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www.elsevier.com/locate/ynimg
NeuroImage 21 (2004) 984–990

Instrumental responding for rewards is associated with enhanced neuronal response in subcortical reward systems

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Received 10 July 2003; revised 7 October 2003; accepted 7 October 2003

The response of human reward systems to different reinforcers, including food, drugs and money, has been investigated in a number of recent functional neuroimaging studies. They have varied, however, in terms of whether or not a behavioural response was required to obtain rewards. The aim of the present study was to determine whether neuronal responses to financial reward are significantly modulated by the requirement to make a behavioural response. Twelve subjects were scanned using functional magnetic resonance imaging (fMRI) while performing a simple target detection task. Certain targets acted as cues predicting financial reinforcement; some additionally required that a movement be executed, while others did not. There were also targets that required a movement but were not predictive of reward.

We observed, as expected, responses within motor and reward systems associated with main effects of movement and reward, respectively. Critically, the reward responses were significantly modulated by the requirement to make an intervening behavioural response. Blood oxygenation level-dependent (BOLD) responses in the amygdala and striatum were significantly enhanced when a movement was required, while reward-related response in the orbitofrontal cortex was independent of movement. These results suggest important dissociations within human reward systems, reflecting different properties of rewards. The striatum and amygdala may mediate the function of rewards in eliciting goal-directed behaviour, while the orbitofrontal cortex mediates incentive value.

Keywords: Financial reward; Neuronal response; Subcortical reward systems

Introduction

Much has been learned about brain reward circuitry from experimental studies in animals, using electrophysiological, pharmacological and lesion techniques coupled with sophisticated pavlovian and instrumental learning paradigms (Balleine and Dickinson, 1998; Hatfield et al., 1996; Parkinson et al., 2000). These studies suggest that core reward-detection systems mediate pavlovian acquisition of incentive value by stimuli that reliably predict reward. Additional, and overlapping systems mediate more flexible instrumental learning of new behaviours that produce rewards and incentive stimuli (Parkinson et al., 2000).

A general concept that has emerged is that striatal regions are selectively engaged by movement toward rewarding stimuli while amygdala and orbitofrontal cortex are important for learning and sustaining instrumental behaviours that produce rewards (Schultz et al., 2000). Neurons in the striatum (as well as the dorsolateral prefrontal cortex and SMA) fire before internally generated movement toward rewarding stimuli, and continue firing until the reward is collected (Kurata and Wise, 1988; Romo and Schultz, 1987; Schultz and Romo, 1990). Neuronal firing in the caudate is seen preferentially for movement toward rewards (Kawagoe et al., 1998) and for rewarded rather than unrewarded movements (Hollerman and Schultz, 1998), evidence that the caudate is particularly concerned with goal-directed action. These findings implicate dorsal striatal structures in mediating response selection and the interaction between movement and reward, which underpins goal-directed behaviour. The ventral striatum, by contrast, is implicated in more general motivational effects of reward (Parkinson et al., 2000). Interactions between the amygdala and ventral striatum are important in instrumental learning and performance, especially for secondary reinforcers, stimuli that reliably predict reward (Everitt et al., 1989; Hatfield et al., 1996; Whitelaw et al., 1996).

Neurons in the orbitofrontal cortex (OFC) appear to code relative reward preference (Tremblay and Schultz, 1999), and to mediate abstract representation of rewards (Schultz, 2000; Schultz et al., 2000). This has been interpreted as indicating a role for the OFC in representing incentive or motivational value of rewards (Baxter et al., 2000; Gallagher et al., 1999; Schoenbaum et al., 1998). The ability of OFC neurons to distinguish between different rewards (Schultz et al., 2000) is seen as reflecting a detailed analysis of rewards encountered by an animal, information that can be important for behavioural guidance and decision-making.

Dopamine neurons innervate and modulate many of the forebrain regions that are responsive to aspects of reward (Schultz, 2000). Unexpected rewards potentially activate dopamine neurons, but anticipation of expected rewards signalled by predictive stimuli also elicits dopaminergic firing. Cue-evoked dopamine release in dorsal striatum has been implicated in selecting responses to produce a reward in well-learned stimulus response habits (Robbins and Everitt, 1992). In ventral striatum, dopamine appears to

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Available online on ScienceDirect (www.sciencedirect.com.)

1053-8119/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2003.10.010

play a more general motivational role in orienting and guiding approach to rewards and stimuli that predict them. Instrumental responding for secondary reinforcers is powerfully modulated by dopamine and this is dependent on amygdala–ventral striatal interactions (Taylor and Robbins, 1984).

Human reward systems are much less well understood, and may be relatively complicated by interactions with higher cognitive processing. In recent years, neuroimaging with functional magnetic resonance imaging (fMRI) has been used to investigate reward processing in humans, using a variety of different reinforcers: food (O'Doherty et al., 2000, 2002; Rolls et al., 1997; Small et al., 2001), drugs (Breiter et al., 1997; Ingvar et al., 1998; Stein et al., 1998; Volkow et al., 2000), money (Breiter et al., 2001; Delgado et al., 2000; Elliott et al., 2000; Knutson et al., 2000, 2001; O'Doherty et al., 2001) or more abstract rewards, such as success (Zalla et al., 2000). These studies have identified roles for regions of an interconnected reward system in response to a range of reinforcers. Regions including the dorsal and ventral striatum, amygdala, thalamus, dopaminergic midbrain and various prefrontal foci, particular ventral and medial structures, have been implicated in responses to food, drugs of abuse, financial reward and more abstract reinforcers. A number of studies have started to dissociate distinct roles for these structures in subtly different aspects of reward processing. However, a question that has yet to be addressed explicitly is the extent to which neuronal responses to reward depend on the execution of an instrumental response. Some designs have required subjects to make behavioural responses to obtain rewards, while others have not, and this may be an important factor in interpreting results.

In this study, we used a simple reward task in conjunction with fMRI to study the modulation of human reward responses by the requirement to execute an instrumental movement. We hypothesised that regions of reward circuitry (striatum, amygdala and OFC) would show enhanced blood oxygenation level-dependent (BOLD) response to reward, which may be selectively modulated by the intervening movement. The experiment was a factorial design with reward and movement as two independent factors. The critical analyses examined the interaction between these two factors, allowing us to assess the extent to which reward-related responses depend on an interaction between reward and behavioural responses.

Methods

Subjects

Twelve right-handed subjects, 6 male and 6 female, were recruited to participate in this experiment. All subjects were students at the University of Manchester (mean age 23.6) and were not wage-earners. The financial rewards used were therefore likely to have a significant and similar value for all subjects. Subjects with self-reported neurological or psychiatric history were excluded and subjects were asked not to use recreational drugs or drink excessive alcohol in the 48 h before scanning. The Beck Depression Inventory was used to screen subjects for clinically significant depression. Subjects who were colour-blind were also excluded.

fMRI scanning

Subjects were scanned using a Phillips 1.5 T Gyroscan ACS NT, retrofitted with Powertrak 6000 gradients, operating at software level 6.1.2 (Hamburg, Germany). One hundred two single shot echo-planar volume images were acquired, with a repeat time (T_r) of 5 s and an echo time (T_e) of 40 ms. Each volume comprised 40 axial slices with 3.5 mm spacing and in-plane resolution of 3 mm × 3 mm. The first two volumes of each run were to allow for T1 equilibration effects and were discarded before analysis. A T1-weighted structural scan was also acquired for each subject and these were examined by a consultant radiologist to exclude any structural abnormality; no such abnormality was reported for any of the 12 subjects.

Cognitive task

Subjects were scanned during performance of a simple target detection task. Different coloured squares were presented on a screen at a rate of one every 1.33 s. Six different colours were used. Subjects were told to respond by squeezing a pneumatic bulb with their right hand every time they saw a green or blue square. They were also told that red and green squares would be financially rewarded; for the red squares, no response was required, while for the green squares, receipt of the reward required a bulb squeeze. The reward stimulus was an image of a coin with the monetary value superimposed, also displayed for 1.33 s, and subjects were told that this represented 'real money' that they would take away at the end of the experiment. Blue squares (which subjects responded to) and yellow squares (which elicited no response) were not rewarded. Presentations of these colours were followed by blank circles. The remaining colours were purple and orange, which were control stimuli requiring no response. The study was divided into blocks 40 s long; each block contained 22 coloured squares, 8 of which were one of the four critical coloured stimuli (green, blue, red or yellow). These were interspersed randomly among 14 control stimuli. In each block, only one of the four critical colours was used. Thus, there were four conditions:

(A) Movement required, reward received. Green targets.
(B) Movement required, no reward received. Blue targets.
(C) No movement required, reward received. Red targets.
(D) No movement required, no rewards received. Yellow targets.

This was therefore a 2 × 2 factorial design with movement (present vs. absent) and reward (present vs. absent) as the two factors. In between the 40-s blocks were 20-s rest blocks. These were included partly to give subjects a break and partly to allow non-specific drift in fMRI signal to be modelled out of the data. Each type of block was repeated twice in a counterbalanced order, to control for order effects.

Subjects were thoroughly trained on the task before scanning to focus on performance and eliminate effects of learning about reward. During scanning, subjects knew with 100% certainty that they would receive a reward when they saw a green or a red target (assuming they made the appropriate response in the latter case), but there was no expectation of a reward when they saw a blue or a yellow target. Reward expectation was therefore fixed throughout the experiment.

Data analysis

Data were analysed using SPM99 (Friston et al., Wellcome Department of Cognitive Neurology). Images were first realigned, using the first image as a reference. They were then normalised

into a standard stereotactic space, using MNI (Montreal Neurological Institute) templates and the co-ordinate system of Talairach and Tournoux (1988), and smoothed using an isotropic Gaussian kernel filter of 10 mm full-width half-maximum to facilitate inter-subject averaging.

Statistical analysis was carried out with a random effects model. First level analysis was performed on each subject to generate a single mean image corresponding to each of the key contrasts. These mean images were then combined in a second level analysis using one-sample t tests to investigate group effects. Statistical maps were descriptively thresholded at $P < 0.001$ uncorrected. Where observed responses survived the more stringent statistical threshold of $P < 0.05$ corrected for multiple comparisons, this is reported. Additionally, small volume corrections (Worsley et al., 1996) were applied to a priori regions of interest: the amygdala, striatum and medial prefrontal regions.

The critical analysis of this study is to determine which of those areas that exhibit BOLD response to financial reward also show a significant modulation by instrumental movement. The 2 × 2 factorial design allows us to look at main effects of movement and of reward, as well as the interaction between the two factors. The interaction term is orthogonal to both main effects. To address the central question, the interaction term is described masked with the main effect of reward. See http://www.fil.ion.ucl.ac.uk/spm for further description of this procedure.

Results

Behavioural responding

All subjects responded to all blue and green targets. Response latencies did not differ significantly under the rewarded and non-rewarded conditions.

fMRI results

The key comparisons in this analysis are the interaction terms; representing how the response to reward is modulated by the requirement to respond for it. However, the main effects of movement and of reward are also reported. The main effect of movement provides validation that signal is being detected in predicted regions, because the neuronal basis of button press responses is well established. The main effect of reward is reported to confirm the expected reward system responses and also to act as an inclusive mask for the interaction terms. See Table 1 for foci of BOLD signal change.

Table 1
Maximally activated voxels in areas where significant evoked activity was related to a main effect of movement

Region	Left/Right	Brodmann's area	Talairach coordinates			Z value
Motor cortex	L	2	−51	−30	54	8.42*
	R	2	48	−27	45	3.82
Cerebellum	L		−27	−72	−21	7.08*
	R		21	−54	−21	6.37*
Cuneus	L	18	−6	−96	21	3.68
Superior temporal gyrus	L	22	−57	12	−3	3.54
Supplementary motor area	R	6	18	6	72	3.35

All other regions are $P < 0.001$ uncorrected.
* $P < 0.05$ corrected for multiple comparisons across the whole brain.

Table 2
Maximally activated voxels in areas where significant evoked activity was related to a main effect of reward

Region	Left/Right	Brodmann's area	Talairach coordinates			Z value
Anterior cingulate	R	32	3	33	30	5.01*
Medial orbitofrontal	L/R	10	0	51	−6	5.08*
Cortex						
Frontal pole	R	9	9	57	36	5.29*
Dorsolateral prefrontal cortex	R	9	45	36	30	5.28*
Lateral orbitofrontal cortex	R	47	54	24	−9	4.10
	L	47/10	−45	51	−9	3.93
	L	47	−57	18	−3	3.85
Amygdala	R		27	0	−21	3.68**
Putamen	R		33	3	0	5.02*
Thalamus	R		3	−18	9	3.54

All other regions are $P < 0.001$ uncorrected.
* $P < 0.05$ corrected for multiple comparisons across the whole brain.
** Regions significant at $P < 0.05$ after small volume correction (Worsley et al., 1996).

Main effect of movement ((A + B) − (C + D))

Significant BOLD responses (at $P < 0.05$ corrected) associated with a right-handed button press were observed in contralateral (left) motor cortex, extending to premotor cortex, and bilateral cerebellum (Table 1). Responses significant at $P < 0.001$ uncorrected were observed in ipsilateral (right) motor cortex, left cuneus (BA 18), left superior temporal gyrus (BA 22) and right supplementary motor area (BA 6).

Main effect of reward ((A + C) − (B + D))

Significant BOLD responses (at $P < 0.05$ corrected) associated with receiving financial reward were observed in anterior cingulate cortex extending anteriorly into medial prefrontal cortex, right amygdala (small volume correction used), frontal pole, right dorsolateral prefrontal cortex (BA 9), medial orbitofrontal cortex (BA 10/25) and right putamen (Table 2). Responses significant at $P < 0.001$ uncorrected were observed in bilateral lateral orbitofrontal cortex and right thalamus.

Modulation of response to reward response by the requirement to make an instrumental response: the interaction term (A − B) − (C − B), masked by the main effect of reward (A + C) − (B + D)

This analysis represents the interaction between reward and movement (thresholded at $P < 0.001$ uncorrected) masked by the main effect of reward (thresholded at $P < 0.05$ uncorrected) (Table 3). This identifies regions responding to financial rewards that

Table 3
Maximally activated voxels in areas where there was a significant modulation of responses to reward by the requirement to make an instrumental response

Region	Left/Right	Brodmann's area	Talairach coordinates			Z value
Amygdala	R		30	−6	−21	3.69*
Putamen	R		27	6	9	3.48*
	L		24	−3	3	3.54*
Dopaminergic midbrain	R		3	−15	−21	2.85*

All other regions are $P < 0.001$ uncorrected.
* Regions significant at $P < 0.05$ after small volume correction (Worsley et al., 1996).

showed significantly greater response when the reward was dependent on an instrumental movement. Enhanced responses, significant at $P < 0.05$ after small volume correction, were observed in the right amygdala, bilateral dorsal striatum (maximally responsive voxels in the caudate) and dopaminergic midbrain (see Fig. 1).

Modulation of response to reward by not having to make an instrumental response ((B − A) − (D − C))

Using the masking procedure described above, no significant enhancement of the reward response was observed when rewards were not contingent on a movement. However, an unmasked analysis revealed a response in the right temporal pole, significant at $P < 0.05$ corrected.

Discussion

The critical analysis of this study was the modulation of neuronal responses to reward by instrumental behaviour (squeezing a bulb to receive the reward). However, the main effects of movement and of reward also served as important validators of the methodology. As predicted, the main effect of movement (button presses with the right index finger) was associated with highly significant neuronal responses in the contralateral motor cortex and the cerebellum. The main effect of reward was also associated with significant neuronal responses in regions predictable on the basis of previous studies, including the medial and ventral prefrontal cortex, dorsal striatum, thalamus and amygdala. The main effect of reward was then used as an inclusive mask to identify brain regions where instrumental behaviour modulated the reward response. Significant enhancement of the reward-related response under the movement condition was seen in the dopaminergic midbrain, dorsal striatum and amygdala. There were no regions responsive to reward that showed an enhanced response when no movement was required, although the right temporal pole responded significantly in this interaction but not in the main effect of reward.

In this study, all rewards, whether or not they required a movement, were fully predictable. Since all subjects responded to all cue stimuli, every green or blue predictor was followed by a financial reward. Therefore, differential responses to instrumental rewards were not due to differences in predictability or expectation. The results also cannot be attributed to learning, because the task and the contingencies associated with different cues were well-learned in the pre-scanning training session. The use of a factorial

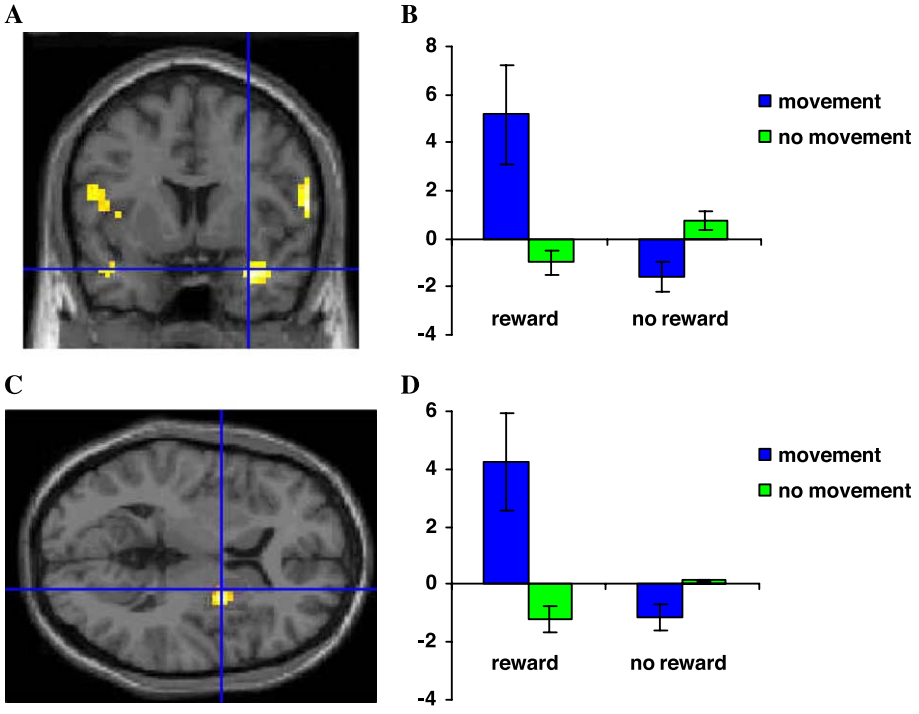

Fig. 1. BOLD responses in the amygdala (A) and putamen (C) which showed a modulation of reward response by movement. The interaction term of the factorial design, thresholded at $P < 0.001$ uncorrected was inclusively masked by the main effect of reward, thresholded at $P < 0.05$ uncorrected. Regional responses survive Bonferroni correction when the small volume procedure (Worsley et al., 1996) is used. Plots of beta values under the four conditions in the amygdala and putamen are given in (B) and (D), respectively.

design allowed us to look explicitly at interactions between movement and reward factors, controlling for the effects of each factor alone.

Significant enhancement of the reward-related responses in the right dorsal striatum and amygdala was seen in the instrumental condition. The relative right lateralisation of these responses corroborates earlier results suggesting that right-sided structures respond more strongly to financial rewards than left-sided structures (Breiter et al., 2001; Elliott et al., 2000, 2003). However, it should be noted that a post hoc test for the significance of these lateralisation effects indicated that this may be a thresholding effect rather than a truly lateralised response.

Enhanced response in the dorsal striatum under the instrumental condition is consistent with studies in experimental animals. Kawagoe et al. (1998) reported marked increases in the firing rate of caudate movement neurons when a movement was rewarded compared to when it was not. Hollerman and Schultz (1998) showed that the behaviour-related firing of neurons of the anterior striatum was significantly influenced by reward expectation, suggesting that these neurons incorporated information about predicted outcomes into their movement-related activity. Similarly, Tremblay et al. (1998) showed that neuronal firing of anterior striatum in a delayed go–no go task was initially seen to both rewarded and non-rewarded movements. However, as the task became well learned, anterior striatal firing was confined to the rewarded movement trials. The task used in the present study was already well-learned before scanning. It should be noted that in the Hollerman and Schultz (1998) and Tremblay et al. (1998) studies, anterior striatal firing was also seen for predictable rewards occurring in the absence of movements. This is not necessarily incompatible with the results presented here; the significant interaction does not necessarily imply that there is *no* reward-related dorsal striatal response to rewards in the absence of movements, simply that any reward-related response is *enhanced* when a movement is required. These findings are consistent with the proposed role for both dorsal and ventral striatal neurons in mediating goal-directed behaviour (Schultz 2000; Schultz et al., 2000). Schultz (2000) suggests that neurons of the striatum, including neurons in the caudate and putamen, may represent both the reward and the movement toward the reward and thus mediate the control of behaviour by expected rewards.

It should be noted that incentive functions have been particularly ascribed to the ventral portion of the striatum, including the nucleus accumbens. Both animal studies (Apicella et al., 1991; Robbins and Everitt, 1992, 1996; Schultz et al., 1993) and human neuroimaging studies (Breiter et al., 2001; Elliott et al., 2000, 2003) have implicated a critical role for ventral striatum in reward responses. Schultz (2000) claims that ''neurons in the ventral striatum have more reward-related responses. . .than neurons in the caudate and putamen''. It is therefore surprising that the present study showed no ventral striatal signal to either the main effect of reward, or the modulation of reward by instrumental movement. This discrepancy is somewhat puzzling, although consistent with some previous neuroimaging studies that have also emphasised a role for dorsal rather than ventral striatum (Delgado et al., 2000; Knutson et al., 2001). A detailed characterisation of functional heterogeneity within the striatum during human reward processing remains an important challenge for neuroimaging research.

The recruitment of dopaminergic midbrain in the instrumental condition is compatible with evidence that dopaminergic cells respond in anticipation of rewards; predicted both by conditioned incentive stimuli and by instrumental behaviour (Schultz, 2000). Both these processes could have operated in the instrumental condition, but only cue-evoked activation could have operated in the non-instrumental condition.

Amygdala responsiveness to reward is clearly predicted by the animal literature. (Hatfield et al., 1996; Holland and Gallagher, 1999; Kalivas and Nakamura, 1999; Killcross et al., 1997; Schoenbaum et al., 1998). It is strongly implicated in basic pavlovian aspects of reward by which animals approach cues, for example, in autoshaping. In addition, lesion studies suggest that the basolateral nucleus has a specific role in the acquisition of instrumental responding for secondary reinforcers (Hall et al., 2001). A general role of the amygdala in stimulus–reward association would account for the main effect of reward observed here, because green and red targets consistently predicted a reward whether or not a movement was required. The potentiation of amygdala response in the instrumental condition may reflect the additional role of the amygdala in associating secondary reinforcers with instrumental responses. A related explanation is that both the cue and the motor response invoke representations of the reinforcer through amygdala mechanisms.

Several previous studies have suggested that the orbitofrontal cortex and amygdala interact closely in associative learning paradigms (Baxter et al., 2000; Kalivas and Nakamura, 1999; Schoenbaum et al., 1998). It has been suggested (Baxter et al., 2000, Schoenbaum et al., 1998) that the connection between OFC and amygdala is critical for response selection on the basis of incentive value. However, the present results suggest that the responses of these regions can be functionally dissociated. While amygdala responses to reward were significantly modulated by movement, OFC responses were not. Recent results from functional neuroimaging (Breiter et al. 2001; Elliott et al. 2003; O'Doherty et al., 2001), as well as animal electrophysiology (Schultz, 2000) and lesion studies (Mobini et al., 2002), suggest that a critical function of the OFC is assigning relative reward value. The rewards in the movement and the no-movement conditions of the present study are of equal value. It has also been argued that the OFC plays a role in analytic reward detection and expectation of reward (Schultz, 2000). Again both the experience of rewards and the expectation of rewards are matched in the movement and no-movement conditions, and a lack of differential OFC activity is therefore plausible. It is important to note that both animal studies reviewed above, and neuropsychological studies of patients with OFC damage (Bechara et al., 1994, 1996; Rolls et al., 1994), suggest that OFC plays a role in behavioural modification in the face of changing reward values. The present study is not incompatible with this hypothesis. Reward values here remain constant and therefore no behavioural modification is required. It is plausible that amygdala and striatum mediate already established reward-eliciting behaviours, while medial OFC monitors ongoing reward experience, ready to modify behaviour (via top-down connections to the amygdala and striatum) if necessary.

The blocked design used in this study had the advantage of increasing the predictability of stimuli; an event-related design would inevitably have introduced a greater element of unpredictability into the stimulus presentation. The disadvantage of the blocked approach is that neuronal responses to the separable components of the reward response (expectation, decision, response and outcome) are conflated. Therefore, an important caveat of our findings is that we cannot say which of these components is responsible for the BOLD responses observed. A further possible

confound is that the requirement for a motor response is conflated with contingency. Thus, the modulation of reward response by movement could also reflect a modulation by enhanced contingency. Additional studies will be required to dissociate these possible confounds.

In conclusion, this study demonstrates dissociable functions of subcortical and cortical structures in human reward response. For rewards that are equally valuable and equally predictable, the OFC responds similarly whether or not an instrumental movement is required to receive the reward. By contrast, subcortical structures (amygdala, dorsal striatum and dopaminergic midbrain) show a significant modulation of reward response by the requirement to make a movement. These structures therefore appear to play a significant role in mediating goal-directed behaviour, while the OFC (and other medial prefrontal regions) may code incentive value. It appears that in humans, monetary reward symbols, and the cues and responses that elicit them, engage remarkably similar brain systems to the basic pavlovian and instrumental reward systems identified in animals.

Acknowledgments

We are grateful to the Medical Research Council and to the Royal Society for their generous support of this project.

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