

Prediction error for free monetary reward in the human prefrontal cortex

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Making predictions about future rewards is an important ability for primates, and its neurophysiological mechanisms have been studied extensively. One important approach is to identify neural systems that process errors related to reward prediction (i.e., areas that register the occurrence of unpredicted rewards and the failure of expected rewards). In monkeys that have learned to predict appetitive rewards during reward-directed behaviors, dopamine neurons reliably signal both types of prediction error. The mechanisms in the human brain involved in processing prediction error for monetary rewards are not well understood. Furthermore, nothing is known of how such systems operate when rewards are not contingent on behavior. We used event-related fMRI to localize responses to both classes of prediction error. Subjects were able to predict a monetary reward or a nonreward on the basis of a prior visual cue. On occasional trials, cue–outcome contingencies were reversed (unpredicted rewards and failure of expected rewards). Subjects were not required to make decisions or actions. We compared each type of prediction error trial with its corresponding control trial in which the same prediction did not fail. Each type of prediction error evoked activity in a distinct frontotemporal circuit. Unexpected reward failure evoked activity in the temporal cortex and frontal pole (area 10). Unpredicted rewards evoked activity in the orbitofrontal cortex, the frontal pole, parahippocampal cortex, and cerebellum. Activity time-locked to prediction errors in frontotemporal circuits suggests that they are involved in encoding the associations between visual cues and monetary rewards in the human brain.

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Introduction

The execution of goal-directed behavior is always followed by monitoring for the successful achievement of the goal. For this process to work effectively, a representation of the expected goal must be compared with the actual outcome. The most widely studied types of outcome in nonhuman primates are appetitive rewards (e.g., fruit juice or food pellets) (Hassani et al., 2001; Tremblay and Schultz, 1999). The neural mechanisms of reward-related prediction error have been extensively studied in nonhuman primates (Hollerman et al., 1998; Leon and Shadlen, 1999; Schultz et al., 1992; Tremblay and Schultz, 1999, 2000b; Tremblay et al., 1998; Watanabe et al., 2001).

The midbrain dopamine systems of the primate brain send projections to the basal ganglia and widespread regions of the frontal lobes (Ghashghaei and Barbas, 2001; Goldman-Rakic et al., 1989). These routes are important for conveying reward-related information to frontostriatal circuitry involved in cognitive processing. Importantly, the firing characteristics of dopamine neurons are determined by the ability of animals to predict rewards in advance of their occurrence and whether predictions about outcomes are violated or verified. Animals can be trained to expect a reward if it is consistently preceded by an instruction cue. During learning, as the reward becomes increasingly predictable, its ability to elicit activity in dopamine neurons transfers to the conditioned stimulus, and activity time-locked to the reward itself declines (Schultz, 1998; Schultz et al., 1993). The same neurons respond to the nondelivery of expected rewards in trained animals. In this situation, dopamine neurons phasically decrease their activity at the time that the rewards are expected. Activity in midbrain dopamine neurons therefore has three important characteristics. They signal (i) the prediction of a future reward, (ii) its unexpected occurrence (increased activity on reward presentation), (iii) and its unexpected absence (decreased activity at the time that reward was expected). All these are important for driving and maintaining reward-based learning (Schultz, 1997; Suri and Schultz, 1999; Waelti et al., 2001).

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Studies in both humans and nonhuman primates have shown that frontostriatal circuits are important for mediating the influence of reward expectation on the selection and preparation of actions. Specific dopamine-rich regions within the prefrontal cortex (Goldman-Rakic et al., 1992; Lidow et al., 1991; Sawaguchi and Goldman-Rakic, 1991), the premotor cortex (Sawaguchi, 1997), and the striatum (Hassani et al., 2001; Hikosaka et al., 1989; Lauwereyns et al., 2002) contain neurons in which task-related activity is altered when the goals of the task are rewards. Activity related to information processing during delays between instruction cues and manual responses can be altered if the cues also signal the level of reward to be expected (Leon and Shadlen, 1999; Ramnani and Miall, 2003). Neuronal activity of this kind is altered by local infusions of dopamine and its antagonists (Sawaguchi et al., 1986, 1988, 1990), suggesting that reward influences this activity through the action of dopamine.

During delayed-response studies of this kind, subjects form associations between instruction stimuli and rewards, but the delivery of rewards is contingent on the performance of correct responses and the outcome is only likely to be a reward if a response is executed. The occurrence of prediction error-related activity in frontostriatal circuits might therefore be specific to the context of actions where the goals are rewards. Although the orbitofrontal cortex is well known to have an essential role in motivational influences on behavior (Elliott et al., 2000a; Rolls, 2001, 2000; Schultz et al., 2000; Tremblay and Schultz, 1999, 2000a), several studies in nonhuman primates have also demonstrated that neurons in the lateral convexity of the prefrontal cortex encode reward expectancy (Hikosaka and Watanabe, 2000; Watanabe, 1990, 1996; Watanabe et al., 2001). Activity in orbital and lateral prefrontal cortex therefore reflects predictive processing for rewards. If these areas encode predictions about impending rewards, they may also have a role in registering the occurrence of reward-related prediction error.

While most studies of the kind described above have examined activity in ‘operant’ models of behavior (where the contingency between conditioned stimuli and rewarding outcomes depends on behavior), little is known about the circuitry involved in the direct formation associations between predictive conditioned stimuli and rewarding outcomes independently of behavior (‘classical’ contingency between the conditioned stimulus and the outcome). Single neurons in the prefrontal cortex can encode conditioned stimuli and outcomes, but this finding is not sufficient to demonstrate that it encodes associations between these. A more stringent criterion is to determine whether the neuron responds specifically to *violations* of cue–reward associations. Although the functional anatomy of monetary reward has been investigated with functional neuroimaging methods (Elliott et al., 1997, 2000b; Knutson et al., 2000, 2001a; O’Doherty et al., 2001; Ramnani and

Miall, 2003; Thut et al., 1997), no study has examined prediction error-related activity in the human brain for classical contingencies between conditioned stimuli and monetary reward. The main aim of the present study was therefore to localize regions of the human brain that in which there were event-related changes in activity specific for two types of reward-related prediction error when monetary rewards were delivered independently of goal-directed actions.

We used event-related fMRI in human subjects to examine activity related the failure of expected rewards, and the occurrence of unexpected rewards, where outcomes were not contingent on any behavior. We compared each type of prediction error with its corresponding control condition in which the predicted event occurred as expected. We demonstrate that these prediction errors evoke activity in two separate frontotemporal networks.

Materials and methods

Subjects

Six healthy volunteers were recruited after they had given written informed consent. The study had local ethical approval.

Stimulus presentation

Subjects lay supine in the scanner and were able to clearly view visual stimuli on a mirror positioned above the eyes 45° to the horizontal, onto which stimuli were projected with an SVGA projector. TTL pulses time-locked with stimulus presentation (controlled by Cogent, <http://www.fil.ion.ucl.ac.uk>, running on a PowerPC) and image acquisition were simultaneously sampled at a rate of 1 kHz (1401 A/D converter; Spike2 PC software; Cambridge Electronic Design, Cambridge, UK) so that the temporal asynchrony between stimulus presentation and image acquisition could be precisely recorded.

Experimental design

We scanned subjects while they passively observed the occurrence of four pseudorandomly presented event types in which outcome and expectation of rewarding and nonrewarding stimuli were manipulated (see Table 1).

Trials consisted of the presentation of a conditioned stimulus (a red or blue circle, see below), followed 2 s later by an outcome (reward, R+, or nonreward, R−). The R+ was an image of a British 1 pound coin. The R− was a blank disk of the same size and color (thus, the physical characteristics of the R− and R+ were closely matched). Subjects were told that they would receive a monetary

Table 1
Experimental design

Conditions	Expected stimulus	Delivered stimulus	
A (100 trials)	R+	R+] Reward error 1 contrast: Unexpected non-reward
B (20 trials)	R+	R−	
C (20 trials)	R−	R+] Reward error 2 contrast: Unexpected reward
D (100 trials)	R−	R−	

Four conditions (A–D) in which rewarding stimuli (R+) or nonrewarding stimuli (R−) were either expected or unexpected. Prediction error occurred in conditions B and C but not in conditions A and D.

reward for each presentation of R+, but not for the R-. Typically, a red circle predicted the occurrence of R+ (trial type 1: expected reward, 100 trials) and a blue circle predicted the occurrence of R- (trial type 2: expected nonreward, 100 trials). Occasionally, the red circle would be followed by nonreward (trial type 3: unexpected nonreward, 20 trials), and the blue circle would be followed by a reward (trial type 4: unexpected reward, 20 trials). The trials were pseudorandomly ordered. In order to optimize statistical modeling of hemodynamic responses (see ‘statistical analysis’ below), 40 ‘null’ events were included and random intertrial intervals were uniformly jittered between 4.96 s ($TR \times 2$) and 7.44 s ($TR \times 3$), thus effectively increasing the sampling rate of the hemodynamic response well beyond that of the TR. Immediately before scanning, subjects were overtrained on the four trial types by presenting them with 120 trials.

Image acquisition

A 2 T MRI scanner (Siemens, Erlangen) was used to acquire 715 T2*-weighted EPI images from each subject. There were 24 slice volumes (TR, 2.48 s; voxel size, 3 mm³). Slices were oriented obliquely, such that the whole anterior–posterior axis was covered and the field of view included the entire cerebellum and basal ganglia, the ventral visual system including the temporal lobes, the medial prefrontal cortex, and the ventral prefrontal cortex. High-resolution T1-weighted structural images were then acquired.

Image preprocessing

All preprocessing was conducted in SPM99. Images were acquired and converted into Analyze format. They were realigned to the first image to correct for head motion and normalized to the MNI template image (Montreal Neurological Institute) that uses the reference system of Talairach and Tournoux, (1988). The normalized images were then spatially smoothed with a Gaussian kernel of 6 mm.

Statistical analysis

Analysis methods used were similar to those used in Ramnani and Miall (2003). Five covariates modeled hemodynamic responses that were time-locked to the beginning of each cue–outcome compound stimulus in each of the four conditions. These were constructed by convolving second order windowed Fourier functions (two sine functions, two cosine functions, and one envelope function; 32 s window) with trial onsets for each trial type. The null events were implicitly modeled as baseline activity between trials. Six parameters describing head motion (three translations and three rotations) were modeled as confounding covariates. A fixed-effects general linear model was constructed from covariates from all subjects and was estimated in SPM99. F-contrasts were used to specify comparisons between the four trial types as reported in Ramnani and Miall (2003). The subject-to-subject consistency of activations from the group analysis was verified in single-subject analyses at a lower threshold ($P < 0.01$). The direction of the BOLD response in the error feedback and corresponding control conditions was also checked in each subject.

The following contrasts were applied

- (i) Effects of visual stimulation common to all conditions (these were found using a conjunction across the four experimental conditions relative to their own baselines).

- (ii) Two types of prediction error:
 - We tested for effects related to differential outcome value that depended on the context of prior expectation for two types of prediction error.
 - (a) Unexpected nonreward (reward vs. nonreward outcome when reward was predicted): [A < > B].
 - (b) Unexpected reward (reward vs. nonreward outcome when a nonreward was predicted): [C < > D].
 - (iii) Reward expectation (expected reward vs. expected nonreward, [A vs. D]).

To exclude activity that might be accounted for simply by the main effect of reward outcome (reward vs. nonreward) irrespective of predicted outcome, both the above contrasts were masked by this main effect (reward vs. nonreward outcome [A+C < > B+D]). Activity in the above contrasts therefore relates to differential outcome value in the context of expectation.

The purpose of contrast (iii) was to examine activity related to the prediction of rewards, outside the context of prediction error. Ramnani and Miall (2003) used identical outcome stimuli and almost identical conditioned stimuli as us. Our analysis methods were also similar to theirs. They reported that when conditioned stimuli predicted rewards, activity was found in the ventral pallidum at [16,2,4]. On the basis of that study, one could predict activity in the same anatomical location in our study for conditioned stimuli that predict rewards compared with conditioned stimuli that predict nonrewards, even if the outcomes are as predicted (i.e., no prediction error). In line with other studies (Pagnoni et al., 2002), we used a region of interest approach to test for this possibility. Bilateral regions of interest were defined, centered around this coordinate. A 10-mm sphere was used to define the outer boundary of each region of interest.

A threshold of $P < 0.001$ (uncorrected for multiple comparisons) was used for SPM{F} maps. Statistical images were overlaid onto the T1 canonical brain from the MNI series.

Results

Activity common to all conditions: [A B C D]

We assessed the internal validity of our experimental design and methods for modeling the hemodynamic response by testing for predictable effects that were orthogonal to the contrasts of interest. Visual stimuli were applied in all conditions, and we predicted the presence of visual effects of stimulus presentation (a factor common to all conditions in the visual system. In line with this expectation, we found robust event-related activity bilaterally in the fusiform cortex (see Fig. 1 for details).

Prediction error

The purpose of our study was to localize activity related to two types of reward-related prediction error (unexpected reward [C] and unexpected nonreward [B]). The control conditions were ones in which the same prediction was made but not violated ([C vs. D] and [B < > A]). In each case, differences might have been due to differences in rewarding vs. nonrewarding outcomes. We excluded

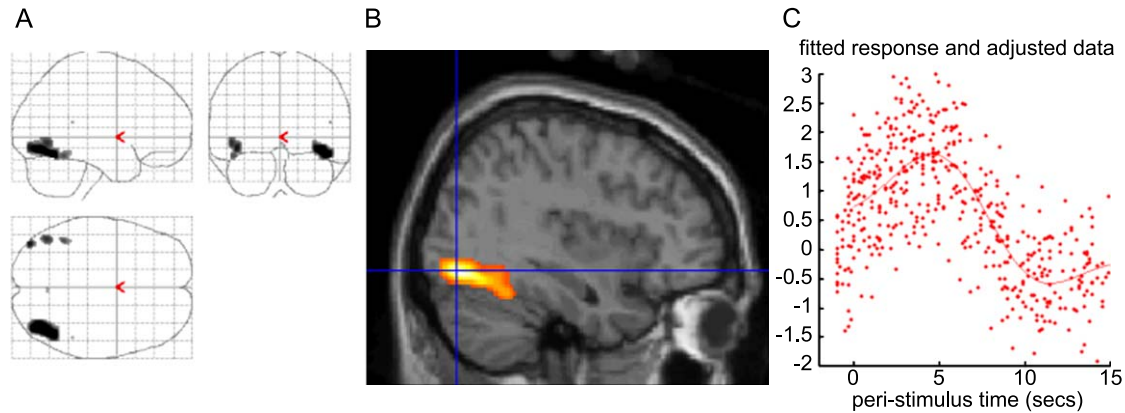


Fig. 1. Areas of common activation in the visual system. A. Maximum intensity projection of voxels in which changes in activity were common to the 4 conditions (derived by inclusive masking of these conditions). B. Activity in the fusiform gyrus (crosshair indicates the maximally activated voxel: 40, -72, 12; $F = 11.03$). The threshold SPM {F} map is displayed on the canonical T1 brain from the MNI series. C. Event-related haemodynamic response in the fusiform gyrus time-locked to trial onset.

this possibility by masking our contrasts with this main effect [(A+C) <> (B+D)].

- (a) Unexpected nonreward: [B <> A] exclusively masked by [(A+C) <> (B+D)].
Robust differences were found in the most anterior region of the left medial prefrontal cortex (frontal pole, BA 10). These were accompanied by differences in the superior temporal sulcus and in the temporal pole bilaterally (Table 2, Fig. 2A). In the anterior prefrontal cortex, unexpected nonrewards evoked phasic decreases in hemodynamic activity. This event evoked increased hemodynamic activity in the temporal lobe areas.
- (b) Unexpected reward: [C <> D] exclusively masked by [(A+C) <> (B+D)]

Differences were found in the anterior prefrontal cortex (frontal pole, BA 10), a medial part of the orbitofrontal cortex and in lateral parts of the dorsal prefrontal cortex (Table 2, Fig. 2B). There were also differences in the parahippocampal cortex and the cerebellar vermis. Unexpected rewards evoked phasic event-related decreases in the anterior prefrontal cortex and parahippocampal gyrus in most subjects but increases in the inferior frontal sulcus and cerebellar cortex.

Reward expectation

While some functional neuroimaging studies have reported that prediction error for reward evokes activity in the basal

Table 2
Table of results

Location	Cluster Size	F	Z equivalent	EHR direction for error condition	Coordinates {x,y,z}
<i>A. Unexpected nonreward</i>					
Prefrontal cortex					
*Anterior prefrontal cortex	162	6.96	4.01	-----(+)	-10, 64, 6
Temporal lobe					
Superior temporal sulcus (posterior)	7	5.71	3.49	++++(+)(+)	-68, -46, -2
*Inferior temporal gyrus (temporal pole)	5	5.29	3.29	+++++	-54, -4, -38
Inferior temporal gyrus (temporal pole)	9	5.1	3.21	++++(+)	52, 10, -40
<i>B. Unexpected reward</i>					
Prefrontal cortex					
Anterior prefrontal cortex	54	7.52	4.23	-----+	16, 62, -10
Anterior prefrontal cortex	132	7.18	4.1	-----+(+)	12, 58, 16
*Orbitofrontal cortex (medial orbital gyrus)	63	6.45	3.8	-----(+)	8, 34, -24
Inferior frontal sulcus	26	5.76	3.51	+++++	44, 20, 22
Temporal lobe					
*Parahippocampal gyrus	42	6.06	3.64	-----(-)(+)	18, -30, -14
Cerebellum					
Crus II (lobule HVIIB)	14	5.78	3.51	-+++++	-48, -56, -42

Coordinates of peak voxel in each cluster are reported. We compared the two prediction error conditions with their corresponding control conditions in which the same predictions were not violated. Unexpected nonrewards were compared with expected rewards, and unexpected rewards were compared with expected nonrewards. Each was masked with the main effect of reward outcome to exclude the possibility of activations being due to differences in outcome value in these conditions. Asterisks denote some key activations for which single subject Z values are reported in Table 3. Six ± signs are given in the sixth column. These denote the direction of the hemodynamic response for the prediction error conditions (+ increase; - decrease). They also indicate the cases that reached significance at $P < 0.01$ (signs for cases with nonsignificant trends are denoted in brackets).

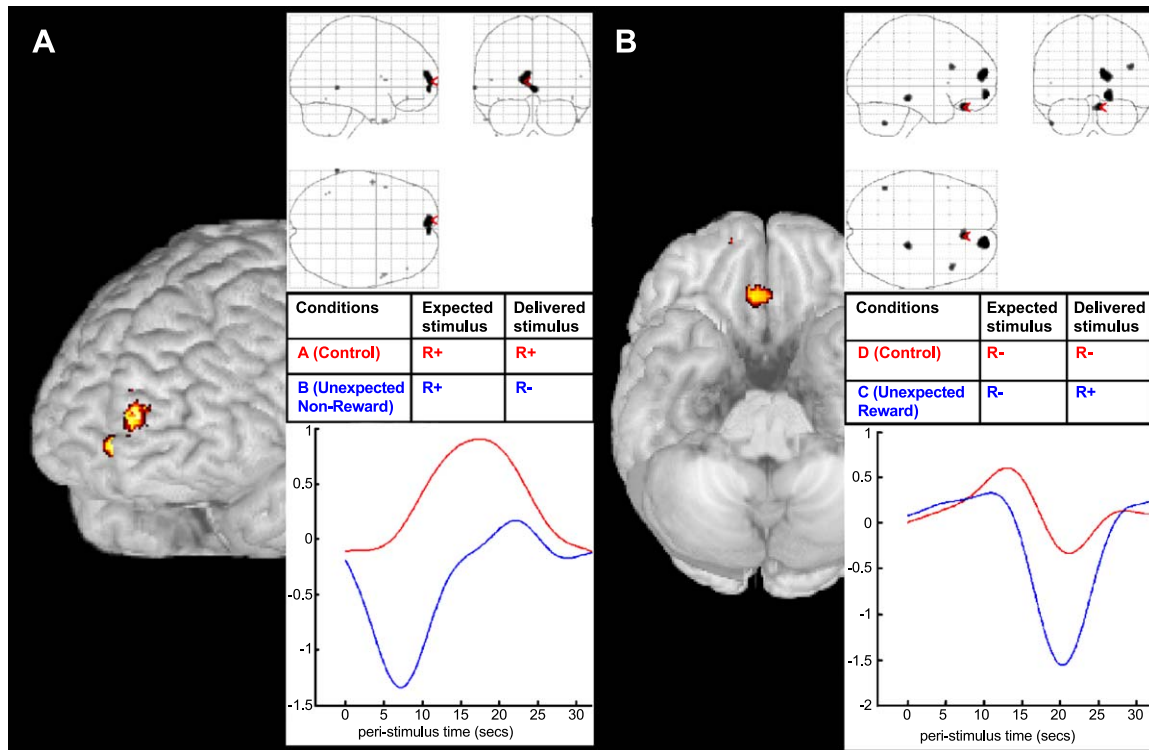


Fig. 2. Prediction error: A. Unexpected non-reward (compared with expected reward). Activation in the most anterior region of the superior frontal gyrus. B. Unexpected Reward (compared with expected non-reward). Activation in the medial orbital gyrus. Background images, SPM {F} map superimposed onto surface renderings of the canonical T1 brain (A: view of left dorsal prefrontal cortex; B: view of orbital surface with activation on the right). Upper panel: Maximum intensity projections of the contrasts. Middle panel: Details of the two conditions contrasted. Lower panel: Fitted haemodynamic responses for the two conditions. Color coding for graphs as for the middle panel.

ganglia, others have reported that it is evoked by conditioned stimuli that predict reward. We note that the studies in which the basal ganglia were activated by prediction error used primary rewards (e.g., juice; (McClure et al., 2003; O’Doherty et al., 2003; Pagnoni et al., 2002), but studies in which the basal ganglia were activated by conditioned stimuli used secondary rewards (i.e., money; Knutson et al., 2001a,b). Moreover, Ramnani and Miall (2003) used very similar methods to our own and reported activations in the ventral pallidum at [16, 2 4] time-locked to conditioned stimuli that predicted rewards compared with stimuli that did not. If this was related purely to the prediction of reward, outside the context of prediction error, then on the basis of this result our study would predict activity in a similar location in the pairwise comparison between conditions

A and D. We found suprathreshold activations in location close to this coordinate within our region of interest in the ventral striatum (18, 8, -6; $F = 5.37$; Fig. 3). This result supports our conclusion

Table 3
Single-subject Z values for key activations marked with an asterisk in Table 2 ($P < 0.01$, uncorrected; NS, not significant)

Case	Unexpected nonreward		Unexpected reward	
	Anterior prefrontal cortex	Inferior temporal gyrus (left)	Orbitofrontal cortex	Parahippocampal gyrus
1	4.84	3.81	3.22	5.99
2	NS	3.49	2.73	NS
3	5.53	3.25	3.96	3.89
4	4.14	3.84	NS	3.94
5	3.9	3.82	3.34	2.68
6	7.7	3.09	2.62	NS

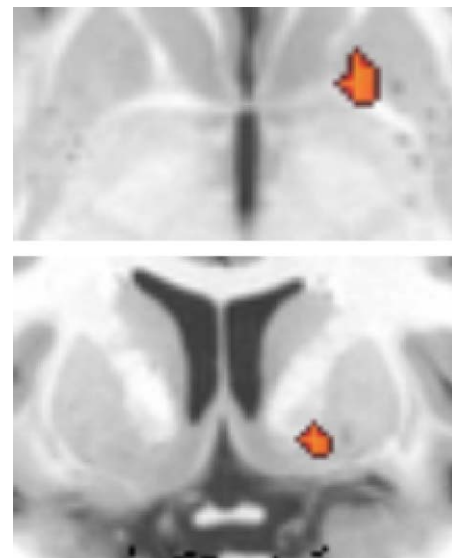


Fig. 3. Reward prediction in the basal ganglia. Trials in which cues successfully predicted rewards vs. trials in which cues successfully predicted non-rewards. Upper panel, transverse section; lower panel, coronal section. Planes of section through the peak value of the activation (coordinate 18, 8, -6) in the right ventral striatum.

that conditioned stimuli that predict monetary reward cause activity changes in the basal ganglia.

Discussion

The primary aim of this study was to localize regions of the human brain that were responsive to violations of expectations related to freely delivered monetary rewards. Before scanning, subjects learned that a red circle would be followed by a rewarding outcome and a blue circle by a nonrewarding outcome. We introduced two types of prediction error by occasionally delivering outcomes that were unexpected: The failure of an expected reward (a nonrewarding outcome was delivered when rewarding outcome was expected) elicited changes in activity in a frontotemporal circuit composed of the anterior prefrontal cortex, the temporal pole, and superior temporal sulcus. The unexpected occurrence of a reward (rewarding outcomes were delivered when nonrewarding outcomes were expected) elicited event-related changes in a different frontotemporal circuit (anterior prefrontal cortex, medial orbital gyrus of the orbitofrontal cortex, and inferior frontal sulcus) and in the parahippocampal cortex. Differences were also found in the cerebellar vermis. We were able to ensure that differences were not due simply to reward delivery by finding such areas (reward delivery vs. nondelivery) and masking them out from these contrasts.

Prediction error elicits event-related activity changes in frontotemporal circuitry

Our results implicate frontotemporal circuitry in the processing of prediction error. Anatomical studies have revealed projections between orbital and polar areas of prefrontal cortex and areas of the temporal cortex in nonhuman primates (Barbas et al., 1999; Cavada et al., 2000; Rempel-Clower and Barbas, 2000; Romanski et al., 1999). These represent important connections that enable visual information from the temporal lobe ‘object’ processing pathways to reach the prefrontal cortex. Studies in nonhuman primates have demonstrated that frontotemporal circuitry is important for the learning associations between pairs of objects and between objects and actions (in both cases, the relationships between the pairs are purely arbitrary in the sense suggested by Wise and Murray, 2000). Nearly all fibers that connect the temporal lobe with the prefrontal cortex pass through the uncinate fasciculus (Ungerleider et al., 1989), and therefore transections of this fiber tract would sever almost all connections of the temporal lobe with the prefrontal cortex. Gaffan and colleagues have shown such disconnections severely impair the ability of animals to learn arbitrary associations between objects and also between objects and actions (Eacott and Gaffan, 1992). They have also demonstrated that this pathway is only required when animals are required to use one visual cue to guide the conditional choice of another (Gutnikov et al., 1997a,b). Furthermore, the ability to form specific object–rewards associations was severely impaired after uncinate fascicle lesions (Parker and Gaffan, 1998). Our study has demonstrated that violations of predictions made on the basis of such associations specifically cause activity changes in frontotemporal circuitry. Lesions may therefore impair learning because frontotemporal circuitry is required for the processing of error feedback.

It is notable that the prediction error conditions (but not the control conditions) elicited changes in the form of event-related decreases in BOLD activity in some areas, most notably in the anterior prefrontal and orbitofrontal cortex. While the causal relationships between neuronal activity and resultant BOLD activity are not well understood, it is reasonable to assume that in our event-related study, differential BOLD activity between two comparable trial types is due to differences in the underlying neuronal activity. Inferences beyond this about the precise form of the neuronal activity on the basis of BOLD activity are speculative. Nevertheless, there are examples of neuronal activity decreases in response to prediction error in the reward system where activity in dopamine neurons phasically decreases at the time that expected rewards fail to appear (Hollerman and Schultz, 1998). While increases in BOLD activity may be due either to increases in excitatory or inhibitory neurotransmission, it has been argued that phasic decreases in BOLD signal are mainly due to phasic decrease in neural activity, whether inhibitory or excitatory (Shmuel et al., 2002; Wade, 2002). In line with this interpretation, other studies have also reported positive and negative changes in event-related BOLD signal in relation to reward-related prediction errors. While unexpected primary rewards (e.g., juice) have commonly evoked positive BOLD responses in the basal ganglia, the locations vary (nucleus accumbens: Pagnoni et al., 2002; dorsal putamen: McClure et al., 2003; ventral putamen: O’Doherty et al., 2003). Negative BOLD responses evoked by unexpected failure of primary rewards have evoked activity in the dorsal putamen (McClure et al., 2003) and in the orbitofrontal cortex (O’Doherty et al., 2003). Apart from the present study, only one other has examined activity related to prediction error for secondary (monetary) rewards but has done so in an operant context where rewards are contingent on subjects’ behavior. Knutson et al. (2001a,b) reported a negative BOLD response in relation to negative prediction error in the ventromedial prefrontal cortex. We suggest that an interpretation of these results is difficult because they are so inconsistent from each other, and also because little is known about the relationship between the directionality of the BOLD response and the dynamics of its underlying neuronal activity.

In the case of appetitive primary rewards (e.g., juice), Pagnoni et al. (2002) reported an increase in activity in the ventral striatum and McClure et al. (2003) reported a decrease in the left dorsal putamen. As in our study, Knutson et al. (2001a,b) reported a decrease in ventromedial prefrontal cortex in response to unexpected monetary reward failure. Thus, the event-related decreases in prefrontal BOLD activity time-locked to prediction error probably reflect a genuine phasic decrease in neuronal activity.

Unexpected rewards and unexpected failure of rewards cause activity changes in separate frontotemporal subsystems

We argue that the two types of prediction error elicit activity changes in separate frontotemporal subsystems. Our contrasts each compared predictable and unpredictable conditions, so it is arguable that the changes in activity were related to prediction error generally rather than prediction error related to rewards. However, the anatomical patterns for both contrasts differed, suggesting that activity changes depended on the reward value of the unexpected outcome.

The failures of expected rewards elicited activity in an anterior part of the prefrontal cortex (frontal pole, area 10) and also in the

temporal pole and the superior temporal sulcus. These areas are arguably part of the same anatomical system since projections between the temporal lobe areas and anterior prefrontal cortex are specific, dense, and direct (Barbas et al., 1999; Cavada et al., 2000; Rempel-Clower and Barbas, 2000; Romanski et al., 1999). We also showed that unexpected rewards elicited decreases in anterior prefrontal cortex as well as the medial orbital gyrus in the orbitofrontal cortex. These were accompanied by changes in parahippocampal areas of the temporal lobe. We argue that this is a distinct system on the basis that medial parts of the orbitofrontal cortex in which there were activity changes in our study are preferentially interconnected with the hippocampus and parahippocampal cortex (Barbas and Blatt, 1995; Cavada et al., 2000).

Unexpected rewards also evoked activity changes in the vermis of the cerebellar cortex. Although the role of the cerebellum is well established in the processing of prediction error (Miall et al., 1993; Ramnani et al., 2000), traditional accounts of cerebellar function suggest that this area is concerned mainly with the control of movement rather than cognition and that the cerebellar vermis is particularly concerned with the control of eye movements. We argue against this interpretation because stimuli in all conditions were of the same size and complexity and appeared in the same spatial location. The unexpected nature of events could not have contributed to differential eye movements since cerebellar activity was present for unexpected rewards but not for unexpected failure of reward. It has been suggested that the human cerebellum has a role in the processing of cognitive information (Leiner et al., 1993) and that the cerebellar vermis has a specific role in the processing of affect (Levisohn et al., 2000; Schmammann and Sherman, 1997, 1998). Physiological and anatomical evidences suggest that the cerebellum can exert an influence on systems concerned with emotion (e.g., noradrenergic projections between locus caeruleus and the cerebellar vermis; Somana and Walberg, 1978). The cerebellar vermis also has a critical role in animal models of fear conditioning (Ghelarducci and Sebastiani, 1997; Sacchetti et al., 2002; Supple and Leaton, 1990; Supple et al., 1987, 1988, 1993). Finally, the human cerebellar vermis is also activated during the anticipation of aversive stimuli (Ploghaus et al., 2000). We tentatively suggest that the activity found in the cerebellar vermis may be related to the processing of affective information related to the unexpected occurrence of rewards.

Prediction and error coding in the prefrontal cortex

Evidence suggests that prefrontal cortex is involved in reward processing at the level of predictive coding. During delayed response tasks, neurons of the lateral and orbital prefrontal cortex change their activity in response to cues that predict future rewards. Prior to the outcome, activity in the lateral convexity related to instruction cues and delay periods often depends on the expected rewarding properties of the trial outcome (Hikosaka and Watanabe, 2000; Leon and Shadlen, 1999; Niki and Watanabe, 1979; Watanabe, 1990, 1996). As in our study, activity often predicts the specific absence of a reward (Watanabe et al., 2002). Functional imaging in humans has also suggested that prefrontal activity is related to predictive coding for reward. Breiter et al. (2001) examined responses associated with both anticipation and outcome phases of trials with good or bad outcomes. Medial orbitofrontal cortex responded to both anticipation and receipt of positive and negative outcomes.

O'Doherty et al. (2002) reported that anticipation of consumatory rewards also activated the orbitofrontal cortex. Furthermore, Berns et al. (2001) reported that predictability of reward modulated responses to rewarding outcomes in medial orbitofrontal cortex. Previous imaging studies have also implicated anterior prefrontal cortex in processing the predictability of rewards. Pochon et al. (2002) showed working memory performance in activated anterior prefrontal cortex if rewards were expected for correct performance. Similarly, Ramnani and Miall (2003) used visual cues and monetary reward outcomes that were very similar to those used in our study during a delayed response task. The color of instruction cues also informed subjects about whether or not a rewarding stimulus would be given for a correctly executed trial. Preparatory activity time-locked to the instruction cues was modulated by reward expectation in anterior prefrontal cortex. Anterior prefrontal areas engaged in the prediction of rewards in their study was also engaged by prediction error in ours.

Computational models of predictive coding of reward in the prefrontal cortex (Contreras and Schultz, 1999) suggest that orbital and lateral prefrontal neurons should fire not only in relation to predictions about rewards, but also when such predictions are violated. Niki and Watanabe (1979) showed that omissions of expected reinforcement activated neurons in lateral prefrontal cortex. As in our study, Schultz et al. reported a subset of orbitofrontal neurons in nonhuman primates in which activity was evoked by unexpected reward that occurred independently of the behavioral context (Schultz et al., 2000). Thus, these neurons can code for associations between predictive instructions and rewarding outcomes independently of behavior.

The human orbitofrontal cortex has also been implicated in reward processing in the context of uncertain or changing contingencies. It is activated by breaches of visual expectation (Nobre et al., 1999), suggesting that processing prediction errors is a general feature of the orbitofrontal cortex. Breaches of reward expectation can be considered as a special case of this general rule. Other imaging studies have also shown such activity changes when predictions about rewards are violated (Elliott et al., 2000a; O'Doherty et al., 2000, 2001; Rogers et al., 1999). O'Doherty et al. (2003) reported that orbitofrontal activity correlated with the degree of prediction error related to the prediction of appetitive rewards. Gottfried et al. (2003) reported that decreasing the motivational significance of rewards caused a decrease in orbitofrontal activity. In monkeys, single unit activity in the orbitofrontal cortex is related to the rapid learning and reversals of stimulus–reward associations (Rolls et al., 1996), suggesting that the orbitofrontal cortex is specialized for rapidly learning such associations and rapidly readapting them in new contexts. In support of this idea, it has been shown that lesions of the orbitofrontal cortex result in perseverative behavior, where the ability to adapt previously learned context–reward associations is severely impaired (Dias et al., 1997; Iversen and Mishkin, 1970; Rolls et al., 1994). Fellows and Farah (2003) have shown that lesions in the region of the medial orbital gyrus did not impair the ability of patients to learn object–reward associations but did impair the ability to subsequently reverse these associations. The prediction error conditions in our study reflected such reversals, and consistent with electrophysiological evidence (Schultz et al., 2000), we have shown that it is specific for the occurrence of unpredicted rewards.

Reward-predicting stimuli cause activity changes in the striatum

The striatum has a well-established role in the processing of monetary rewards in humans and appetitive rewards in nonhuman primates (Martin Soelch et al., 2001; Schultz and Dickinson, 2000; Schultz et al., 2000). In nonhuman primates, neurons respond to both reward-predicting stimuli (Aosaki et al., 1994) and to rewards themselves (Apicella et al., 1991a,b). They do so in a variety of contexts. Responses are related to unsignalled rewards, to rewards predicted by a visual stimulus, and also rewards in the context of an instrumental task (Apicella et al., 1997). Unlike dopamine neurons, they do not respond in any way to omitted rewards (Schultz and Dickinson, 2000) but do activate in response to stimuli that predict rewards (Schultz et al., 1992). On the basis of this finding, we would not expect activity in the striatum in relation to unexpected reward omissions. In the present study, we did not use unsignalled rewards or rewards that were contingent on behavior. We did use reward-predicting stimuli, and consistent with electrophysiological evidence in nonhuman primates (Aosaki et al., 1994; Schultz et al., 1992), an activation was present in the ventral striatum in a pairwise comparison between expected rewards and expected nonrewards (Fig. 3). The ventral striatum has also been shown to respond in anticipation of predicted monetary rewards in other functional imaging studies (Knutson et al., 2001a,b, 2003; Ramnani and Miall, 2003), suggesting that in the case of monetary reward, activations in the basal ganglia are not responsive to errors in prediction but to stimuli that predict rewards. In order to conclusively demonstrate that basal ganglia activity is time-locked to conditioned stimuli that predict rewards rather than to outcomes in a classical paradigm, future studies would need to dissociate activity time-locked to each of these components by introducing temporal variability between them as in previous studies (Ramnani and Miall, 2003, 2004). It would then be possible to model conditioned stimuli and outcomes as separate events in an event-related experimental design. Ramnani and Miall (2003) have used this strategy in an operant paradigm. They have dissociated activity time-locked to instruction cues (conditioned stimuli) from activity time-locked to responses and outcomes in a delayed response task. While the shapes of conditioned stimuli instructed the required responses, the color simultaneously indicated whether or not monetary rewards were likely for a correct response at the end of the trial. Activity time-locked to instructions for action was modulated by reward expectation in the anterior prefrontal and premotor cortex. No such activity was found in the basal ganglia. Our study and theirs showed that activity was evoked in the ventral striatum by conditioned stimuli that predicted reward, irrespective of whether or not reward-related predictions were violated.

Convergent evidence discussed above and from studies of prediction error suggests that the human basal ganglia may operate in two modes during the processing of reward-related information. Some studies show that if primary rewards are used (e.g., juice), the basal ganglia are activated by prediction error (McClure et al., 2003; O'Doherty et al., 2003; Pagnoni et al., 2002). Others (including the present study) show that if secondary rewards are used (e.g., money), the basal ganglia show activity changes in relation to conditioned stimuli that predict rewards, but not by reward-related prediction error (Knutson et al., 2001a,b; Ramnani and Miall, 2003). In both modes, these relationships appear to be independent of the type of contingency between the conditioned stimulus and the outcome, whether classical or operant. Future studies are required

that explicitly test this hypothesis by varying, in the same subjects, the nature of the contingency (classical vs. operant) and the type of reward (primary vs. secondary) and using experimental designs that can determine whether activity is time-locked to conditioned stimuli or to outcomes (predicted vs. unpredicted).

In summary, our study has used prediction errors for monetary reward in human subjects that reliably evoke activity changes in dopamine neurons when appetitive rewards are used. We show distinct activity changes in separate frontotemporal circuits in relation to prediction error for monetary rewards delivered independently of behavior. Furthermore, our experimental design enabled us to separately determine activity changes related to unexpected rewards and unexpected failures of reward in reversal trials. We show activity changes in anterior prefrontal cortex in relation to both types of prediction error, but that a medial part of orbitofrontal cortex (middle orbital gyrus) shows activity changes that are specific to the presentation of unexpected reward. Our results are consistent with the view that changes in activity in frontotemporal circuits do not simply represent the processing of predictive stimuli and rewards but actively encode the associations between them.

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