus the rest of the trial; (2) anticipation of monetary gain versus anticipation of no monetary outcome; (3) anticipation of monetary loss versus anticipation no monetary outcome; (4) outcomes versus the rest of the trial; (5) "hit" vs "miss" outcomes on potential gain trials; and (6) hit vs miss outcomes on potential loss trials. Regressors of interest were convolved with a gamma-variate function which modeled a prototypical hemodynamic response prior to inclusion in the regression model (Cohen, 1997).

Maps of t statistics for the regressors of interest were transformed into Z scores, coregistered with structural maps, spatially normalized by warping to Talairach space, slightly spatially smoothed (FWHM = 4 mm) to account for anatomical variability, and combined into a group map using a meta-analytic formula (average Z*sqrt(n)). Group maps were thresholded at an omnibus value of $P < 0.0001$, which was based on a prior convention for multiple test correction in subcortical (i.e., NAcc, putamen, caudate, thalamus) and prefrontal cortical gray matter (i.e., OFC, MPFC, anterior cingulate, supplementary motor area, primary motor cortex) regions in a representative brain (i.e., a Bonferroni correction for ~500 voxels at $P < 0.05$) (Knutson et al., 2000).

Activation foci (peak values) appearing in striatal and prefrontal volumes of interest (Breiter et al., 1997) that passed this threshold were used to construct spherical volumes of interest (VOIs) of 4-mm diameter. This size was chosen because it uniformly fit within significant thresholded regions of the group activation maps, and so minimized the risk of partial voluming, while simultaneously equating VOI size across all individuals. BOLD contrast time series data for each voxel were recalculated as percentage change from the overall intensity mean and bandpass-filtered to remove high- and low-frequency trends (i.e., <6 s and >90 s) (O'Doherty et al., 2002). These filtered time series were extracted from the spherical VOIs and averaged for each trial type within each individual. Averaged time-series for right NAcc and MPFC VOIs were then analyzed with 2 × (hit vs miss) × 4 (incentive magnitude, within) × 9 (epoch, within) repeated-measures analyses of variance (ANOVAs; hypothesized interaction P values < 0.05). Average BOLD contrast during anticipation and outcome periods were then compared across trial types in each VOI at a 4- to 6-s lag using paired t tests ($P < 0.05$, Bonferroni-

corrected for multiple comparisons) (Breiter et al., 2001; Knutson et al., 2001a).

Behavior

Percentage of hits and reaction times for hits on each trial type were averaged for each individual and subjected to repeated-measures within-subjects 2 (valence) × 4 (magnitude) ANOVAs. In the event of a significant interaction, paired *t* tests were used to compare differences among trial types ($P < 0.05$, Bonferroni-corrected for three comparisons).

Affect

Cue-elicited "happiness" and "unhappiness" were mean-corrected across different cue types within item and within subject to ensure comparability. The mean-corrected ratings for each cue type were then subjected to repeated-measures within-subjects 2 (valence) × 4 (magnitude) ANOVAs. In the event of a significant interaction, paired *t* tests were used to compare differences among trial types ($P < 0.05$, Bonferroni-corrected for three comparisons).

Results

Behavior

Overall, volunteers achieved criterion or hit on an average of 63.62% of all trials, approximating the targeted 66% hit rate. Additionally, repeated-measures ANOVAs indicated a main effect of incentive magnitude on hit rate ($F(3,33) = 19.54$, $P < 0.001$). Specifically, volunteers hit on a greater percentage of +$1.00 and +$5.00 trials than on +$0.00 trials ($P$ values < 0.016, corrected for three comparisons), as well as on a greater percentage of −$1.00 and −$5.00 trials than on −$0.00 trials ($P$ values < 0.016, corrected for three comparisons). A second repeated-measures ANOVA also indicated a main effect of incentive magnitude on reaction times for hits ($F(3,33) = 4.98$, $P < 0.05$), but pairwise comparisons revealed no significant differences in hit reaction times for incentive versus nonincentive trials (P values > 0.016). Thus, although volunteers hit on more high-incentive trials, this effect applied equally to trials involving monetary gain and loss, and reaction time for hits did not significantly differ by trial type.

Affect

Two subjects' affective ratings could not be analyzed due to greater than 50% data loss caused by a malfunctioning response key. For the remaining 10 subjects, a repeated-measures ANOVA indicated a significant interaction of incentive valence × magnitude on ratings of cue-induced happiness ($F(3,27) = 15.70$, $P < 0.001$). Specifically, paired comparisons indicated that volunteers reported greater happiness when presented with +$1.00 and +$5.00 cues than with +$0.00 cues ($P$ values < 0.016, corrected for three comparisons). A second repeated-measures ANOVA also indicated a significant interaction of valence × magnitude for cue-elicited unhappiness ($F(3,27) = 14.20$, $P < 0.001$). Paired comparisons indicated that volunteers reported more unhappiness when presented with −$1.00 and −$5.00 cues than with −$0.00 cues ($P$ values < 0.016). Since gain cues elicited increased happiness, while loss cues induced increased unhappiness, we inferred that unlike hit rate, incentive cues differentially altered valenced affect during the anticipatory interval (see Fig. 2).

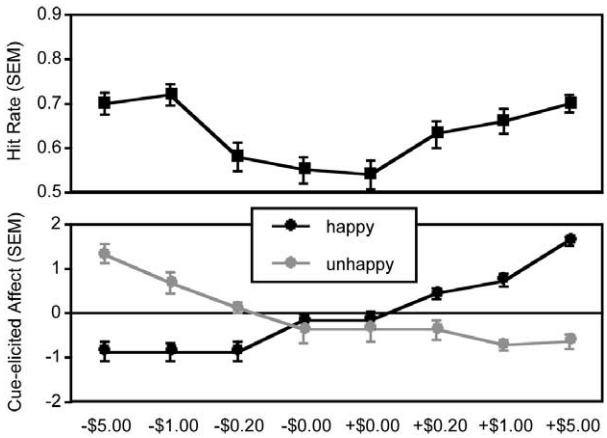

Fig. 2. Hit rate ($n = 12$) and cue-elicited affect ($n = 10$) for different types of incentives.

Voxelwise analysis

Using a voxelwise analysis that focused on subcortical and mesial cortical prefrontal regions, we initially examined whether we could replicate prior findings of NAcc recruitment by anticipation of monetary rewards versus nonreward. We additionally examined whether reward versus nonreward outcomes would differentially recruit regions of the MPFC (see Table 1).

Replicating prior observations, the contrast of anticipation of potential monetary gain versus no outcome revealed activation of the ventral striatum (including the NAcc), the dorsal striatum (i.e., the medial caudate), the anterior thalamus, the right anterior insula, medial premotor and motor cortical regions, and the cerebellar vermis (see Fig. 2). The contrast of anticipation of potential monetary loss versus no outcome revealed significant activation of all of these areas except for the ventral striatum (i.e., NAcc) and supplementary motor area. On the other hand, constrasts for different types of outcomes revealed entirely different patterns of activation. The contrast of hit versus miss outcomes on potential gain trials revealed activation of regions of the mesial prefrontal cortex, the parietal cortex, and posterior cingulate. The contrast of hit (no monetary loss) versus miss

Table 1
Group maximum *Z* scores and Talairach coordinates of activation foci ($P < 0.0001$, uncorrected; $n = 12$)

Area (Brodmann's Area)	Anticipation: Potential gain vs no outcome		Anticipation: Potential loss vs no outcome		Outcome: Gain vs no outcome		Outcome: No outcome vs loss	
	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. Ant. insula (13)	4.30	36, 14,1	4.26	35, 14, 1				
L. Ant. insula (13)								
R. NAcc	**4.89**	**11, 12, 0**						
L. NAcc	5.11	−9, 10, 0						
R. Caudate	5.76	10, 9, 4	4.62	11, −3, 14				
L. Caudate	6.42	−8, 1, 7	4.16	−16, −3, 8				
R. Putamen								
L. Putamen								
Thalamus	4.86	−3, −13, 13	4.92	−8, −2, 10				
R. amygdala								
L. amygdala								
Mes. prefrontal ctx (10/32)					**4.45**	**1, 53, −6**		
Frontal pole (10/32)					4.33	2, 65, 7		
Ant. cingulate (24)								
Post. cingulate (26/30)					4.03	5, −51, 22		
Parietal ctx (7)					3.91	4, −62, 53		
Mes. prefrontal ctx (32)	4.51	3, 27, 35	4.33	4, 32, 38				
Sup. motor area (6)	3.96	0, −4, 49						
L. motor ctx. (4)	4.94	−28, −55, 42	4.22	−34, −14, 59				
Cerebellar vermis	4.67	0, −70, −26	5.24	0, −63, −19				

Note. Boldface indicates foci that were used to construct volumes-of-interest. TC, Talairach coordinates; R, right; A, anterior; S, superior.

(monetary loss) outcomes on potential loss trials (equated for probability) revealed no significant activations or deactivations at the preestablished threshold. Together, these results extended a previously reported dissociation: while anticipation of monetary reward preferentially recruited the ventral striatum (including the NAcc), receipt of monetarily rewarding outcomes instead recruited regions of the mesial prefrontal cortex (Knutson et al., 2001b). Activation foci in these regions were used to construct spherical VOIs in order to examine whether monetarily rewarding outcomes would have bidirectional effects on activation in the MPFC.

Volume of interest analyses

VOI analyses included averaged activation time courses focused on potential gain trials, with auxiliary analysis of potential loss trials for purposes of comparison. These analyses focused on the NAcc, since it was the primary focus activated by anticipation of potential gain versus no outcome (but not of potential loss versus no outcome), and on the MPFC, since it was the primary focus of activation by gain versus no outcomes (but not of no outcome versus loss outcomes) (see Table 1).

Analysis of individual time series extracted from the right NAcc revealed a significant predicted interaction of magnitude (4) × epoch (9) ($F(24,264) = 4.47$, $P < 0.001$), indicating that some trial types differed significantly over time. Paired comparisons indicated that the NAcc was significantly more activated during anticipation of both +$1.00 and +$5.00 gains than during anticipation of +$0.00 (see Fig. 3) for both hit and miss trials (P values < 0.012, corrected for four comparisons). None of the paired comparisons for the outcome period were significant, with the exception of decreased activation for miss outcomes on +$5.00 trials relative to miss outcomes on +$0.00 trials ($P < 0.012$). Analysis of individual time series for potential loss trials also showed a significant interaction of magnitude (4) × epoch (9) ($F(24,264) = 4.27$, $P < 0.001$). Paired comparisons revealed that anticipation of −$5.00 loss elicited significantly greater activation than anticipation of −$0.00 loss, for both hit ($T(11) = -3.25$, $P < 0.012$) and miss ($T(11) = -3.03$, $P < 0.012$) trials. However, further paired comparisons verified that anticipation of +$5.00 gains elicited greater NAcc activation than anticipation of −$5.00 losses ($T(11) = 3.35$, $P < 0.012$). Thus, this set of analyses confirmed that the NAcc was most powerfully activated by anticipation of large monetary gains.

In contrast, voxelwise analysis indicated that a region of the MPFC was differentially activated by gain hit versus miss outcomes. Analysis of individual time series for potential gain trials extracted from this region revealed a significant predicted interaction of outcome (2) × magnitude (4) × epoch (9) ($F(24,264) = 2.93$, $P < 0.001$), indicating that some trial types differed as a function of both time and outcome. Paired comparisons indicated that activation differed for hit versus miss outcomes for the +$5.00 trials only (see Fig. 4). Specifically, +$5.00 hit outcomes elicited significantly greater MPFC activation than +$0.00 hit outcomes, while +$5.00 miss outcomes elicited signif-

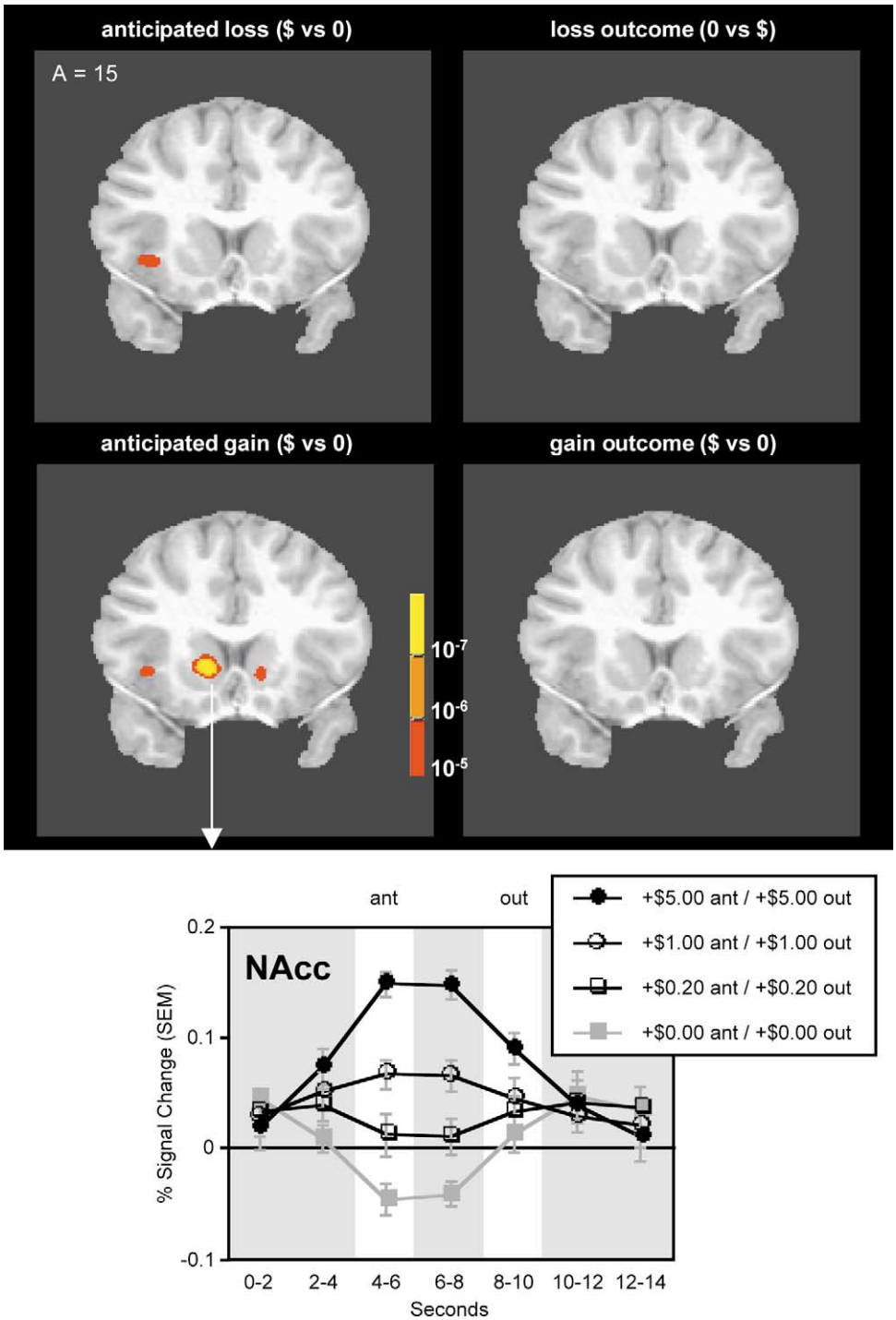

Fig. 3. Group maps (n = 12) in the coronal plane contrasting: (1) anticipation of −$5.00, −$1.00, and −$0.20 vs −0.00 (upper left); (2) anticipation of +$5.00, +$1.00, and +$0.20 vs +0.00 (lower left); (3) −0.00 vs −$5.00, −$1.00, and −$0.20 outcome (upper right); (4) +$5.00, +$1.00, and +$0.20 vs +0.00 outcome (lower right). The bottom figure depicts averaged time courses from a right NAcc volume of interest. Group maps are superimposed onto the spatially normalized structural scan of a representative volunteer, which has been sectioned at Anterior = 15 mm.

icantly less activation than +$0.00 miss outcomes ($P$ values < 0.012, corrected for four comparisons). Paired comparisons also verified that anticipatory activation for hit versus miss trials did not significantly differ for potential gain trials. On the other hand, analysis of MPFC time series for potential loss trials did not reveal a significant interaction of outcome (2) × magnitude (4) × epoch (9) ($F(24,264) = 1.09$, NS). Thus, this region of the MPFC was activated by gain outcomes but deactivated by neutral outcomes following anticipation of large monetary gains.

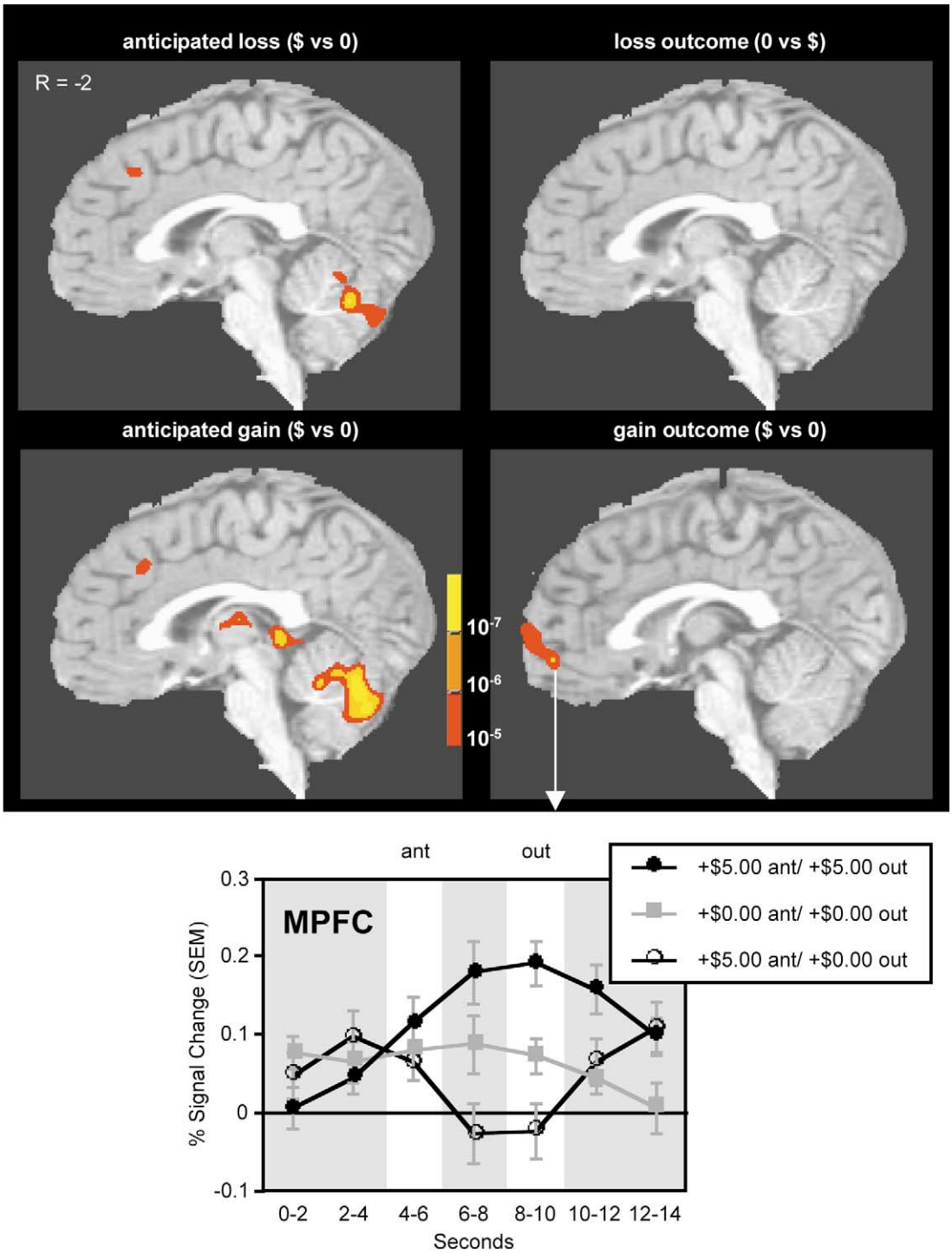

Fig. 4. Group maps ($n = 12$) in the sagittal plane contrasting: (1) anticipation of −$5.00, −$1.00, and −$0.20 vs −0.00 (upper left); (2) anticipation of +$5.00, +$1.00, and +$0.20 vs +0.00 (lower left); (3) −0.00 vs −$5.00, −$1.00, and −$0.20 outcome (upper right); (4) +$5.00, +$1.00, and +$0.20 vs +0.00 outcome (lower right). The bottom figure depicts averaged time courses from a MPFC volume of interest. Group maps are superimposed onto the spatially normalized structural scan of a representative volunteer, which has been sectioned at Right = −2 mm.

Discussion

Anticipation of responding for reward and finding out the reward has been obtained recruit different brain regions. Cued anticipation of increasing monetary rewards proportionally activated the ventral striatum (including the nucleus accumbens: NAcc). In contrast, receiving the information that reward has been successfully obtained activated the mesial prefrontal cortex (MPFC), parietal cortex, and posterior cingulate. These results confirm prior findings regard-

ing reward anticipation (Knutson et al., 2001a), and clarify and extend our initial report regarding rewarding outcomes. In an earlier study of a functional neuroanatomical dissociation between reward anticipation and outcomes (Knutson et al., 2001b), we reported that omission of expected monetary rewards *deactivated* a region of MPFC. However, now using a parametric task involving larger levels of monetary outcomes ($5.00 rather than $1.00), we find that in addition to deactivation when an expected reward fails to appear, the MPFC also shows *activation* when an expected reward is obtained. This finding illustrates a bidirectional effect of incentive outcomes on this region of the MPFC. Additionally, by including comparable conditions involving potential monetary losses, we found that successful or failed avoidance of aversive monetary outcomes do not recruit this particular region. Together, these results suggest that a region of the MPFC can track monetarily rewarding outcomes.

Two other FMRI studies have examined brain responses to varying levels of reward outcomes. O'Doherty et al. (2001) examined prefrontal activity during different monetary outcomes in a two-alternative choice task. Although they did not examine or control for anticipation, these investigators did report recruitment of an almost identical region following gain versus neutral outcomes, but not following loss versus neutral outcomes. Importantly, activity in this region scaled to the amount of reward received. Additionally, Breiter et al. (2001) examined both mesial prefrontal and ventral striatal activity during anticipation and outcome of monetary gambles. However, they did not observe the dissociations that we report here, concluding instead, ". . . there was little tendency for prospect phase responses to be restricted to one set of clusters and outcome phase responses to another" (p. 629). One reason for the discrepancy of their findings with the present findings might involve task timing. In the MID task, both anticipation and outcome intervals are short (~2 s), whereas in the Breiter et al. gambling task, each of these intervals lasted substantially longer (~6 s). The longer intervals may have allowed for increased prefrontal modulation of striatal activations. The feasibility of such an interpretation requires empirical verification in future research.

The observation that monetary outcomes can have bidirectional effects on MPFC activation potentially hones and extends existing theory regarding the psychological function of this region. First, in brain imaging studies, MPFC activations have been observed during monetarily rewarding tasks (Bush et al., 2002; Delgado et al., 2000; Elliott et al., 2000b; Knutson et al., 2000; O'Doherty et al., 2001; Pochon et al., 2002; Thut et al., 1997). The present findings, acquired with rapid event-related FMRI, indicate that these activations may reflect task components that are preferentially related to rewarding outcomes (Elliott et al., 2000a; Knutson et al., 2001b).

Second, irrespective of valence, MPFC activation has been observed in the context of emotional arousal and introspection (Critchley et al., 2000; Lane et al., 1997; Price, 1999). The present findings extend these observations by indicating that at least part of the MPFC may represent the valence as well as intensity of emotional outcomes. In light of our hypothesis that ventral striatal circuitry may play a role in generating positive feelings associated with reward anticipation (Burgdorf et al., 2001; Knutson et al., 2001a), it is interesting to speculate whether MPFC activations may be related to positive feelings associated with rewarding outcomes. Unfortunately, that speculation cannot be addressed by the present data, since post-goal attainment affect was not measured. Empirical examination of this possibility awaits future investigation.

Third, MPFC activations which occur when people are resting or not engaged in experimental tasks have been interpreted as evidence of a "default state" of semantic processing (Binder et al., 1999; Gusnard et al., 2001). This interpretation of MPFC activity implies that this region is more likely to be recruited in the service of personal goals than in the service of experimental demands. In the case of the MID task, the participants' and experimenter's goals should have coincided, since participants were both instructed and motivated to make as much money as possible. Accordingly, we were able visualize both increases and decreases in MPFC activation in the context of the same task, depending on whether participants obtained a desired reward. However, personal relevance alone is probably not sufficient to account for MPFC recruitment during the MID task, since this activation also depended on the reward value of the outcome. Thus, these findings raise the possibility that some MPFC "resting activations" observed in brain imaging studies may result from participants imagining desirable personal goal outcomes that are more motivationally compelling than the task at hand (e.g., as in the case of "daydreaming").

Neuroanatomically, studies of both rats and monkeys have indicated that ascending dopaminergic projections from the ventral tegmental area (VTA) play a central role in reward assessment (Ikemoto and Panksepp, 1999). Specifically, some VTA neurons increase their firing when monkeys are presented with reward cues or during intervals that precede reward delivery, and phasically cease firing when expected rewards are not obtained (Schultz et al., 1998). These projections target the NAcc as well as the MPFC, which shows the densest dopaminergic innervation of any cortical region (Gaspar et al., 1989). Although FMRI indirectly indexes oxygen utilization in the brain (i.e., via BOLD contrast) rather than dopaminergic activity, studies in rats indicate that increased firing of dopamine enhances BOLD contrast in the NAcc and MPFC (Chen et al., 1999; Marota et al., 2000). Thus, the observed activation of NAcc by reward anticipation, activation of MPFC by reward outcomes, and deactivation of both by nonreward might result, in part, from the changing dynamics of dopamine release. However, the distinct patterns of activation observed during different stages of reward processing suggest that the activ-

ity of local neurons may also play a role in altering BOLD contrast in these regions.

The current findings raise the possibility that short-term and long-term aspects of reward representation may computationally invoke two separate brain regions, both of which lie along the trajectory of ascending dopamine neurons (Dragoi and Staddon, 1999). These two functions may not be the same, and may sometimes even oppose one another (Bechara et al., 1998). On the basis of lesion data, theorists have postulated a critical role for mesial prefrontal and orbital frontal regions in the inhibition of behavior when short- and long-term outcomes conflict (Bechara et al., 2000). Here, we have identified an area of this larger region that responds differentially to reward outcomes, but not reward anticipation. How the MPFC and NAcc negotiate conflict between short- and long-term outcomes is unclear, but it is possible that even in the absence of MPFC influence, salient cues can trigger the NAcc to enable appetitive responses, regardless of long-term outcome.

While dopaminergic projections to the NAcc may provide the motivational "engine" that fuels attainment of immediate rewards, the MPFC may provide the "steering wheel" that focuses and directs these appetitive impulses, perhaps via glutamatergic back-projections to the NAcc (Tzschentke and Schmidt, 2000). Future comparative electrophysiological and human brain imaging studies may empirically address these possibilities by examining changes in the functional connectivity of these regions during rewarding tasks. The present study lays some groundwork for these types of analyses by identifying dissociable neural components related to reward anticipation and outcome (Berridge and Robinson, 1998; Knutson et al., 2001b).

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References

Aharon, I., Etcoff, N.L., Ariely, D., Chabris, C.F., O'Connor, E., Breiter, H.C., 2001. Beautiful faces have variable reward value: FMRI and behavioral evidence. Neuron 32, 537–551.

Bechara, A., Damasio, H., Damasio, A.R., 2000. Emotion, decision making and the orbitofrontal cortex. Cerebral Cortex 10, 295–307.

Bechara, A., Damasio, H., Tranel, D., Anderson, S.W., 1998. Dissociation of working memory from decision making withing the human prefrontal cortex. J. Neurosci. 18, 428–437.

Berridge, K.C., Robinson, T.E., 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res. Rev. 28, 309–369.

Binder, J.R., Frost, J.A., Hammeke, T.A., Bellgowan, P.S., Rao, S.M., Cox, R.W., 1999. Conceptual processing during the conscious resting state: a functional MRI study. J. Cogn. Neurosci. 11, 80–95.

Blood, A.J., Zatorre, R.J., Bermudez, P., Evans, A.C., 1999. Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. Nature Neurosci. 2, 382–387.

Breiter, H.C., Aharon, I., Kahneman, D., Dale, A., Shizgal, P., 2001. Functional imaging of neural responses to expectancy and experience of monetary gains and losses. Neuron 30, 619–639.

Breiter, H.C., Gollub, R.L., Weisskoff, R.M., Kennedy, D.N., Makris, N., Berke, J.D., Goodman, J.M., Kantor, H.L., Gastfriend, D.R., Riorden, J.P., Mathew, R.T., Rosen, B.R., Hyman, S.E., 1997. Acute effects of cocaine on human brain activity and emotion. Neuron 19, 591–611.

Burgdorf, J., Knutson, B., Panksepp, J., Ikemoto, S., 2001. Nucleus accumbens amphetamine microinjections unconditionally elicit 50-kHz ultrasonic vocalizations in rats. Behavior. Neurosci. 115, 940–944.

Bush, G., Vogt, B.A., Holmes, J., Dale, A.M., Greve, D., Jenike, M.A., Rosen, B.R., 2002. Dorsal anterior cingulate cortex: a role in reward-based decision making. Proc. Natl. Acad. Sci. USA 99, 523–528.

Chen, Y.I., Brownell, A.L., Galpern, W., Isacson, O., Bogdanov, M., Beal, M. F., Livni, E., Rosen, B.R., Jenkins, B.G., 1999. Detection of dopaminergic cell loss and neural transplantation using pharmacological MRI, PET and behavioral assessment. NeuroReport 10, 2881–2886.

Christoff, K., Prabhakaran, V., Dorfman, J., Zhao, Z., Kroger, J.K., Holyoak, K.J., Gabrieli, J.E., 2001. Rostrolateral prefrontal cortex involvement in relational integration during reasoning. NeuroImage 14, 1136–1149.

Cohen, M.S., 1997. Parametric analysis of fMRI data using linear systems methods. NeuroImage 6, 93–103.

Courtney, S.M., Petit, L., Haxby, J.V., Ungerleider, L.G., 1998. The role of prefrontal cortex in working memory: examining the contents of consciousness. Philos. Trans. R. Soc. London 353, 1819–1828.

Cox, R.W., 1996. AFNI: Software for analysis and visualization of functional magnetic resonance images. Computers Biomed. Res. 29, 162–173.

Critchley, H.D., Elliott, R., Mathias, C.J., Dolan, R.J., 2000. Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study. J. Neurosci. 20, 3033–3040.

Delgado, M.R., Nystrom, L.E., Fissell, C., Noll, D.C., Fiez, J.A., 2000. Tracking the hemodynamic response to reward and punishment in the striatum. J. Neurophysiol. 84, 3072–3077.

Dragoi, V., Staddon, J.E., 1999. The dynamics of operant conditioning. Psychologic. Rev. 106, 20–61.

Elliott, R., Dolan, R.J., Frith, C.D., 2000a. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cerebral Cortex 10, 308–317.

Elliott, R., Friston, K.J., Dolan, R.J., 2000b. Dissociable neural responses in human reward systems. J. Neurosci. 20, 6159–6165.

Gaspar, P., Berger, B., Febvret, A., Vigny, A., Henry, J.P., 1989. Catecholamine innervation of the human cerebral cortex as revealed by comparative immunohistochemistry of tyrosine hydroxylase and dopamine-beta-hydroxylase. J. Comp. Neurol. 279, 249–271.

Gusnard, D.A., Akbudak, E., Shulman, G.L., Raichle, M.E., 2001. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc. Natl. Acad. Sci. USA 98, 4259–4264.

Haxby, J.V., Petit, L., Ungerleider, L.G., Courtney, S.M., 2000. Distinguishing the functional roles of multiple regions in distributed neural systems for visual working memory. NeuroImage 11, 145–156.

Ikemoto, S., Panksepp, J., 1999. The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. Brain Res. Rev. 31, 6–41.

Knutson, B., Adams, C.M., Fong, G.W., Hommer, D., 2001a. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J. Neurosci. 21 (RC159), 1–5.

Knutson, B., Fong, G.W., Adams, C.M., Varner, J.L., Hommer, D., 2001b. Dissociation of reward anticipation and outcome with event-related FMRI. NeuroReport 12, 3683–3687.

Knutson, B., Westdorp, A., Kaiser, E., Hommer, D., 2000. FMRI visualization of brain activity during a monetary incentive delay task. NeuroImage 12, 20–27.

Lane, R.D., Fink, G.R., Chua, P.M., Dolan, R.J., 1997. Neural activation during selective attention to subjective emotional responses. NeuroReport 8, 3969–3972.

Lane, R.D., Reiman, E.M., Axelrod, B., Yun, L.S., Holmes, A.P., Schwartz, G.E., 1998. Neural correlates of levels of emotional awareness: evidence of an interaction between emotion and attention in the anterior cingulate cortex. J. Cognit. Neurosci. 10, 525–535.

Marota, J.J., Mandeville, J.B., Weisskoff, R.M., Moskowitz, M.A., Rosen, B.R., Kosofsky, B.E., 2000. Cocaine activation discriminates dopaminergic projections by temporal response: an FMRI study in rat. NeuroImage 11, 13–23.

McDermott, K.B., Buckner, R.L., Petersen, S.E., Kelley, W.M., Sanders, A.L., 1999. Set- and code-specific activation in frontal cortex: an FMRI study of encoding and retrieval of faces and words. J. Cognit. Neurosci. 11, 631–640.

Neter, J., Kutner, M.H., Nachtsheim, C.J., Wasserman, W., 1996. Applied Linear Statistical Models, fourth ed. Irwin, Chicago.

O'Doherty, J., Kringelbach, M.L., Rolls, E.T., Hornak, J., Andrews, C., 2001. Abstract reward and punishment representations in the human orbitofrontal cortex. Nature Neurosci. 4, 95–102.

O'Doherty, J.P., Deichmann, R., Critchley, H.D., Dolan, R.J., 2002. Neural responses during anticipation of a primary taste reward. Neuron 33, 815–826.

Panksepp, J., 1998. Affective Neuroscience: The Foundations of Human and Animal Emotions. Oxford Univ. Press, New York.

Pochon, J.B., Levy, R., Fossati, P., Lehericy, S., Poline, J.B., Pillon, B., Le Bihan, D., Dubois, B., 2002. The neural system that bridges reward and cognition in humans: an FMRI study. Proc. Natl. Acad. Sci. USA 99, 5669–5674.

Price, J.L., 1999. Prefrontal cortical networks related to visceral function and mood. Ann. N.Y. Acad. Sci. 877, 383–396.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. USA 98, 676–682.

Schultz, W., Tremblay, L., Hollerman, J.R., 1998. Reward prediction in the primate basal ganglia and frontal cortex. Neuropharmacology 37, 421–429.

Schultz, W., Tremblay, L., Hollerman, J.R., 2000. Reward processing in primate orbitofrontal cortex and basal ganglia. Cerebral Cortex 10, 272–283.

Thut, G., Schultz, W., Roelcke, U., Nienhusmeier, M., Missimer, J., Maguire, R.P., Leenders, K.L., 1997. Activation of the human brain by monetary reward. NeuroReport 8 (5), 1225–1228.

Tzschentke, T.M., Schmidt, W.J., 2000. Functional relationship among medial prefrontal cortex, nucleus accumbens, and ventral tegmental area in locomotion and reward. Crit. Rev. Neurobiol. 14, 131–142.