Instructed Delay Activity in the Human Prefrontal Cortex is Modulated by Monetary Reward Expectation

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Goal-directed actions are executed with greater efficiency when the goals of the actions are rewarded and so the reward expectation must influence systems concerned with action-planning and motor control. However, little is known about how this influence is achieved in primates. Here, we demonstrate in human subjects that manual performance is enhanced when the goals of the visually cued actions are monetary rewards. We also used event-related fMRI in the same subjects to localize neural activity related to action preparation and selection that was influenced by the reward. We found three areas with significant interaction between reward and preparation: the prestriate visual cortex, the premotor cortex and the lateral prefrontal cortex. The latter two areas appear to be frontal systems integrating the expectation of rewards with selection and preparation of actions.

Introduction

Anecdotal evidence suggests that the expectation of monetary rewards biases human performance and monetary rewards act as a powerful motivational factor in the selection of our actions. However, the pathways in the human brain through which this influence occurs are not clear. Recent studies in non-human primates have suggested that there are at least two areas in which performance-related neuronal activity can be influenced by the expectation of consumatory rewards. These are dorsal sectors of the lateral prefrontal cortex (Leon and Shadlen, 1999; Watanabe, 1996) and the basal ganglia (Petrides and Pandya, 1999; Hassani *et al.*, 2001), areas that are heavily interconnected with both the motor system and with systems involved in the processing of reward-related information (Alexander *et al.*, 1990).

The above studies used conditional delayed response tasks, in which instruction cues signalled how the animals were to respond with eye or hand movements at the time of a later trigger cue. Cells in the mid-dorsolateral prefrontal cortex (the middle one-third of the dorsal and ventral banks of the principal sulcus) and the anterior bank of the arcuate sulcus exhibited a variety of firing properties in this task, from transient responses to the cue to sustained firing that reflected the operation of working memory during the instructed delays (Goldman-Rakic, 1995). The instruction cues have also been used to signal the type or amount of reward to be expected after the trial. 'Delay activity' in the prefrontal cortex is influenced both by varying the type of food reward expected (Watanabe, 1996) and by varying the expected amounts of the same reward (Leon and Shadlen, 1999). It is therefore possible that the reward expectation activity in these neurons forms the basis on which subsequent behaviour is influenced.

Reward and delay-related neuronal activity has also been extensively investigated in the primate striatum. Schultz and colleagues (Hollerman *et al.*, 1998) described transient and sustained responses to the instruction cues that were modulated by reward expectation, located predominantly in anterior portions of the striatum. The types of reward expected also modulated response-related activity in the anterior striatum (Hassani *et al.*, 2001). Hikosaka and colleagues (Kawagoe *et al.*, 1998) reported similar effects in the caudate nucleus during an oculomotor conditional delayed response task. The striatum may therefore also be an important part of the circuitry that mediates the influence of reward expectation on performance.

Prefrontal and basal ganglia circuitry has also been implicated in the processing of monetary reward in the human brain. In a PET study, Thut *et al.* (Thut *et al.*, 1997) compared a condition in which feedback for correct task performance was a monetary reward, with one in which feedback was the word 'OK'. Activations associated with the reinforcing effects of monetary reward were found in the orbitofrontal cortex. Elliott *et al.* (Elliott *et al.*, 2000) compared reward related activity in the contexts of monetary reward and punishment using a gambling task. They reported an anatomical dissociation between reward- and punishment-related activity: activity in the ventral striatum was sensitive to the context of reward, and activity in the hippocampus was sensitive to the context of punishment. Knutson *et al.* (Knutson *et al.*, 2000) also examined activity related to monetary reward and punishment, and did so in the context of a delayed response task. The region scanned extended from the genu of the corpus callosum posteriorly to the medial parietal cortex, and included posterior parts of the prefrontal cortex and the whole of the basal ganglia and temporal lobes. In contrast to the results of Elliott *et al.* (Elliott *et al.*, 2000), basal ganglia (caudate and putamen) and mesial prefrontal cortex was responsive to both rewards and punishments, although there was additional punishment-related activity in the thalamus and anterior cingulate cortex. In a later study, Knutson *et al.* (Knutson *et al.*, 2001a) parametrically manipulated the expectation of both monetary reward and punishment. They found the nucleus accumbens to be increasingly active during the expectation of increasing reward, but not punishment. Knutson *et al.* (Knutson *et al.*, 2001b) manipulated reward expectation and outcome independently during a delayed response task. They reported that regions of the basal ganglia (nucleus accumbens, caudate and putamen) and mesial prefrontal cortex were activated by the anticipation of rewards in the context of action. Finally, in a recent study, Pochon *et al.* (Pochon *et al.*, 2002) investigated activity related to an N-back working memory task in which subjects were given variable levels of monetary rewards for correct performance. They reported that prefrontal regions were activated by the main effect of working memory. These regions, and in addition a region of the anterior prefrontal cortex (BA10, frontal pole), also showed increases in the context of monetary reward. No such activity was observed in the basal ganglia.

Some recent event-related fMRI studies have used delayed-response tasks to isolate preparatory activity that precedes

action. These have attempted to differentiate and localize transient activity time-locked to the instruction cues, the trigger cues, and sustained activity reflecting continuous activity in the delay period. Thus, activity time-locked to the cue was considered to be either transient or sustained. D'Esposito *et al.* (D'Esposito *et al.*, 2000a) have attempted to isolate preparatory delay-period activity using a delayed response task. In a visual conditional task, instruction cue colour specified whether subjects were required to move the index or middle finger at the time of a later trigger (thus, they could prepare a specific response during the intervening delay). In the control task, the instruction cue colour did not specify which finger to move – this was done by the trigger cue itself, and subjects were not able to plan which finger to move during the instructed delay period. A region of interest analysis that focussed on the frontal lobes showed some delay-specific activity in dorsolateral prefrontal cortex, but none was reported in the premotor system even though expected on the basis of single unit studies in non-human primates (Weinrich *et al.*, 1984; Wise and Kurata, 1989). Others have used an alternative approach. Toni *et al.* (Toni *et al.*, 1999) have also used a visual conditional task in which subjects had learned arbitrary associations between visual cues and responses, but their study differs in two important ways from the study by D'Esposito *et al.* (D'Esposito *et al.*, 2000a). First, they introduced trial-to-trial temporal variability in the delays between cues and triggers, so activity related to cues, triggers and delays was temporally uncorrelated. Hence, activity related to these three components could be estimated independently. Secondly, event-related activity was judged against an inter-event baseline instead of activity related to 'no preparation' trials to control for non-specific sensory, motor and general anticipatory factors. Transient activity time-locked exclusively to instruction cues (but not explained by the other components) was found in the striate and prestriate cortex, and in the intraparietal sulcus. No significant activity was reported in the frontal lobes. However, there was some activity in an anterior region of the dorsal premotor cortex that exhibited all three properties (transient peaks associated with the instruction and trigger cues, and also a sustained component during the delay). Furthermore, activity was also present in the prefrontal cortex that was related to the delay and to the trigger cue. This was located in a region described as the ventral prefrontal cortex that we believe to be sufficiently anterior to be in the frontal pole (BA 10).

The lack of activity exclusive to the delay period in the dorsal prefrontal and premotor cortex might at first seem inconsistent with studies recording from single-units in the monkey dorsal prefrontal and premotor cortex (see above). However, single units in the prefrontal and premotor cortex typically respond in a complex manner to instruction cues, with an initial transient burst of activity, followed by more sustained activity that lasts throughout the delay (Crammond and Kalaska, 2000; Constantinidis *et al.*, 2001), sometimes becoming less stable as the delay progresses (Wise and Kurata, 1989). The relatively small proportion of single units in frontal lobe areas that exhibit such exclusivity might explain why so little delay activity was found in these imaging studies (Kurata and Wise, 1988b; Chafee and Goldman-Rakic, 2000).

The present study aimed to address two issues. One aim was to determine whether the impact of reward expectation is maximal at the time that actions are planned or at the time that actions are executed. We achieved this by using a delayed response task, where the visual instruction cue indicated both the level of reward to be expected and controlled whether subjects could plan a specific manual response in advance of the trigger cue. The second aim was to use event-related fMRI to localize brain sites where activity related to all pre-movement processes time-locked to instruction cues was specifically modulated by the expectation of monetary rewards. We were able to isolate instruction-related activity by introducing a variable delay between instruction and trigger cues, so that activity time-locked to these components could be dissociated. In light of the evidence described above, evoked haemodynamic responses (EHRs) to instruction cues might be more efficiently detected if modelled as complex unitary responses, rather than as separate transient and sustained components. Given the typically complex nature of instruction-related EHRs, we applied statistical methods specifically designed for detecting EHRs without the need to make prior assumptions about their form (Josephs and Henson, 1999). Our experimental design imposed stringent control over preparatory processes by manipulating the specificity of action-related information in instruction cues, allowing us to exclude non-specific sensory, motor and anticipatory effects. This combination of methods allowed us to localize regions of the brain in which the expectation of monetary rewards modulated action-specific preparatory activity.

Materials and Methods

Subjects

Eight healthy right-handed volunteers were recruited after they had given informed consent. The study had local ethical approval. Subjects lay supine in the MRI scanner, with the fingers of the right hand positioned on a four-button response box. They wore prism-lens glasses to enable them to view a back-projection screen positioned outside the scanner, onto which images were projected with a SVGA resolution LCD projector.

Visual Conditional Delayed Response Task

Trials (see Fig. 1) consisted of a visual instruction cue displayed for 300 ms followed by a variable delay of 3–9 s, terminated by a visual trigger cue indicating that the subject should make an immediate response using index or middle finger to press buttons 1 or 2 of the response box. Their response was immediately followed by presentation of an 'outcome' image for 300 ms. On rewarded trials, the reward was symbolically represented as an image of a British pound coin. On non-rewarded trials, a blank disk of the same size and colour was displayed. On trials in which subjects made an incorrect response, a non-reward was always delivered (these trials constituted 3.02% of all trials and were modelled as separate trial types from the others, so that they did not contribute to the fMRI results). All stimuli were presented at the centre of the screen. The next trial followed after a variable post-trigger interval of up to 3 s. The total trial-to-trial interval therefore varied between 3 and 12 s (mean, 4.5 s). Subjects were informed that they would receive a monetary reward related to their performance. Subjects were over-trained, without reward, on the task for 30 min prior to scanning.

We employed a 2 × 2 factorial design in which one factor was reward expectation (two levels: reward and no reward expected) and the other was the specificity of preparation (two levels: specific preparation or non-specific preparation of response). There were four resulting conditions (60 trials in each condition, pseudorandomly presented):

1. Subjects neither prepared specific responses nor expected any rewards.
2. Subjects were not able to prepare for a specific response but expected a reward.
3. Subjects were able to prepare for a specific response but did not expect any reward.
4. Subjects were able to prepare for a specific response and expected a reward.

Instruction Cues

The *shape* of the instruction cue allowed subjects to prepare a specific

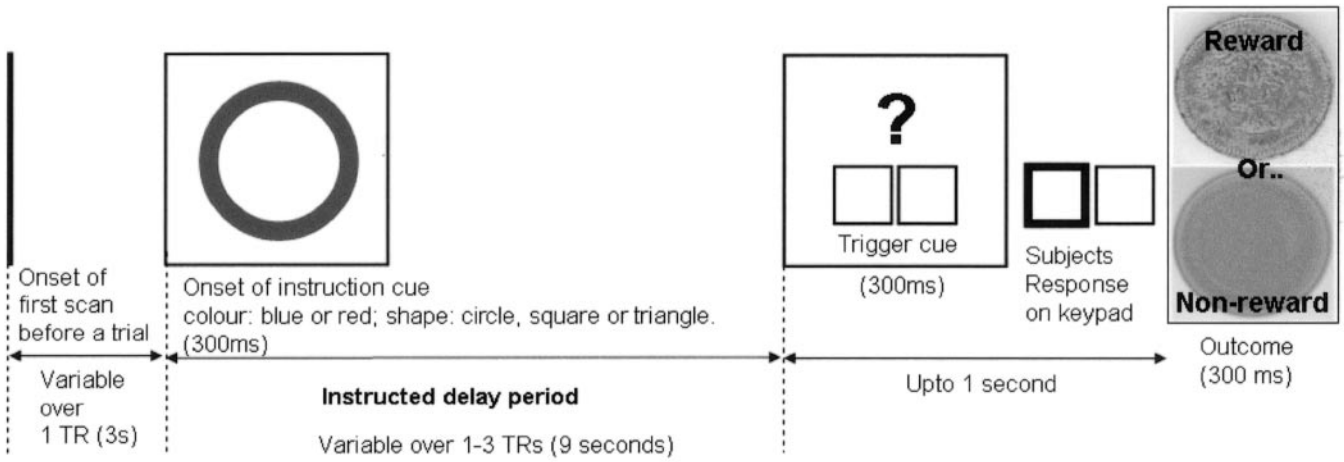


Figure 1. Behavioural task.

response or non-specific response whereas the *colour* of the cue signalled the probability of reward for the correct action. In 'specific preparation' trials (50%), a square cue instructed index finger responses; a circle, middle finger responses. In 'non-specific preparation' trials (50%), a triangle indicated that either the index or middle finger responses were required with equal probability of either finger, as identified later. Consequently, at the time of the instruction cue, subjects were either able to prepare a specific response or were required to wait until the trigger cue specified which action to make. In 'reward' trials (50%), a red instruction cue signalled 80% chance of a reward for a correct trial; in 'no-reward' trials (50%), a blue instruction cue signalled 20% chance of a reward for a correct trial. The instruction cues therefore independently manipulated both reward expectation and preparation level. Subjects were told that they were likely to receive a monetary reward on trials in which they performed correctly if the cue was a red shape, but unlikely to do so if the cue was a blue shape. As in some other studies using monetary reward (Pochon *et al.*, 2002), the amount was not specified. This strategy avoided mental calculation of cumulative gains. The proportion of incorrect trials was negligible, so at the end of the session, all subjects received the maximum amount (£10.00).

Trigger Cue, Response and Outcome

In 'specific preparation' trials, the trigger cue was an image composed of two squares (representing the two response buttons), with a question mark above them, indicating that the subject must choose the appropriate response as previously specified by the instruction cue (see Fig. 1). In 'non-specific preparation' trials, one of the two squares was highlighted to indicate which button was to be pressed. The question mark was replaced by an exclamation mark, indicating that there was no choice to be made. The trigger was displayed for up to 1000 ms (response onset time-window). The outcome image appeared immediately after the response was made, ending the trial. If no response was made in this time window, subjects were shown the non-reward followed by the next trial.

Behavioural Recording

Reaction times were calculated from the intervals between the triggers and responses. A repeated-measures analysis of variance was used to determine whether there was a significant difference between the four trial types, and whether there was a significant interaction between the main effects.

Functional Imaging and Analysis

Data Acquisition

A total of 1350 T2*-weighted EPI images were acquired for each subject using a 3T Siemens Vision scanner with a GEM BEST sequence. The field of view covered the whole brain: 256 × 256 × 125 mm, 64 × 64 × 24 voxels; T_R = 3s, T_E = 30 ms, flip angle = 90°. The functional scanning sequence lasted 67.5 min. High-resolution T_1-weighted structural images were also acquired.

Image Preprocessing

Scans were pre-processed using SPM99 (www.fil.ion.ucl.ac.uk/spm) by spatial realignment with reference to the first scan (Friston *et al.*, 1995), normalization to the ICMB template using both linear affine transformations and non-linear transformations using basis functions (Ashburner and Friston, 1999). Lastly, a Gaussian kernel of 10 mm was applied to spatially smooth the images.

Statistical Analysis

Experimental Timings and Event Definition

It was important to sample evoked haemodynamic responses (EHRs) optimally, so EHRs time-locked to the instruction cue were evenly sampled by the uniform distribution of random trial-to-trial variability in the interval between scan onset and cue onset, over a range of one T_R (3 s). Since the time window after the cue was sampled continuously, the effective temporal sampling resolution was much finer than the T_R. Another important goal of the study was to model EHRs time-locked to the instruction cues separately from the EHRs time-locked to the trigger cue. This was facilitated by introducing random intervals uniformly and continuously distributed between 1 and 3 T_Rs (3–9 s). We were therefore able to model the instruction and trigger cues as independent event types (see 'Modelling' below). The four types of instruction cue were modelled as four separate event types. Trigger cues for all four trial types were treated as a single, fifth event type (this modelled all haemodynamic activity related to the visual trigger, the subjects' motor response and the outcome). Trials in which motor responses were incorrect or late (RT > 1000 ms) were modelled as a sixth event-type, and comprised 3.02% of all trials.

Modelling

Each event-type was used to construct a series of regressors by convolution of event time delta functions with a Fourier set of seven harmonic functions (three sine, three cosine, one envelope function, 20 s post-stimulus time window). This strategy was motivated by the need to model potentially complex haemodynamic activity without making stringent prior assumptions about its amplitude-timecourse profile (Josephs and Henson, 1999). Twenty-four null events (in which no stimuli or responses occurred) were implicitly modelled as baseline activity between trials. Their statistical properties were identical to those of the other trial types. The six parameters describing head motion calculated from the realignment stage of the preprocessing were included as confounding covariates in order to model residual effects of head motion. All 48 regressors from each of the eight subjects were incorporated into a general linear model (GLM). Prior to the study, experimental timings

Table 1
F-contrast comparing the seven basis functions in conditions 1 and 3

C	1	1	1	1	1	1	1	2	2	2	2	2	2	2	3	3	3	3	3	3	3	4	4	4	4	4	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6
BF	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Contrast structure																																										
[	1	0	0	0	0	0	0	0	0	0	0	0	0	0	–1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	–1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	–1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	–1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	–1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	–1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	–1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0]

C, condition; BF, basis function; bracketed matrix, contrast structure. The condition order is: [1] non-specific preparation, reward not expected; [2] non-specific preparation, reward expected; [3] specific preparation, reward not expected; [4] specific preparation, reward expected; [5] all trigger-related activity; and [6] incorrect trials.

were carefully checked so that they resulted in an estimable GLM in which the independence (or 'rank') of the six event types was preserved. The degree of rank deficiency was assessed by examining the correlations between all regressors, and found not to be significant. The GLM was estimated in SPM99 on a Dual Pentium III 800 MHz PC with 1 GB of RAM, running Red Hat Linux (v6.1) and Matlab 5.3 (MathWorks Inc). After parameter estimation, *F*-contrasts (see below) were applied in the context of a fixed-effects group analysis to specify comparisons between the trial types. The resulting SPM{F} maps identified voxels in which linear combinations of the seven basis functions resulted in estimated responses significantly different between the conditions of interest.

The *F*-tests reported in the SPM{F} are the same as completely standard parametric *F*-tests in ANOVA and related procedures. These tests are defined with an *F*-contrast matrix that can be thought of as a collection of *T*-contrasts. The *F*-statistic tests the null hypothesis that the treatment sum of squares (or contrasts of basis function coefficients), spanned by the *F*-contrast, is zero. The implementation of *F*-contrasts with several basis functions in SPM99 is described in Buechel *et al.* (Buechel *et al.*, 1996) and the statistical background is given elsewhere (Andrade *et al.*, 1999). A comparison among conditions of interest is made for all basis functions. For example, there are seven such basis functions in our study. The structure of the contrast is such that the comparison of each basis function coefficient is represented by one row, where the columns run over basis functions. Since each comparison is specified in a row for a given basis function, there were seven rows in the contrast structure. An example *F*-contrast row comparing conditions 1 and 3 would be [1 0 –1 0 0 0]. The complete contrasts is represented by the matrix in Table 1.

The F-contrast comparisons used in our study were:

1. Specific preparation versus non-specific preparation: [–1 –1 1 1 0 0].
2. Reward expectation versus no reward expectation: [–1 1 –1 1 0 0].
3. Interaction: [1 –1 –1 1 0 0]. This is a standard contrast applied to factorial designs that reveals regions in which one main effect is significantly modulated by the context of the other.

Localization

Anatomical details of significant signal changes were obtained by superimposing the SPF{F} maps on the T_1 canonical MNI template image. Results were checked against structural images of each subject. The atlas of Duvernoy and Bourgouin (Duvernoy and Bourgouin, 1999) was used as a general neuroanatomical reference, and that of Schmahmann *et al.* (Schmahmann *et al.*, 2000) was used for localization within the cerebellum. The nomenclature of Larsell (Larsell, 1972) was used in anatomical descriptions of the cerebellar cortex.

Results

Behavioural Responses

An analysis of variance (ANOVA) revealed that subjects' mean reaction times were significantly reduced when they were able to prepare movements in advance of execution, irrespective of the level of reward expectation [main effect of preparation: $F(1,7) = 12.24$; $P < 0.01$]. Reward expectation also reduced reaction times significantly [main effect of reward expectation: $F(1,7) = 15.9$; $P < 0.005$]. There was a significant effect of reward expectation on reaction times in the preparation condition [paired *t*-test: $t(7) = 4.59$, $P < 0.005$]. The interaction between reward and preparation factors was highly significant [$F(1,7) = 25.98$; $P < 0.001$]: reward expectation reduced reaction times only when subjects were able to prepare their movements (Fig. 2). We conclude that the main impact of reward expectation on performance was at the time of action selection and preparation, rather than at the time of execution.

Functional Imaging

Areas showing a significant response to all four visual instructions cues are listed in Table 2, and some anatomical renderings are shown in Figure 3. These include the major brain systems expected to be involved in sensory motor control as well as prefrontal cortex and prestriate visual cortex (Fig. 2). Note that in our analysis all post-trigger events (including the subjects' finger responses) were modelled separately, and so do not contribute to the effects seen in the contrasts reported.

The Main Effects of Motor Preparation

Table 3 shows differences in activity between those conditions when subjects were able to prepare for actions and when they could not.

Differential haemodynamic activity was present in almost the whole of the cortical premotor system (Table 3) including the border between the SMA and pre-SMA (Vorobiev *et al.*, 1998) (see Fig. 4) and the precentral gyrus. This activation probably includes the left primary motor cortex, BA4. Preparation-specific activity was also present in the left posterior parietal cortex, the right anterior lobe of the cerebellar cortex and bilaterally in the basal ganglia (on the border between the posterior putamen and GPe). This anatomical profile is similar to that reported in a previous PET study of motor preparation (Krams *et al.*, 1998), although we did not find activity in ventral premotor cortex. The use of F-contrasts enabled us to detect differences in the haemodynamic response regardless of their directionality. However, inspection of the estimated haemodynamic responses for each of the areas revealed that activity in the specific motor preparation conditions always exceeded activity in non-specific preparation conditions in all the areas.

Main Effect of Reward Expectation

This contrast (Table 4) revealed areas in which differential activity was seen between high and low reward expectation conditions, regardless of the level of preparation. Regions in which significant differences existed included the left lateral prefrontal cortex and the right orbitofrontal cortex, the basal

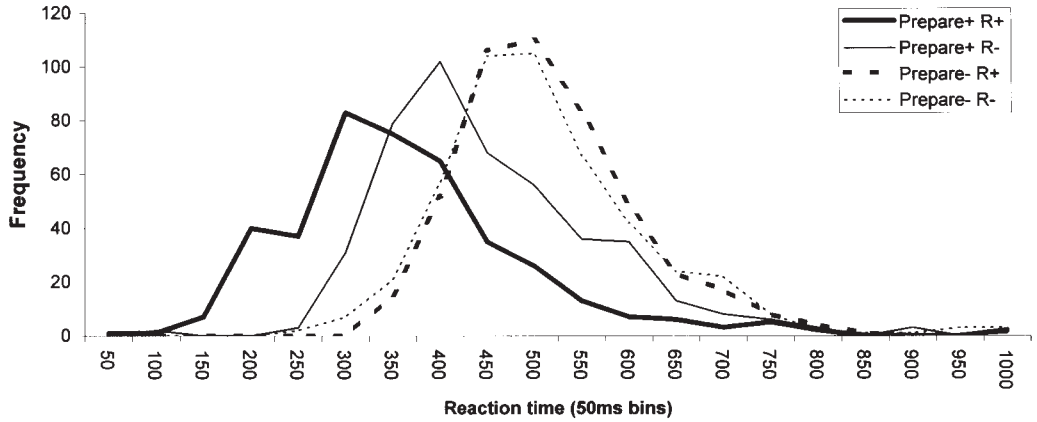


Figure 2. Distributions of reaction times in the four conditions.

ganglia (right ventral pallidum; see Fig. 4) and the temporal lobes (including the left parahippocampal cortex and amygdaloid complex). Again, activation in these areas was higher in the rewarded conditions.

Interaction between Reward Expectation and Preparation

The primary purpose of the study was to localize preparatory activity in the brain that was modulated by the level of reward expectation. We found such activity in the right prestriate cortex and in the left dorsal premotor cortex (Table 5). However, the most significant activation lay in the right frontal pole of the prefrontal cortex (BA 10; see Fig. 5*A*). The estimated haemodynamic response curves (Fig. 5*B*) show that in both frontal lobe areas activation was greatest in the high reward, preparation condition. In PMd the haemodynamic response peaked 5 s after the instruction cue, whereas in BA10 the response was more sustained with a peak ~10 s post-instruction cue.

Table 2
Regions activated in all four conditions (inclusive masking of all four cue-related conditions; $P < 0.05$, corrected for multiple comparisons)

Region	*F*	Equiv. *Z*	Coordinates (mm)		
			x	*y*	*z*
Prefrontal cortex					
L frontal pole (BA 10)	21.51	>8	–18	62	20
R superior frontal gyrus	16.45	7.59	2	42	40
L middle frontal gyrus (BA46)	19.9	>8	–40	32	24
L middle frontal gyrus (posterior)	19.04	>8	–30	–2	50
Premotor cortex					
L pre-SMA	56.53	>8	–6	8	54
Insular cortex					
L anterior insular cortex	15.71	7.38	–34	12	6
Posterior parietal cortex					
L intraparietal sulcus	48.57	>8	–26	–60	44
R intraparietal sulcus	20.94	>8	30	–62	52
L supramarginal gyrus	40.95	>8	–46	–36	40
L/R medial parietal cortex	15.92	7.44	0	–56	42
Visual cortex					
R prestriate cortex	19.1	>8	12	–76	2
Basal ganglia					
R dorsal putamen	14.59	7.07	32	0	8
L ventral putamen	15.59	7.35	–28	–2	–8
Cerebellum					
R cerebellar cortex (lobule HV/HVI)	29.92	>8	24	–58	–30
L cerebellar cortex (crus I)	18.84	>8	–36	–58	–38

Discussion

We have shown that human performance in a visual conditional button-pressing task in which subjects were either able to plan their response in advance, or not, can be biased by expectations of monetary reward, and that the effect is significantly greater at the response planning stage than at the response execution stage.

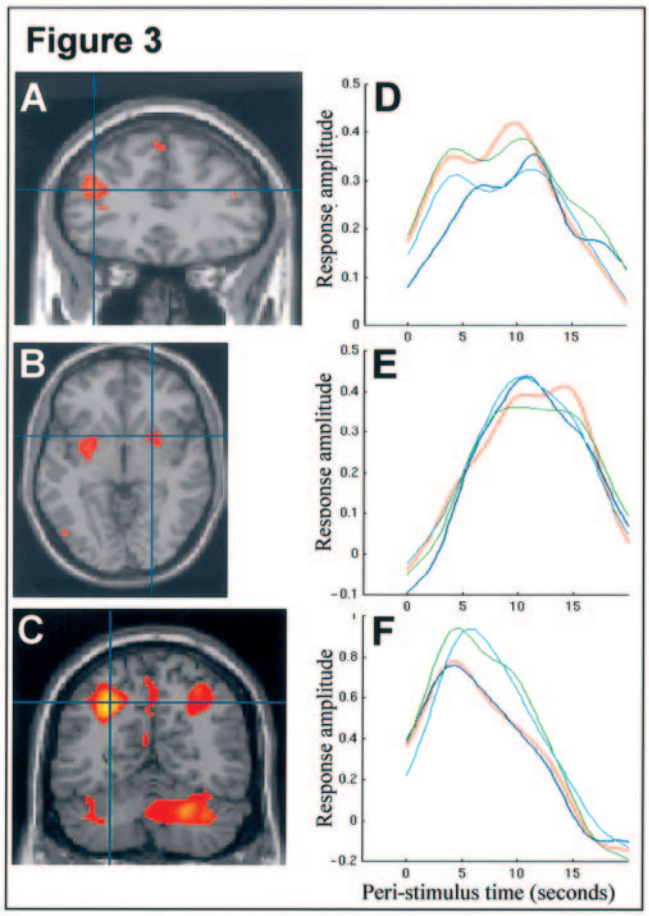
We also localized regions of the human brain responsive during the delayed response interval of this task and found robust planning-related activity in the premotor network, in the cerebellum and in the basal ganglia. In all cases, activity in the preparation condition was greater than in the non-specific preparation condition. This finding is similar to a previous study (Krams *et al.*, 1998) of motor planning that that used PET rather than fMRI, and used a 'blocked' experimental design rather than an event-related design. This is therefore an important validation of our methods. We also report activity related to reward-expectation in regions of the human brain known to process reward-related information. These regions included the orbitofrontal cortex, the ventral pallidum, the amygdaloid complex and the parahippocampal gyrus. Again, this replicates earlier studies (Thut *et al.*, 1997; Knutson *et al.*, 2000, 2001b; O'Doherty *et al.*, 2001) and validates the reward paradigm we used.

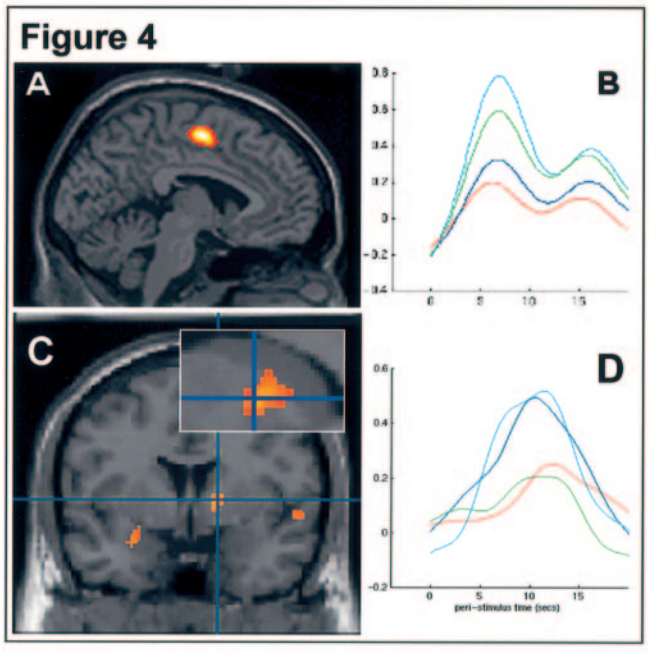
However, the main purpose of our study was to localize regions in which instruction cue-related activity was modulated by the expectation of rewards, using analyses that specified interactions in the factorial design. Significant interactions were found in prestriate visual cortex, in dorsal premotor cortex (PMd) and in the frontal pole of the prefrontal cortex. It is clear that these are not parts of the classical reward circuitry. However, interaction effects were those in which reward-expectation *modulated* cue-related activity. We did not expect motor preparatory effects in classical reward areas. The translation of visual information into motor commands for a specific response is a complex process that includes the processing of the visual cue, the application of previously learned rules from memory and also the representation of the motor plan ahead of its execution. It is likely to invoke several diverse sub-processes, a sub-set of which is likely to be modulated by the expectation of rewards.

Prestriate Cortex: Anticipating the Trigger Cue

The saving of subjects' reaction times in the high reward condition must have been partly dependent on their ability to

rapidly detect and process the trigger cue. It is likely that the visual system was ready to process the trigger cue more during the reward condition. The prestriate cortex was indeed more responsive in this condition, and this may be related to the increased reward-related vigilance for the trigger cue during reward expectation. However, vigilance alone cannot explain this activity, since this region was also more active during specific preparation than non-specific preparation, and it is only in the latter trials that the trigger cue provides information about the required response. The effects were clearly modulated by both reward expectation and the ability to plan actions. It is possible that this prestriate visual area received 'top-down' modulation from areas in the prefrontal cortex. It has been suggested that top-down signals from the prefrontal cortex to lower levels of the visual heirarchy trigger the retrieval of visual associations. Such an influence has been demonstrated in areas of the visual system during working memory (Miyashita and Hayashi, 2000).





Dorsal Premotor Cortex: Reward Effects on Response Planning

Premotor areas occupy strategic positions in the hierarchy of the cortical motor system: they receive inputs from prefrontal cortex, and send outputs to primary motor cortex. In macaque monkeys, both the dorsal and ventral portions of the lateral premotor cortex receive inputs from BA 46 and send outputs to arm representations of the primary motor cortex (Lu *et al.*, 1994). It seems that high-level representations of action goals in the prefrontal cortex are formulated by the premotor system into motor plans. The primary motor cortex then interprets these in terms of the activity of specific motor programmes. During visually guided delayed response tasks, neurons in PMd exhibit set-related activity which is thought to reflect the process of motor preparation (Kurata and Wise, 1988a,b), and in the present study we demonstrated preparation specific activity in this area. However, it might be argued that such activity does not reflect only motor preparation, since activity time-locked to instruction cues is likely to reflect both motor preparation and working memory. Given the prominent role of the prefrontal systems in working memory (D'Esposito *et al.*, 2000b; Levy and Goldman-Rakic, 2000; Petrides, 2000) and of premotor cortices in motor preparation (see above), it could be argued that differential activity would be present in both premotor and prefrontal systems. Indeed, in visual-conditional tasks, where preparation is dependent on the prior application of previously

Figure 3. Activity time-locked to instruction cues in all four conditions. (*A*) Prefrontal cortex: mid-dorsal prefrontal cortex (BA 46; –40 32 24; $F = 19.9$). (*B*) Basal ganglia: putamen (–28 –2 –8; $F = 15.59$). (C) Intraparietal sulcus (–26 –60 44; $F = 48.57$). The SPM{F} maps are overlaid on the canonical T_1 image from the MNI series (the right side of the brain is represented on the right of the figure for coronal and transverse sections; on saggital sections, the right side of the figure is anterior). Fitted haemodynamic responses in the peak voxels in the prefrontal cortex (*D*), the basal ganglia (*E*) and the intraparietal sulcus (*F*). Graphs of fitted responses of post-stimulus haemodynamic activity were time-locked to the instruction cue, but not to the trigger cue (red, non-specific preparation, low reward expectation; blue, non-specific preparation, high reward expectation; green, specific preparation, low reward expectation; cyan, specific preparation, high reward expectation; *x*-axis, time in s; *y*-axis, response magnitude in arbitrary units).

Figure 4. Main effects. Cue-related activity from the main effect of preparation (*A*) and (*B*); cue-related activity from the main effect of reward expectation (*C*) and (*D*). (*A*) The supplementary/pre-supplementary motor area (SMA/pre-SMA): the peak of the activtion lay dorsal to the cingulate sulcus, and posterior to the VCa line ($y = 0$). This landmark reliably divides the pre-SMA from the SMA proper (Vorobiev *et al.*, 1998). The activation is therefore likely to lie at the border between the SMA and the pre-SMA. (*B*) Graph of fitted responses of post-stimulus haemodynamic activity in SMA/pre-SMA. (*C*) Crosshair through basal ganglia activation (ventral pallidum; 16 2 4; $F = 4.82$); Large background image, coronal section through basal ganglia; inset, magnified saggital section through basal ganglia, indicating peak of activation in gray matter below anterior limb of the internal capsule, ventral to the head of the caudate nucleus. The left temporal lobe activation is in the amygdaloid complex (peak at –16 –12 –24; $F = 5.49$). (*D*) Graph of fitted responses of post-stimulus haemodynamic activity in the ventral pallidum (see *C*). Legend as for Figure 3.

Table 3
Main effects of motor preparation ($P < 0.001$)

Region	F	Equiv. Z	Coordinates (mm)		
			x	y	z
Premotor cortex					
L superior frontal gyrus SMA, medial BA 6	23.9	>8	–2	–4	54
L precentral gyrus PMd, lateral BA 6	19.18	>8	–36	–26	56
L supramarginal gyrus, lateral BA 6	16.18	7.46	–58	–22	28
R precentral gyrus PMd, lateral BA 6	8.12	4.84	42	–26	64
L frontal operculum, BA 6	13.99	6.84	–44	–4	6
Primary sensorimotor cortex					
L inferior postcentral gyrus	17.86	>8	–56	–26	40
R posterior wall of postcentral sulcus PPC	8.26	4.89	32	–40	40
Posterior parietal cortex					
R supramarginal gyrus BA 40	9.46	5.35	54	–32	40
Basal ganglia					
L putamen/GPe	7.03	4.32	–24	–10	0
Cerebellum					
R cerebellar cortex, anterior lobe (lobules HIV, HV, HVI)	14.85	7.09	22	–56	–30

Table 4
Main effect of reward expectation ($P < 0.001$)

Region	F	Equiv. Z	Coordinates (mm)		
			x	y	z
Prefrontal cortex					
L frontal pole	7.19	4.46	–20	58	24
L superior frontal sulcus	5.59	3.72	–22	18	48
L middle frontal gyrus	4.87	3.34	–40	20	38
R orbital cortex BA	4.86	3.34	32	18	–20
Medial premotor cortex					
L pre-SMA	6.94	4.35	–2	10	52
L pre-SMA	5.31	3.57	–2	–4	56
R SMA	4.75	3.28	6	0	58
Posterior parietal cortex					
	6.07	3.95	28	–54	70
	5.1	3.47	–40	–74	40
Temporal cortex					
L middle temporal gyrus	4.7	3.25	–28	16	54
L superior temporal gyrus	6.2	4.01	–64	–28	16
L superior temporal gyrus	5.68	3.76	–60	–50	28
L superior temporal gyrus	5.3	3.57	–60	–8	4
Cingulate cortex					
L posterior cingulate gyrus	8.66	5.05	–4	–38	38
Amydgaloid complex and parahippocampal cortex					
R parahippocampal cortex	6.05	3.94	22	–26	–8
L parahippocampal cortex	6.61	4.2	–16	–36	–2
L amygdaloid complex	5.49	3.66	–16	–12	–24
Basal ganglia					
R ventral pallidum	4.82	3.31	16	2	4
Striate and prestriate visual cortex					
R fusiform cortex	5.45	3.64	16	–72	–14
L primary visual cortex (BA 17)	5.46	3.65	–18	–102	–12
R primary visual cortex (BA 17)	4.99	3.41	12	–104	6

Table 5
Areas significantly activated by the interaction of reward and preparation levels ($P < 0.001$)

Region	F	Equiv. Z	Coordinates (mm)		
			x	y	z
Prefrontal cortex					
R frontal pole (BA 10)	7.22	4.47	38	60	–2
Premotor cortex					
L superior precentral sulcus (PMd, BA 6)	5.54	3.69	–34	–2	64
L postcentral gyrus (PMd, BA 6)	5.31	3.57	–52	–24	54
Prestriate cortex					
R lateral occipital sulcus	5.04	3.43	30	–82	8
R lateral occipital sulcus	5.02	3.42	32	–90	–8
L calcarine sulcus	5.26	3.55	–6	–54	8

learned arbitrary visuomotor rules, motor preparation might not be possible without the prior engagement of working memory. However, it is possible that working memory can take place without motor preparation. We argue that working memory demands were matched in the specific and non-specific preparatory conditions, but that levels of preparation for action were different (subjects were required to exercise working memory in both, but only in one were they also required to prepare a specific movement). Consistent with our interpretation, specific and non-specific preparation elicited differential activity in the premotor cortex, but not in the prefrontal cortex (Results, Table 3). Cue-related activity was present in prefrontal cortex (Table 2, Fig. 3*A*), but this was not significantly affected by manipulating the specificity of preparation (Fig. 3*D*). In our study, differential activity in specific and non-specific preparation is more likely to reflect the preparation of specific responses than the process of working memory.

The premotor cortex contains one of the highest concentrations of dopamine D1 receptors within the primate frontal lobes, and is a major target of midbrain dopamine neurons. Sawaguchi (Sawaguchi, 1997) has demonstrated that monkeys are severely impaired in their performance of a delayed response task by local microinfusions of D1 receptor antagonists into PMd. This impairment was accompanied by a decreased firing rate of neurons in the same region. However, no specific role has been proposed for these dopaminergic projections. On the basis of our data indicating basal ganglia activity related to the main effect of reward expectation (Fig. 4*C*,*D*), we suggest that the augmentation of behavioural performance by reward expectation could be mediated by the activity of these neurons influencing cells in PMd.

The Prefrontal Cortex: Reward Expectation Influences Motor Goals

In the prefrontal cortex, delay activity during delayed-response tasks has typically been reported in the mid-dorsal prefrontal cortex on the lateral convexity of the macaque monkey brain. Cells here fire in a sustained manner during the instructed delay periods of delayed-response tasks, and are thought to reflect the processes of working memory and response selection. These neurons are located in the upper and lower banks of the principle sulcus (BA 46), a region homologous to the upper and lower banks of the inferior frontal sulcus in the human brain. As in the premotor cortex, experimental manipulation of dopamine inputs into this region in the monkey affects both delay activity and performance in working memory tasks (Sawaguchi *et al.*, 1986, 1990; Sawaguchi and Goldman-Rakic, 1991, 1994). Hence we expected BA 46 in the human brain to be modulated during the expectation of rewards. However, in our study, such an interaction was not found in BA 46, but much more anteriorly in BA 10. In monkeys this is a difficult area of the cortex to access experimentally and comparatively little is known about its physiology or connections. It is not known, for example, whether neurons in polar cortex of non-human primates (BA 10) exhibit delay activity during delayed response tasks as do BA 46 neurons. However, anatomical tracers injected into both banks

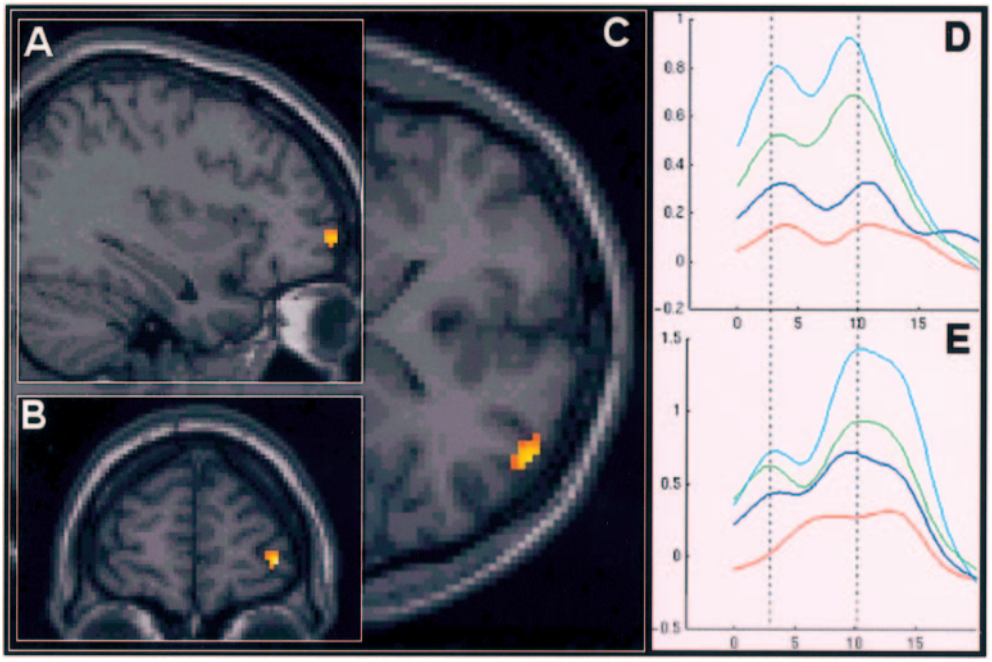


Figure 5. Interaction effect in the frontal pole (BA 10). Anatomical images: (*A*) large foreground inset, saggital section; (*B*) small foreground inset, coronal section; (*C*) background anatomical rendering, horizontal section through peak of activation. Legend as for Figure 3. Graphs represents activity in the peak voxel in the frontal pole activation; each graph is from a different subject. Both subjects demonstrate bimodal activity, and the vertical broken lines demonstrate that peak activity is reached at similar times in each subject.

of the principal sulcus lead to labelling of the frontal pole (Cavada *et al.*, 2000). Thus, frontal pole has access to reward-related information from the orbitofrontal cortex that it could then transmit to BA 46 and then on to premotor and primary motor regions. Imaging evidence suggests that the frontal pole in humans exhibits set-related activity. Toni *et al.* (Toni *et al.*, 1999) reported sustained instruction-related activity in a delayed response task in a prefrontal region close to frontal polar areas activated in our study. Burgess *et al.* (Burgess *et al.*, 2001) have reported activity in the frontal pole in relation to prospective memory, where a response was to be performed after a delay. Ramnani and Passingham (Ramnani and Passingham, 2001) reported that activity in the frontal pole increased as the delays between consecutive visual cues became increasingly predictable during visuomotor rhythm learning. Finally, Pochon *et al.* (Pochon *et al.*, 2002) have recently showed that an 'N-back' task elicited activations in a variety of prefrontal areas associated with working memory and executive function, but when conducted under the influence of reward expectation, there was additional activation in the frontal pole. Activity in the anterior prefrontal cortex may work in concert with more specialized regions to mediate the influence of reward expectation on their operations. While Pochon *et al.* (Pochon *et al.*, 2002) have shown that in the case of working memory, it is co-activated with mid-dorsal prefrontal cortex during reward expectation, we have shown that in the case of motor preparation, the anterior prefrontal cortex is co-activated with the dorsal premotor cortex during reward expectation.

Midbrain dopamine neurons project not only to the frontal lobes, but also to the striatum. In the Introduction, we raised the possibility that reward expectation might influence motor preparation and selection by convergence within the basal ganglia. Kawagoe *et al.* (Kawagoe *et al.*, 1998) describe a task similar to ours where the cue signalled both the direction of an eye movement and also the level of reward expected. Delay activity of many caudate nucleus neurons was not only specific to the nature of the action, but also to the expectation of rewards. However, there were also neurons that were selectively *unresponsive* to the high reward cue. Responsive and unresponsive cells were distributed over most of the caudate, and they did not form clusters. Thus it is unlikely that this population would lead to significant signal in fMRI and the absence of significant reward/preparation interaction within the basal ganglia in our study may be due to this lack of a detectable population response. In contrast, non-selective activity was found in the putamen (see Results, Fig. 3*B*,*E*).

The same argument might also be made for our lack of observed effects in BA 46 of the prefrontal cortex. However, these cells are clustered around the principal sulcus (Leon and Shadlen, 1999) and single unit studies in monkeys and imaging studies in man have demonstrated robust delay activity in this region (Funahashi *et al.*, 1991; Postle *et al.*, 2000). Indeed, we did find cue-related activity in area 46 (see Fig. 3*A*,*D*). However, although this activity was significant in all four cue-related conditions, it was not modulated by the expectation of rewards. Finally, the discrepancy between our results and those from non-human primates reporting reward modulations of delay activity in basal ganglia and area 46 might be accounted for in two ways. Firstly, the non-human primate studies all used primary food or liquid rewards whereas our study used an image of a coin as a reward cue, which serves as secondary reinforcer. It is possible that in humans the impact of secondary reinforcers occurs in regions of the prefrontal cortex other than in BA 46. Second, the organization of the prefrontal cortex may be fundamentally different in human and non-human primates. It is known that the prefrontal cortex has undergone evolutionary expansion, and BA 10 in humans occupies a substantially larger portion of the cerebral cortex than it does in macaques or even in other hominids. It has also been suggested that human BA 10 is a newly evolved region of the prefrontal cortex that is not homologous to

area 10 in other primate species (Semendeferi *et al.*, 2001), and thus it may have subsumed functions performed by BA 46 in non-human primates. It is an open question whether inactivation of BA 10 in the human (through permanent lesions or TMS blockade) would disrupt performance in financially rewarded tasks.

Notes

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