



# Ventromedial prefrontal cortex mediates guessing

R. Elliott<sup>a,\*</sup>, G. Rees<sup>a</sup>, R.J. Dolan<sup>a,b</sup>

<sup>a</sup> Wellcome Department of Cognitive Neurology, Institute of Neurology, 12 Queen Square, London WC1N 3BG, UK

<sup>b</sup> Royal Free Hospital School of Medicine, Rowland Hill Street, London, NW3 2PF, UK

## Abstract

Guessing is an important component of everyday cognition. The present study examined the neural substrates of guessing using a simple card-playing task in conjunction with functional magnetic resonance imaging (fMRI). Subjects were scanned under four conditions. In two, they were shown images of the back of a playing card and had to guess either the colour or the suit of the card. In the other two they were shown the face of a card and had to report either the colour or the suit. Guessing compared to reporting was associated with significant activations in lateral prefrontal cortex (right more than left), right orbitofrontal cortex, anterior cingulate, bilateral inferior parietal cortex and right thalamus. Increasing the guessing demands by manipulating the number of alternative outcomes was associated with activation of the left lateral and medial orbitofrontal cortex. These data suggest that while simple two choice guessing depends on an extensive neural system including regions of the right lateral prefrontal cortex, activation of orbitofrontal cortex increases as the probabilistic contingencies become more complex. Guessing thus involves not only systems implicated in working memory processes but also depends upon orbitofrontal cortex. This region is not typically activated in working memory tasks and its activation may reflect additional requirements of dealing with uncertainty. © 1999 Elsevier Science Ltd. All rights reserved.

*Keywords:* Decision-making; Working memory; Orbitofrontal cortex; Dorsolateral prefrontal cortex

## 1. Introduction

The process of guessing involves making choice responses under incompletely specified situations. Guessing is an important component of everyday cognition and many laboratory cognitive tasks also involve some degree of uncertainty. In the most extreme case, the relationship between a response and desired outcome is entirely determined by chance. Real life examples of this are gambling situations; tossing coins, rolling dice, drawing playing cards from unbiased packs. In this study we used a gambling situation to determine the neural correlates of guessing.

Gambling tasks have recently been used in a series of studies by Damasio and colleagues [4–7, 10]. These studies found that patients with frontal lobe lesions, encompassing ventromedial regions, show pronounced impairments on gambling tasks. Strikingly, patients with lesions *restricted* to ventromedial foci show these impairments in the context of intact performance on most other cognitive tasks, including tests of working memory and

planning [32]. The task used in these studies involved choosing one of four decks of cards, where one deck was relatively likely to be associated with positive outcomes and another with negative outcomes. Patients with ventromedial prefrontal lesions were unable to choose advantageously on this task despite demonstrating correct knowledge of the relevant contingencies [5, 6]. They also failed to show the anticipatory autonomic response seen in normal subjects prior to receiving feedback for high-risk responses [5]. These findings suggest that although the orbitofrontal cortex is not essential for learning about contingencies per se, it is crucial for selecting the appropriate action based upon knowledge of these contingencies.

Despite neuropsychological findings suggesting a key role for the ventromedial frontal cortex in gambling or guessing tasks, there is relatively little functional imaging work addressing this issue. Two-choice tasks where there is no correct response have been used in the context of imaging studies of self-initiated or willed action [11, 18, 20, 21]. In these studies, the selection of a particular response compared to the execution of a specified response was typically associated with activation of the dorsolateral prefrontal cortex but not the orbitofrontal cortex. However, the paradigms used in these studies

\* Corresponding author. Tel.: +44 (0)171 833 7472; fax: +44 (0)171 813 1420; e-mail: r.elliott@fil.ion.ucl.ac.uk

differed critically from gambling tasks in that there was no feedback; that is the selected response was not subsequently deemed correct or incorrect. It therefore seems plausible that the role of the orbitofrontal cortex in guessing or gambling is not the selection of the response per se but the evaluation of the emotive consequences or behavioural significance of the selection. Consistent with this, our recent functional imaging study of the neural correlates of performance feedback [14] found differential activation of the ventromedial orbitofrontal cortex during performance of a guessing task in conditions where feedback was given compared to no feedback conditions.

In the present study, we aimed to use functional imaging to assess the neural correlates of a guessing task, in order to extend the neuropsychological findings. The task we used involved a simple gambling situation where subjects simply had to predict either the colour or the suit of the next card in an unbiased pack. In this situation, unlike the gambling task used by Damasio and colleagues, subjects cannot learn contingencies to allow them to make advantageous choices. Damasio and colleagues interpret their results in terms of decision making and working memory, an interpretation we agree with. However, other interpretations can be placed on Damasio's findings; for example, the task can be considered in terms of associative learning, relating decks to outcomes. In our task, the correct response is entirely determined by chance on each trial and therefore there is no possibility of associative learning. However, the task still involves an element of risk and subjects were given feedback as to whether their prediction was correct on each trial. Our hypothesis was that orbitofrontal cortex, and particularly medial regions, would be activated in association with guessing.

## 2. Method

### 2.1. Subjects

Five right-handed male volunteers, three male and two female, aged between 29–41 were recruited. Subjects who reported any neurological or psychiatric history were excluded, as were subjects with any evidence of abnormality on a structural MRI scan. The study was approved by the local hospital ethics committee and informed written consent was obtained prior to the study.

### 2.2. Cognitive activation paradigm

This experiment was a  $2 \times 2$  factorial design with predicting compared to reporting as one factor and level of difficulty (colour compared to suit) as the other. See Fig. 1.

### 2.3. Predicting task

In each trial, subjects were presented with an image of the back of a standard playing card for 1.75 s. During

this time they had to predict either the colour or the suit of the next card by a key press with the right hand. Prior to scanning, subjects were asked to pick a suit at random. Subjects who chose 'hearts', in the 'guess colour' condition were instructed to press the left key if they thought the card would be red when it turned over, right if they thought it would be black. In the 'guess suit' condition they were instructed to press the left key if they thought the card would be a heart, right if they thought it would be any other suit. They were told to guess what the suit would be, i.e., choose from one of four options, but express their guess in this two-choice response. Reducing a four choice situation to two choices in this way, raises the possible confound that non-compliant subjects would not make the choice required but simply decide (e.g.,) 'hearts or non-hearts'. However, given that our unpaid volunteer subjects are typically compliant, we felt this was a less problematic confound than the alternative motor selection confound of 4 compared to 2 motor response choices. After 1.8 s, the card back was replaced by an image of a playing card (chosen at random from a full pack of 52 cards) which remained on the screen for 1.75 s and gave the subject information about whether the guess was correct. Subjects were told 'try to guess right as often as possible'. In each block of the test, no card was used twice and subjects were told to imagine the pack being picked up and shuffled between blocks.

### 2.4. Reporting task

In each trial of this task, subjects were presented with an image of the front of a playing card chosen at random from the full pack for 1.8 s. During this time subjects had to report either the colour or the suit of the next card using a key press with the right hand. Subjects who chose 'hearts' prior to scanning, in the 'report colour' condition, were instructed to press the left key if the card was red, right if it was black. In the 'report suit' condition, they were instructed to press the left key if the card was a heart, right if it was any other suit. After 1.75 s, the playing card was replaced by an image of the back of a card which remained on the screen for 1.75 s. Again in each block of the task, no card was used twice and subjects were told to imagine the pack being picked up and shuffled between blocks. In this control task, the perceptual input and the motor output were exactly matched with the guessing task.

During each scanning block, twelve trials were presented, each lasting 3.5 s so that the whole block lasted 42 s. There were six blocks of each condition, presented in a counterbalanced order. Between each block there was a 42 s period of rest and 3 s prior to the start of the next test block subjects were given a verbal instruction of which task to perform (four instructions: 'guess colour', 'guess suit', 'report colour' and 'report suit').

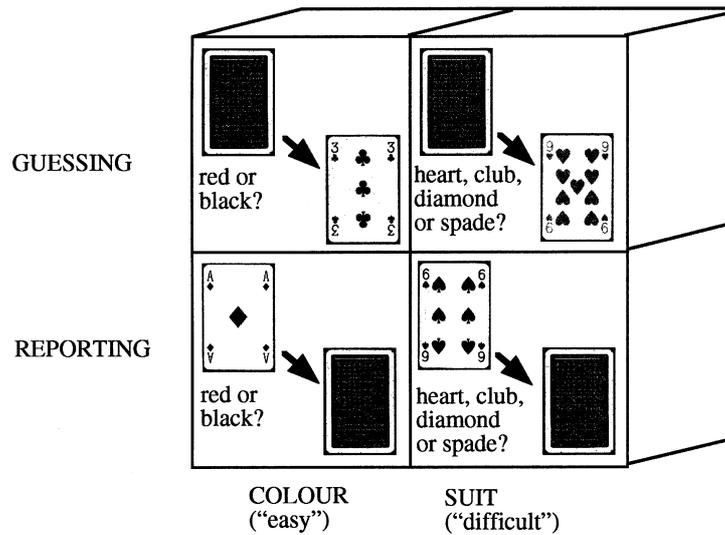


Fig. 1. Schematic depiction of the four different task conditions of the factorial design.

### 2.5. MRI scanning technique

A Siemens VISION system at 2T was used to acquire both T1 weighted structural images and gradient-echo, echo-planar T2\* weighted images with BOLD (Blood Oxygenation Level Dependent) contrast. Functional images were acquired in two runs, with a total of 480 volumes acquired for each subject. Each volume comprised 48 3 mm axial slices with 3 mm in-plane resolution. The slices were positioned to cover the whole brain. During each run, volumes were acquired continuously every 4.2 s and 10 volumes were thus acquired per task or rest block. Each run began with six 'dummy' volumes to allow for T1 equilibration effects; these volumes were subsequently discarded.

### 2.6. Data analysis

Data were analysed using Statistical Parametric Mapping (SPM97, Wellcome Dept of Cognitive Neurology, London, U.K.) implemented in MATLAB (Mathworks Inc., Sherborn, MA, U.S.A.) and run on a SPARC workstation (Sun Microsystems Inc., Surrey, U.K.). Scans were realigned using the first as a reference and were subsequently transformed into a standard space corresponding to the stereotactic atlas of Talairach and Tournoux [31] using MNI templates (Montreal Neurological Institute). These normalised images were smoothed with an 8 mm FWHM isotropic Gaussian kernel.

Analysis of this factorial experiment was carried out using the general linear model with a delayed boxcar wave form. Any subject-specific low-frequency drift in signal was removed by modelling with low frequency sine and cosine waves and global changes were removed by proportional scaling [19]. Effects at each and every voxel

were estimated and regionally specific effects were compared using linear contrasts. The resulting set of voxel values for each contrast constituted a statistical parametric map of the  $t$  statistic ( $SPM\{t\}$ ) which was then transformed to the unit normal distribution,  $SPM\{Z\}$ . Statistical inferences were based on the theory of random Gaussian fields [17]. We report activations significant at  $P < 0.05$  corrected for multiple comparisons, except those activations which occur in orbitofrontal regions about which we had a prior hypothesis. In orbitofrontal areas, we report activations significant at  $P < 0.001$  uncorrected. Since  $n = 5$  is a relatively small sample size, we report only those activations which are seen in *all* individuals. The findings can therefore be considered very robust in spite of the limited number of subjects.

The stereotactic coordinates of Talairach and Tournoux [31] are used to report the observed activation foci. However, descriptions of the anatomical localisation of the foci were determined using averaged structural MRIs of the group and the atlas of Duvernoy [13].

## 3. Results

### 3.1. Performance data

In the guessing task, all five subjects adopted a probability matching approach, that is, in the 'guess colour' condition they pressed the left and right hand keys with approximately equal frequency. In the 'guess suit' condition, they pressed the left hand key (corresponding to their chosen suit) on approximately 25% of trials and the right hand key (corresponding to all other suits) on approximately 75% of trials. This suggests that subjects were complying with the instruction to guess which of the four suits was correct but to express it in one of two

choices. Had they been making a ‘hearts–non hearts’ type decision, they would maximise their chances of being correct by choosing the ‘non-hearts’ button on each trial. The strategies reported by subjects in debriefing also suggest that subjects were complying and that they were basing their responses on cross trial monitoring of outcome. Example comments are:

“There was one block where I don’t think I saw a single club.”

“I had a couple of blocks where I got really lucky and kept guessing right when a diamond was coming up” (subject in question was choosing spades).

“If there were three red cards in a row, I always thought the next one would be black.”

“If there was a picture card, the next card was more likely to be red” (not empirically true).

### 3.2. Activations associated with guessing compared to reporting

This comparison represents the main effects of task requirement; predicting compared to reporting (see Fig. 2; Table 1). Significant evoked activity associated with predicting compared to reporting was observed in all five subjects in an extensive region of right and more restricted

region of left middle frontal gyrus, including dorsolateral prefrontal cortex (BA 9/46), bilateral anterior cingulate (BA 32), bilateral inferior frontal gyrus (BA 47), bilateral inferior parietal cortex (BA 40), right medial parietal cortex, right dorsomedial nucleus of the thalamus and left cerebellum. There was also significant activity in the right medial orbitofrontal cortex (BA 11/25), as hypothesized.

Significant evoked activity associated with reporting compared to guessing was observed in the bilateral hippocampal gyrus (BA 36), left (BA 38) and right (BA 42) superior temporal gyrus, left posterior cingulate (BA 31) and two regions of left middle temporal gyrus (BA 39 and BA 21).

### 3.3. Activations association with task difficulty

We use the term ‘difficulty’ as shorthand for increasing the number of categories from which a response must be selected. These comparisons represent the main effect of colour compared to suit across the predicting and reporting tasks (see Table 2). Significant evoked activity associated with suit compared to colour was observed in the left inferior frontal gyrus (BA 46). There were no

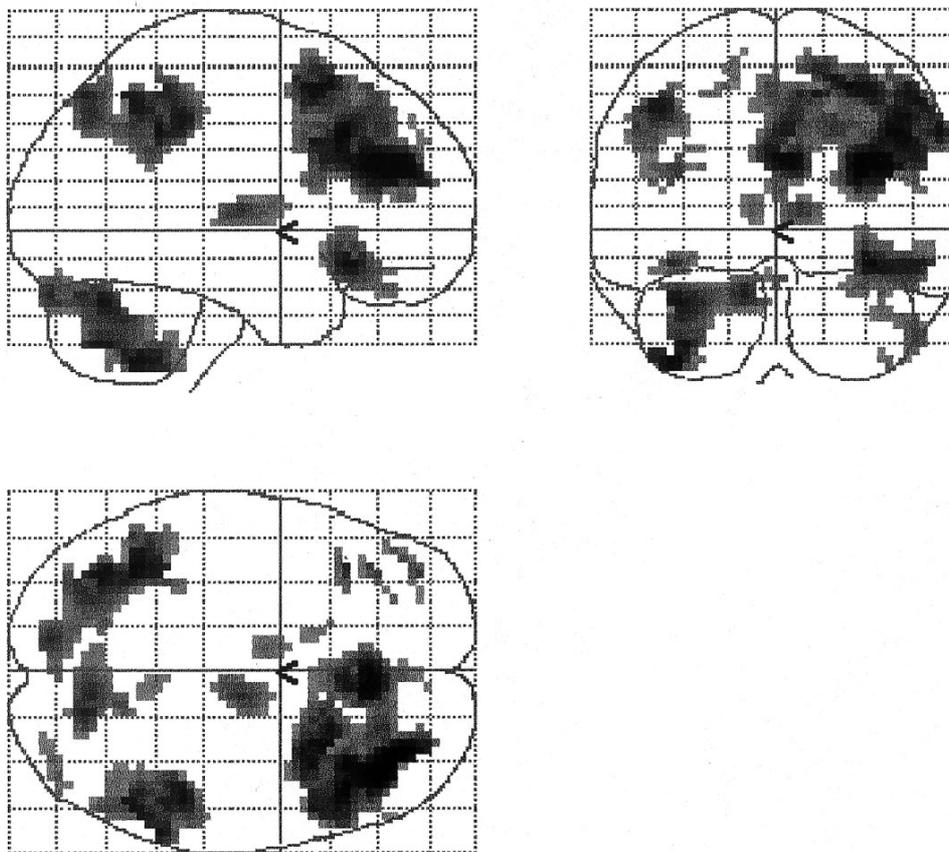


Fig. 2. Activations associated with guessing compared to reporting as shown by the statistical parametric map of the  $t$ -statistic (after transformation to a SPM{ $Z$ }) thresholded at  $P < 0.001$ .

Table 1  
Areas where evoked activity was significantly different between guessing and reporting

Area	Left/ right	Brodmann's area	Talairach co-ordinates of voxel of maximal activity			Z value
			x	y	z	
Predicting–reporting						
Dorsolateral prefrontal cortex	R	9/46	33	42	24	7.76
	L	9/46	–36	36	24	4.90
Anterior cingulate	R	32	6	33	24	6.90
	L	32	–3	33	54	4.63
Inferior frontal gyrus	L	47	36	24	–12	6.70
	R	47	–39	24	–12	5.41
Medial orbitofrontal cortex	R	11/25	15	27	–12	3.27
Inferior parietal cortex	R	40	60	–45	36	6.75
	L	40	–45	–51	45	6.17
Medial parietal cortex	R	7	15	–72	51	5.82
Dorsomedial thalamus	R		9	–15	9	4.98
Cerebellum	L		–39	–54	–48	7.05
Reporting–predicting						
Hippocampal gyrus	R	36	24	–33	–21	5.51
	L	36	–30	–33	–15	5.48
Superior temporal gyrus	L	38	–57	–3	–12	4.79
	R	42	42	–30	8	5.12
Posterior cingulate	L	31	–12	–45	30	5.30
Middle temporal gyrus	L	39	–45	–75	24	4.94
	L	21	–57	–15	–15	4.93

Table 2  
Areas where evoked activity was significantly different in association with increasing difficulty (suit compared to colour)

Area	Left/ right	Brodmann's area	Talairach co-ordinates of voxel of maximal activity			Z value
			x	y	z	
Inferior frontal gyrus	L	46	–33	42	12	4.94

significant foci of activity associated with colour compared to suit.

### 3.4. Modulation of guessing by task difficulty

This comparison represents the interaction term in the analysis (see Table 3). Evoked activity associated with the modulation of predicting compared to reporting by difficulty (suit compared to colour) was observed in medial orbitofrontal cortex (BA 11) and lateral orbitofrontal cortex (BA 47) bilaterally.

### 3.5. Activations associated with difficulty in the context of prediction

This comparison represents the simple main effect of difficulty (suit compared to colour) just in the guessing

task (see Fig. 3; Table 4). Significant evoked activity was observed in the medial orbitofrontal cortex (BA 11) and the left lateral orbitofrontal cortex (BA 47). Corresponding activity in the right lateral orbitofrontal cortex was also observed at a lower level of significance. There was also activity in the inferior frontal gyrus (BA 46) on the left that was close to corrected significance.

## 4. Discussion

The results of this study demonstrated that simple guessing was associated with significant changes in evoked activity in a network of structures, including the right dorsolateral prefrontal cortex, anterior cingulate, lateral orbitofrontal cortex, posterior parietal cortex, thalamus and cerebellum. There was also activation in

Table 3

Areas where significant evoked activity was associated with the modulation of guessing compared to reporting by increasing difficulty (suit compared to colour)

Region of activation	Left/ right	Brodmann's area	Talairach co-ordinates			
			x	y	z	Z value
Medial orbitofrontal cortex	R/L	11	3	39	−12	3.59
Lateral orbitofrontal cortex	L	47	−30	24	−30	3.67
	R	47	45	21	−36	3.87

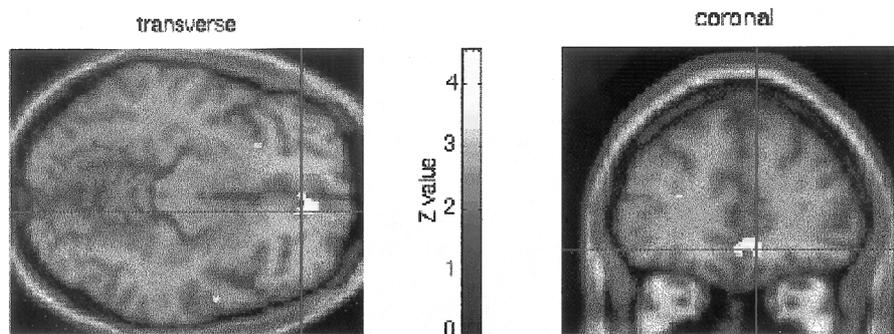


Fig. 3. Activations associated with increasing task difficulty shows this activation rendered onto a standard MRI template and focused on the ventromedial orbitofrontal cortex.

Table 4

Areas where significant evoked activity was associated with increasing difficulty in the guessing task

Region of activation	Left/ right	Brodmann's area	Talairach co-ordinates			
			x	y	z	Z value
Lateral orbitofrontal cortex	L	47	−30	24	−30	4.73
Medial orbitofrontal cortex	R	11	9	42	−12	4.58
Middle frontal gyrus	L	46	−33	45	12	4.43

the medial orbitofrontal cortex, confirming our hypothesis that this area is involved in gambling tasks. Consistent with this conclusion is the observation that this region became more strongly activated as task difficulty increased. Evoked activity in both medial and lateral orbitofrontal cortices was higher when subjects were predicting the suit of the next card, with only a 25% chance of their chosen suit being correct, than when they were predicting the colour, with a 50% chance of their chosen colour being correct. Increased difficulty was also associated with significant activation in the left dorsolateral prefrontal cortex.

The network of structures activated in the guessing task overlaps considerably with regions implicated in working memory [e.g., 9, 22, 24, 25, 27]. The majority of these

studies reported activations in dorsolateral prefrontal cortices (more significantly on the right in non verbal studies, as seen here) and inferior parietal cortices bilaterally. Other areas identified in the present study; anterior cingulate, inferior frontal gyrus, thalamus and cerebellum are also frequently activated with working memory paradigms, as well as other tasks involving high level 'executive' functions [e.g., 2, 8, 22, 27]. However, it is right dorsolateral activation that is most reliably linked to working memory and to related tasks requiring on line manipulation and monitoring of information. This was the most significantly activated region in our study which suggests engagement of working memory processes by the guessing task. It is not possible in the context of this chance-determined task for subjects to show associative

learning of contingencies. But, although the guessing task could be performed by making a series of independent decisions, subjects actually reported a strategic approach to the task where they remembered which responses had been rewarded on previous trials in order to guide their predictions. This process involves holding a number of pieces of information on line and constantly monitoring and updating current strategies in the light of subsequent information. These are classic components of working memory tasks.

The right prefrontal activation in the present study is almost identical to that identified by Jahanshahi et al. [21] in association with self-initiated compared to externally triggered movements. Dorsolateral prefrontal activation, more significant on the right than the left, has also been reported in a number of other studies where subjects were required to select the nature of a response [11, 18, 26]. In our study, the guessing task involves self-selection of responses, compared to the reporting task which involves responses cued by external stimuli. It is therefore plausible that the requirement to select a response also contributes to right dorsolateral prefrontal activity. This is also consistent with the activation observed in the anterior cingulate cortex, a region that the studies discussed above also identify as critical for self selected behavioural responses.

Although task performance overall was more strongly associated with activity in right than left lateral prefrontal cortex, increased task difficulty was associated with activity in *left* lateral prefrontal cortex alone. The focus of this difficulty-related activation was relatively ventral, in inferior rather than middle frontal gyrus. This was a somewhat surprising finding; however, there are a number of possible explanations. In general, the left lateral prefrontal cortex, particularly more inferior regions, is more strongly activated in verbal memory tasks compared to non-verbal tasks [e.g., 15, 23, 24, 25, 30]. Further, a recent fMRI study by Barch et al. [3] found that in a letter-based working memory task, increasing working memory demands led to increased activity in left lateral prefrontal cortex. It is possible that in our paradigm, predicting suit compared to colour places greater demands on verbal processing of information. This may be because there are more possible outcomes, each with a specific verbal label, or because subjects attempt to maintain longer verbal sequences of recent outcomes in memory, placing greater demands on a short-term phonological loop [1]. However, it should be noted that the left lateral activation in the present study is substantially anterior to the region around Broca's area typically associated with verbal rehearsal. Another possible explanation is that the left prefrontal region is involved in categorisation and semantic elaboration. A recent study by Fletcher et al. [16] identified a region of left lateral prefrontal cortex involved in categorisation of items on the basis of a rule based system. In the present

study, each card can be categorised according to either suit or colour depending on the current 'rules'. In the suit condition, there are more categories and therefore may be more activity in left lateral prefrontal cortex.

The key finding in this study was an involvement of medial orbitofrontal cortex in guessing, confirming our a priori hypothesis. Interestingly, we found that medial orbitofrontal activity was significantly greater for the more difficult prediction condition when subjects had more alternative outcomes to consider. This is the region which previous neuropsychological studies of gambling tasks have identified as critical [4, 5, 6, 10, 28]. It is also a region we identified in a recent PET study in association with feedback on a guessing task [14]. We suggested that a possible explanation for the role of the medial orbitofrontal cortex is that it is involved in cross-trial processing of response-reinforcement relations. In guessing or gambling tasks, performance cannot be assessed for a single trial. It is only by assessing the instances of success and failure across a number of trials that subjects can monitor overall performance. This is in contrast to many cognitive tasks where each trial with its associated outcome is a discrete entity and success or failure on a single trial is meaningful and informative about performance.

This account of the role of orbitofrontal cortex in guessing tasks is compatible with the findings that animals [12] and patients [29] with orbitofrontal lesions are impaired on tasks involving reversal learning and extinction. By their very nature, these tasks require cross-trial processing of stimulus-reward relations. It is also consistent with the hypothesis of Damasio and colleagues that this region is necessary for assessing future consequences of ongoing behavioural responses. They suggest that the deficits on gambling tasks shown by patients with ventromedial lesions reflect the fact that immediate prospects (i.e., the outcome on the trial in hand) outweigh longer term consequences. In the present study ventromedial activity was more significant for predicting suit than colour. In the suit condition, the chance of the chosen suit being correct was 1 in 4, compared to 1 in 2 for the colour condition. In order to assess whether performance was at, above, or below chance, subjects would probably need to adopt a longer term approach. Consider, for example, a hypothetical four trial sequence. In the colour condition, the probability of being incorrect on all trials is 0.062 and while subjects probably do not know this, they do know that being correct on all four is unlikely and represents 'poor' or 'unlucky' performance. For the suit condition, the probability of being incorrect on all trials is 0.32 and subjects realise that being incorrect on all four trials is not statistically unlikely and would need more trials (a longer term assessment) to judge their performance as particularly poor or unlucky. Greater medial orbitofrontal activity being associated with the more difficult prediction condition is also consistent with the fact that the gambling tasks on which ventromedial

patients show deficits are typically relatively complex, for example involving four alternative responses with different reward contingencies [4].

Although we observed activity associated with guessing in the medial orbitofrontal cortex, this activity was less significant than that in lateral frontal and posterior regions, the areas often associated with working memory. A recent study [7] identified a dissociation of working memory from 'decision making' within the prefrontal cortex. Patients with ventromedial prefrontal lesions showed selective impairments on a gambling task which the authors describe in terms of decision-making, while patients with dorsolateral prefrontal regions showed selective impairments on a working memory task. However, the dissociation was not complete. Subjects with right dorsolateral prefrontal lesions showed lower than normal performance on the gambling task, and those subjects with the most posterior ventromedial lesions, who did have impaired working memory, showed the most marked impairments on the gambling task. The authors interpreted these findings in terms of an asymmetric dependency between working memory and decision making, such that while working memory is independent of the intactness of decision making, the converse is not true. Decision making, as measured by the gambling task, *does* depend on intact working memory. Our results are consistent with this account. Performance of the simple gambling task is associated with activity in a network of structures, particularly the right dorsolateral prefrontal cortex, which have been shown to support non-verbal working memory. Additional activity in the ventromedial prefrontal cortex, not typically associated with working memory, is specific to the gambling aspect of the task. While there may be other interpretations of the cognitive demands of gambling tasks, which do not stress roles for working memory and decision making, we feel, like Damasio and colleagues, that these processes are recruited by such paradigms.

It is possible that the task used here placed greater demands on working memory than the gambling task used by Bechara et al. [7] due to the very different structure of the task. In that task, subjects were able to learn that certain decks were associated with long-term positive outcomes while others were associated with long-term negative outcomes. Once subjects had learned this premise, they could use it to guide their responses. In our task, the relationship between response and outcome was less certain, being entirely determined by chance. The strategy subjects adopted was to generate pseudo-random sequences influenced by the outcome of previous trials (e.g., 'the last three cards have been red, the next one's most likely to be black'), a strategy which is very demanding of working memory processes.

In conclusion, this study showed that guessing was associated with activity in a distributed network of struc-

tures which subserve processes of working memory and self-selection of response. In addition, there was activity in the medial orbitofrontal cortex, an area not typically activated in working memory tasks and this activity was greater as prediction became more difficult. This pattern of activity is consistent with the hypothesis that this region is important for processing the relationship between responses and outcomes across a number of trials. This conclusion is also consistent with the recent neuropsychological findings [7] which demonstrate that although working memory performance is independent of decision making, decision making depends on intact working memory. Our findings develop and extend those of neuropsychological studies by demonstrating the neural correlates of guessing in normal subjects. Guessing and gambling paradigms are simple models of many aspects of real-life where contingencies are uncertain. The task used in this study was a simplistic one; however, it provides a baseline task which can be modified and developed to address specific questions in future studies. A better understanding of the neural substrates of these tasks may therefore prove extremely important in understanding both behavioural deficit of patients with prefrontal lesions and normal cognition.

## References

- [1] Baddeley AD. Working memory. Oxford: Clarendon Press, 1986.
- [2] Baker SC, Rogers RD, Owen AM, Frith CD, Dolan RJ, Frackowiak RSJ, Robbins TW. Neural systems engaged by planning: a PET study of the Tower of London task. *Neuropsychologia* 1996;6:515–26.
- [3] Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD. Dissociation of working memory from task difficulty in human prefrontal cortex. *Neuropsychologia* 1997;35:1373–80.
- [4] Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994;50:7–15.
- [5] Bechara A, Tranel D, Damasio H, Damasio AR. Failure to respond autonomically to anticipated future outcomes following damage to the prefrontal cortex. *Cerebral Cortex* 1996;6:215–25.
- [6] Bechara A, Damasio H, Tranel D, Damasio AR. Deciding advantageously before knowing the advantageous strategy. *Science* 1997;275:1293–5.
- [7] Bechara A, Damasio H, Tranel D, Anderson SW. Dissociation of working memory from decision making within the human prefrontal cortex. *Journal of Neuroscience* 1998;18:428–37.
- [8] Berman KF, Ostrem JI, Randolph C, Gold J, Goldberg TE, Coppola R, Carson RE, Herscovitch P, Weinberger DR. Physiological activation of a cortical network during performance of the Wisconsin Card Sorting Test: a positron emission tomography study. *Neuropsychologia* 1995;33:1027–46.
- [9] Courtney SM, Ungerleider LG, Keil K, Haxby JV. Transient and sustained activity in a distributed neural system for human working memory. *Nature* 1997;386:608–11.
- [10] Damasio AR. *Descartes' error*. New York: Putnam, 1994.
- [11] Deiber M-P, Passingham RE, Colebatch JG, Friston KJ, Nixon PD, Frackowiak RST. Cortical areas and the selection of movement: a study with positron emission tomography. *Experimental Brain Research* 1991;84:393–402.

- [12] Dias R, Robbins TW, Roberts AC. Dissociation in prefrontal cortex of affective and attentional shifts. *Nature* 1996;380:69–72.
- [13] Duvernoy HM. The human brain: surface, three-dimensional sectional anatomy and MRI. New York: Springer-Verlag, 1991.
- [14] Elliot R, Frith CD, Dolan RJ. Differential neural response to positive and negative feedback in planning and guessing tasks. *Neuropsychologia* 1997;35:1395–1404.
- [15] Fiez JA, Raife EA, Balota DA, Schwartz JP, Raichle ME, Petersen SE. A positron emission tomography study of the short-term maintenance of verbal information. *Journal of Neuroscience* 1996;16:808–22.
- [16] Fletcher PC, Josephs O, Friston KJ, Buechel C, Dolan RJ. Learning-related temporal dynamics in the prefrontal cortex. *Neuroimage* 1997;5:S56.
- [17] Friston KJ, Holmes AP, Worsley KJ, Poline J-B, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: A general approach. *Human Brain Mapping* 1995;2:189–210.
- [18] Frith CD, Friston KJ, Liddle PF, Frackowiak RSJ. Willed action and the prefrontal cortex in man: a study with PET. *Proc Royal Soc London* 1991;B244:241–6.
- [19] Holmes AP, Josephs O, Buechel C, Friston KJ. Statistical modelling of low-frequency confounds in fMRI. *Neuroimage* 1980;5:S480.
- [20] Hyder F, Phelps EA, Wiggins CJ, Labar KS, Blamire AM, Shulman RG. Willed action: a functional MRI study of the human prefrontal cortex during a sensorimotor task. *Proceedings of the National Academy of Sciences, U.S.A.* 1997;94:6989–94.
- [21] Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements. *Brain* 1995;118:913–33.
- [22] Owen AM, Doyon J, Petrides M, Evans AC. Planning and spatial working memory: a positron emission tomography study in humans. *European Journal of Neuroscience* 1996;8:353–64.
- [23] Paulesu E, Frith CD, Frackowiak RSJ. The neural correlates of the verbal component of working memory. *Nature* 1993;362:442–4.
- [24] Petrides M, Alivisatos B, Evans AC, Meyer E. Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proceedings of the National Academy of Sciences, U.S.A.* 1993a;90:873–7.
- [25] Petrides M, Alivisatos B, Evans AC, Meyer E. Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proceedings of the National Academy of Sciences, U.S.A.* 1993b;90:878–82.
- [26] Playford E, Jenkins IH, Passingham RE, Nutt J, Frackowiak RSJ, Brooks DJ. Impaired mesial frontal and putamen activation in Parkinson's disease: a positron emission tomography study. *Annals of Neurology* 1992;49:144–8.
- [27] Rao SM, Bobholz JA, Woodley SJ, Rosen AC, Hammeke TA, Fuller SA, Cunningham JM, Cox RW, Binder JR, Stein EA. Functional neuroanatomy of human concept formation skills. *Neuroimage (abstracts)* 1996;3:S239.
- [28] Rogers RD, Baldacchino A, Johnson AJ, Swainson R, London M, Deakin JFW, Sahakian BJ, Robbins TW, Everitt BJ. Altered decision making following frontal lesions: a comparison with amphetamine and opiate addicts. *Journal of Psychopharmacology* 1997;11(suppl.):A83.
- [29] Rolls ET, Hornak J, Wade D, McGrath J. Emotion related learning in patients with social and emotional changes associated with frontal lobe damage. *Journal of Neurology, Neurosurgery and Psychiatry* 1994;57:1518–24.
- [30] Salmon E, Van der Linden M, Collette F, Delfiore G, Maquet P, Degueldre C, Luxen A, Franck G. Regional brain activity during working memory tasks. *Brain* 1996;119:1617–25.
- [31] Talairach J, Tournoux P. Coplanar stereotactic atlas of the human brain. Stuttgart: George Thieme Verlag, 1988.
- [32] Tranel D, Anderson SW, Benton AL. Development of the concept of 'executive function' and its relationship to the frontal lobes. In: F Boller, J Grafman (Editors). *Handbook of neuropsychology*. Amsterdam: Elsevier. 1994:125–147.