

Dissociable Functions in the Medial and Lateral Orbitofrontal Cortex: Evidence from Human Neuroimaging Studies

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Recent imaging studies show that the orbitofrontal cortex (OFC) is activated during a wide variety of paradigms, including guessing tasks, simple delayed matching tasks and sentence completion. We suggest that, as with other regions of the prefrontal cortex, activity in the OFC is most likely to be observed when there is insufficient information available to determine the appropriate course of action. In these circumstances the OFC, rather than other prefrontal regions, is more likely to be activated when the problem of what to do next is best solved by taking into account the likely reward value of stimuli and responses, rather than their identity or location. We suggest that selection of stimuli on the basis of their familiarity and responses on the basis of a feeling of 'rightness' are also examples of selection on the basis of reward value. Within the OFC, the lateral regions are more likely to be involved when the action selected requires the suppression of previously rewarded responses.

In recent years, neuroimaging techniques have provided a means to study regional neural responses in a wide variety of cognitive contexts. Converging evidence has allowed us to draw relatively firm functional conclusions and make clear predictions about circumstances in which a particular region will be activated. However, for the orbitofrontal cortex (OFC), the situation is far less clear cut. It is a region that has been activated, and indeed deactivated, in disparate paradigms, suggesting that diverse functions may be subsumed. In this review, we focus on studies carried out in our laboratory that illustrate a diversity of functions in the OFC as demonstrated by functional imaging. We attempt to draw out common themes and unifying principles that may provide a more coherent account for this seemingly diverse array of cognitive functions. Our suggestion is that, like the rest of the prefrontal cortex (PFC), the OFC has a fundamental role in making behavioural choices, particularly in incompletely specified or unpredictable situations. The special function of the OFC within the prefrontal system is to signal the likely value or behavioural relevance of available choices of action. Different regions of the OFC may subserve subtly different aspects of this function.

Anatomy of the OFC

The OFC is defined as the cortex on the orbital surface of the frontal lobe. In primates, it comprises areas 14 medially and 13/25 caudally, together with areas 11 and 12 around the inferior convexity. The ventral part of area 10, towards the frontal pole, also falls within the orbitofrontal region. These regions defined in monkeys (Walker, 1940) do not always have direct homologues in the human prefrontal architecture as classically described by Brodmann (Brodmann, 1909). Brodmann's areas 25 and 12 form the caudal part of medial OFC, extending forwards to area 10 and ventrally to area 11. Both areas 10 and 11 also extend around to the lateral side of the OFC. The posterior part of the lateral OFC is designated area 47.

However, more recently, Petrides and Pandya have reanalysed and compared the prefrontal, including the orbitofrontal, architecture in monkeys and man (Petrides and Pandya, 1994). They have modified numbering schemes to provide easier interspecies comparison. The most caudal part of the medial OFC is delineated as area 25, extending to area 10 towards the frontal pole. On the lateral surface, area 47/12 is the most caudal region, incorporating the human equivalent of primate area 13. Area 11 extends both medially and laterally on the ventral surface and an analogue of primate area 14 can also be identified on the ventromedial surface of the human cortex. A more detailed discussion of orbitofrontal anatomy can be found elsewhere in this volume.

Connectivity of the OFC

The OFC receives inputs from various regions of the sensory cortex. The lateral region receives inputs from taste areas (Rolls, 1990) while more medial parts receive olfactory inputs (Morecraft *et al.*, 1992; Rolls and Baylis, 1994). There are also direct inputs from visual association areas, somatosensory cortex and inferior temporal cortex and temporal pole (Petrides and Pandya, 1988; Morecraft *et al.*, 1992; Barbas, 1995). Direct projections from subcortical structures also reach the OFC, including substantial projections from the amygdala and medio-dorsal thalamus (Krettek and Price, 1977; Ray and Price, 1993). The OFC, in turn, projects to the inferior temporal and entorhinal cortices, anterior cingulate, hypothalamus, ventral tegmental area and caudate nucleus (Nauta, 1964; Kemp and Powell, 1970; Insausti *et al.*, 1987). This heterogeneous pattern of connectivity suggests that the OFC acts as a convergence zone for afferents from limbic and heteromodal association areas. Such a diversity of connectivity is consistent with either a wide range of functions or a supramodal, integrative role.

Within this general heterogeneity, different regions of the OFC exhibit different patterns of connectivity. The medial subdivision has its strongest connections with the hippocampus and associated areas of the cingulate, retrosplenial and entorhinal cortices, anterior thalamus and septal diagonal band (Pandya *et al.*, 1981; Mesulam *et al.*, 1983; Vogt and Pandya, 1987; Morecraft *et al.*, 1992). The lateral subdivision can be further divided into three sectors, although there are no definite boundaries between these. They are characterized, instead, by a continuous gradient of cytoarchitectonic differentiation (Morecraft *et al.*, 1992). The most caudal sector is characterized by strong connections with the amygdala, midline thalamus, non-isocortical insula and temporal pole (Mesulam and Mufson, 1982; Yeterian and Pandya, 1988; Barbas and De Olmos, 1990). The most anterior sector has more pronounced connections with the granular insula, association cortex, mediodorsal thalamus, inferior parietal lobule and dorsolateral PFC, involved in higher-order cognition (Goldman-Rakic, 1987; Fuster, 1997).

This differential pattern of connectivity suggests that different regions of the OFC may be specialized for distinct functional roles; in particular, there is likely to be a functional distinction between medial and lateral subdivisions.

Regions to be Considered from Imaging Studies

The orbitofrontal regions identified in the imaging studies described here include most of the anatomical subdivisions discussed above. In particular, we draw a distinction between the medial OFC, extending from area 25 through the homologue of primate area 14 to the ventromedial part of area 10, and the lateral OFC, extending from area 47/12 through area 11 on the ventral surface to the ventrolateral part of area 10.

Theories of Orbitofrontal Function

General Role of the PFC

It is generally agreed that the PFC has a role in generating behaviour that is flexible and adaptive rather than slavishly determined by the current sensory input. Many different terms have been used to characterize the function or nature of this flexible control system, such as planning (Luria, 1966), memory for the future (Ingvar, 1985), working memory (Goldman-Rakic, 1987), executive control (Baddeley, 1986), supervisory attention (Shallice, 1988) and top-down modulation of bottom-up processes (Frith and Dolan, 1997). The executive control exerted by the PFC upon behaviour has a number of different aspects including (i) an ability to choose a course of action in novel situations when no obvious course is indicated by the current environment, (ii) an ability to suppress a course of action that is no longer appropriate and (iii) an ability to monitor current, on-going action (Shallice, 1988). While there is agreement that there are separable aspects to executive control and that these are probably subserved by different regions of the PFC, there is less agreement about how these high-level cognitive components can be related to the distinct regions of the PFC. One view (Goldman-Rakic, 1995) is that distinct regions are concerned with *content*, such that the dorsolateral PFC (DLPFC) is involved principally with spatial locations while the ventrolateral PFC (VLPFC) is involved with visual object information. In contrast, Petrides has suggested that the different regions mediate distinct *processes*, such that the DLPFC is concerned with monitoring actions, while the VLPFC is concerned with active maintenance of information in working memory (Petrides, 1996). In our opinion the precise function of the various regions of the PFC has yet to be determined. One of the aims in this article is to explore whether data from recent neuroimaging studies suggest a particular role for the OFC as a component of the prefrontal executive system. Our tentative hypothesis is modelled on the suggestion that the DLPFC has a role in 'sculpting' the response space in order to control action (Frith, 2000). We suggest that the OFC is concerned with sculpting the reward space.

Findings from Lesion and Single-unit Recording Studies in Animals

Lesions of the OFC in animals have pronounced consequences for adaptive behaviour. In monkeys, orbitofrontal lesions result in disruption of feeding and social behaviour (Butter and Snyder, 1972; Baylis and Gaffan, 1991). It has been argued that these deficits represent impairments in the ability to process reward-related information and particularly in the detection of changes in reinforcement contingencies necessary to make appropriate modifications to ongoing behaviour (Jones and Mishkin, 1972;

Rolls, 1975, 1990, 1994, 1996). This argument is based on findings that orbitofrontal lesions cause deficits in tasks dependent on reward-related learning, e.g. discrimination reversal learning and extinction (Butter, 1969; Jones and Mishkin, 1972; Rolls *et al.*, 1994). There is also lesion evidence for a distinction between medial and lateral orbitofrontal function. Iversen and Mishkin showed a double dissociation in the effects of medial and lateral lesions on a visual discrimination reversal learning task (Iversen and Mishkin, 1970). Lesions to the medial OFC impaired the animals' ability to learn to associate a previously non-rewarded stimulus with reward, while lesions to the lateral OFC resulted in a failure to inhibit responding to the previously rewarded stimulus.

Direct single-electrode recording from the OFC of monkeys (Thorpe *et al.*, 1983) demonstrated that the neural response to sensory stimuli depends upon the behavioural and motivational significance of those stimuli. In addition, certain orbitofrontal neurons show activity occurring after a response, suggesting that such neurons code behavioural outcomes of trials. This suggests that the OFC is sensitive to the reinforcement properties, or value, of stimuli and, further, rapidly modulates the nature of this influence in the light of recent experience.

Findings from Lesion Studies in Humans

In humans, like primates, orbitofrontal lesions have been shown to disrupt social and emotional behaviour. Common sequelae of orbitofrontal damage include inappropriate euphoria, lack of affect and social irresponsibility (Bechara *et al.*, 1994; Damasio, 1994; Rolls *et al.*, 1994). There are also complex deficits in reasoning, judgement and creativity (Benton, 1968; Milner, 1982; Eslinger and Damasio, 1985; Mesulam, 1986). Recent neuropsychological studies by Damasio and colleagues, discussed in more detail elsewhere in this volume, found that patients with lesions of the medial OFC manifest impairments in real-life decision making, in the context of otherwise preserved intellectual abilities (Damasio, 1994). Bechara and co-workers developed a gambling task to model certain key aspects of real life decision-making which is typified by uncertain premises and outcomes, together with the requirement to process both positive and negative reinforcement (Bechara *et al.*, 1994). These authors found that patients with orbitofrontal lesions were significantly impaired on this gambling paradigm, being overly guided by immediate prospects at the expense of potential long-term consequences. It was noted that even when patients could accurately describe the contingencies governing the task, they failed to actually use this knowledge to guide their behaviour. This apparent dissociation between understanding of the contingencies and an ability to make appropriate behavioural responses has also been reported elsewhere (Rolls, 1996).

In addition to these behavioural abnormalities resulting from orbitofrontal lesions, Bechara *et al.* also reported autonomic effects (Bechara *et al.*, 1996). They compared anticipatory skin conductance responses (SCRs) in patients with orbitofrontal lesions and controls performing the gambling paradigm. Both patients and controls generated SCRs in response to reward or punishment. During the gambling task, however, control subjects began to show anticipatory SCRs prior to high-risk response selection as they learned about the contingencies associated with particular response selections. The patient group failed to show this effect; their SCRs were not elevated prior to the execution of a high-risk response. This suggests that signals arising from the OFC are normally involved in generating the

autonomic reactions associated with the anticipation of reward and punishment.

Summary

It is clear from the lesion literature in both animals and humans that the OFC is a functionally complex structure which is implicated in high-level aspects of cognition, as well as mediating aspects of emotional behaviour. This apparent dual role is also reflected in its patterns of interconnectivity involving afferent inputs from the association cortex as well as from regions traditionally associated with the experience and expression of emotion. However, in spite of this apparent functional heterogeneity it is possible to suggest an underlying general function. We suggest that the OFC is involved in the process of making choices in incompletely specified situations. Such situations incorporate a degree of uncertainty or unpredictability with respect to outcomes and require subjects to make responses on the basis of partial information. Further, we propose that different areas within the orbitofrontal region subsume different aspects of this process. More specifically, we will argue that the medial OFC is implicated in monitoring associations between stimuli, responses and outcomes under changing circumstances, while the more lateral regions are involved in the overriding of behavioural choices based on the previous reward values of stimuli and responses. In the remainder of this article, we present evidence from neuroimaging studies carried out in our laboratory, that provide empirical support for this contention.

Evidence for Stimulus–Response–Outcome Association in the Medial OFC

Response Selection Tasks

Modulation of Cognitive Performance by Feedback

One index of behavioural relevance is provided by feedback about performance. To study its neural concomitants, we used positron emission tomography (PET) in conjunction with a high-level planning task based on the Tower of London (Shallice, 1982). We employed a computerized one-touch version of the task, previously used in studies assessing the neural substrates of planning in normal subjects and patients with depression (Baker *et al.*, 1996; Elliott *et al.*, 1997b). The task presents subjects with two arrays of coloured balls and requires them to work out the minimum number of moves required to transform one array into the other according to certain pre-specified rules. The study of performance feedback used a variant of this task with several additional constraints. Firstly, subjects were presented only with the relatively difficult three- to six-move problems and secondly, they were allowed only 10 s to consider a solution after which they had to generate a response. Ten seconds is significantly less than the 15–25 s that subjects typically need to solve problems of this level of difficulty and therefore subjects were not given long enough to be certain of their responses. Thirdly, explicit visual feedback was given after each response. This feedback was in fact independent of subjects' responses and was provided according to a pre-specified schedule. In one condition, positive feedback was given to all responses; in another, negative feedback was given to 80% of responses; and in a third, no feedback condition, the display simply told subjects 'please wait'.

Performance of this planning task was compared with a control condition, which was a guessing task where subjects were required to monitor two identical arrays of coloured balls

until they disappeared. This was the signal for subjects to press any one of the six response buttons. They were told that on each trial, three of the buttons were 'correct' and that the correct buttons were assigned randomly on a trial-by-trial basis, such that each trial constituted a 50:50 guess.

There were few differences in regional cerebral blood flow associated with a comparison of the positive and negative feedback conditions (Elliott *et al.*, 1997a). However, there was a significant interaction between task type and the presence of feedback (positive and negative feedback combined and compared with the no feedback condition). In the guessing task, but not the planning task, the presence of feedback was associated with increased rCBF in the ventromedial OFC.

One reason why the medial OFC might be especially concerned with processing feedback in a guessing task (in contrast to a planning task) is that in the guessing task the subject has no rational basis for choosing one response rather than another. Nevertheless a choice must be made. If feedback is available to indicate whether or not one's previous responses were correct, a 'gambling' strategy can be adopted by which responses can be made on the basis of which one seems most likely to be 'lucky'. This feeling of luck is presumably based on the likely reward value of a particular response which is based in turn on the previous sequence of responses and rewards. Thus guessing tasks are likely to induce in subjects the strategy of monitoring the reward values of responses.

Alternatively this OFC activity may be associated with an implicit requirement to process feedback across trials. During planning, each trial (incorporating problem, response and feedback) is a discrete and meaningful entity. During guessing, by contrast, feedback to a single trial is less meaningful; only when feedback is assimilated across a number of trials can subjects evaluate their performance against chance. Although subjects were told to guess randomly, anecdotal evidence of behaviour in response to chance events predicts that subjects probably monitored performance and chose their responses in the light of previously rewarded responses. Reinforcement in the guessing task was believed by the subjects to be dependent solely on the button chosen, and the relation between the buttons and the outcomes was thought to vary across trials. Thus stimulus–reward relations were continually shifting in an unpredictable manner. A putative involvement of the OFC in acquiring and monitoring changing stimulus–reinforcement relations is consistent with findings from studies of monkeys (Thorpe *et al.*, 1983) and patients with orbitofrontal lesions as discussed above (Bechara *et al.*, 1994, 1996; Damasio, 1994; Rolls *et al.*, 1994).

Two- and Four-choice Guessing Task

Having serendipitously established a role for the OFC in a guessing task, we decided to examine more explicitly an orbitofrontal involvement in guessing. Accordingly, we developed a guessing paradigm, based on naturalistic playing card stimuli, for use in functional magnetic resonance imaging (fMRI) (Elliott *et al.*, 1999). In this task subjects were presented with an image depicting the back of a playing card where the task requirement was to predict either the colour (two-choice guess condition) or the suit (four-choice guess condition) of the card. Subjects registered their guesses via a button press and the card then flipped over to show the front of a card, selected at random from a full pack. This image served to provide feedback as to whether the prediction was correct. The guessing task was compared with a control task, where subjects were presented with the image of the front of a playing card and simply had to report either the

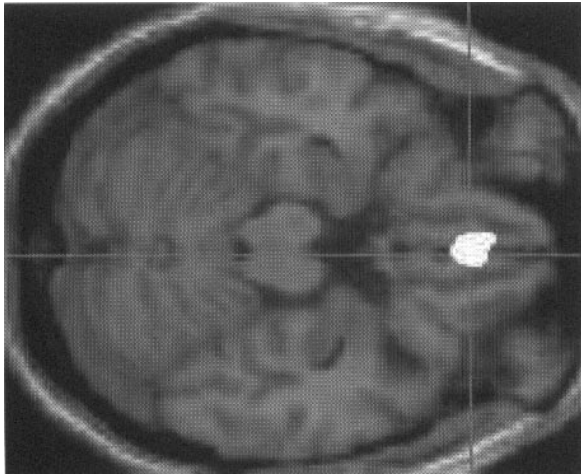


Figure 1. Areas in the OFC where a four-choice guessing task elicited more activity than a two-choice guessing task. Areas where there were significant differences in activity between the two conditions are shown superimposed on a co-registered structural image. Activity in the medial OFC is seen in a horizontal slice through the brain at 12 mm below the plane defined by the anterior–posterior commissures (Elliot *et al.*, 1999).

colour or the suit of the card before it flipped over to the card back. The two tasks were identical in that subjects saw a series of randomly presented playing card faces, alternating with the card back image. However, they differed in whether subjects responded to the card front, reporting what they saw, or the card back, predicting what they would see next. This constituted a factorial design that examined guessing compared with reporting at two levels of contingency (choosing one of two or one of four responses).

Guessing compared with reporting was associated with increased neural response in many regions, including the posterior perceptual regions, subcortical structures and regions of the PFC, and both the dorsolateral and orbitofrontal cortices. There was also a significant modulation of this pattern of activation associated with guessing, by changing the contingencies from 50 to 25% (see Fig. 1). This interaction term was associated with significant focal augmentation of activation in both the medial and lateral OFC (this lateral activation will be discussed further below). The involvement of the medial OFC in this guessing task may again reflect the requirement to monitor the reward value of possible responses. As the number of possible outcomes increases from two to four, this monitoring process becomes more demanding and the activation of the medial OFC increased accordingly.

Delayed Matching and Non-matching to Sample

Somewhat unexpectedly, we have also observed activity in the OFC in simple matching-to-sample tasks which did not involve any component of guessing. In this study fMRI was used to identify the neural substrates of delayed matching compared with delayed non-matching to sample. In both tasks subjects were initially shown a complex, abstract visual stimulus, then after a delay interval were presented with two stimuli, one of which was the sample stimulus. In delayed matching to sample, the subjects' task was to choose the familiar stimulus; in delayed non-matching, it was to choose the novel stimulus. Two delay intervals were used, 5 and 15 s. When the matching condition was compared with non-matching, a significant neural response was seen in the medial caudate and ventromedial OFC. This

differential response occurred for both delay intervals but was slightly, though not significantly, more pronounced at the short delay.

Regions of the OFC have previously been implicated in short-term memory tasks in humans and animals (Milner *et al.*, 1985; Bachevalier and Mishkin, 1986; Meunier *et al.*, 1997). Indeed, Bachevalier and Mishkin argued that the ventromedial prefrontal regions are more implicated in short-term memory tasks than the dorsolateral regions (Bachevalier and Mishkin, 1996). However, the medial OFC activation observed in this task is unlikely to reflect short-term memory processes *per se*. Both delayed matching and delayed non-matching-to-sample performance are likely to recruit short-term memory processes, but the medial orbitofrontal activation is a differential one, seen for matching but not for non-matching. A crucial difference between matching and non-matching is that for matching, subjects know which stimulus they will be responding to from the point where they see the sample. Thus, an association between a specific stimulus and the forthcoming response can be formed and maintained through the delay interval. For non-matching, the sample stimulus does not specify a forthcoming response and therefore no association is formed. It may therefore be the case that the differential orbitofrontal activation reflects the maintenance of stimulus–response mappings in the matching-to-sample task. While delayed matching to sample cannot be said to contain the same degree of unpredictability as the guessing tasks discussed above, a version with trial-unique stimuli, as used here, does require subjects to continually update stimulus–response mappings. A new association between stimulus and forthcoming response must be made on each trial. Therefore, although the situation is not as incompletely specified as in a guessing or gambling task, it shares the requirement to continually update the representation of associations between stimuli and correct responses.

The task can also be seen as one in which subjects have to attend to the familiarity of stimuli and, in the matching-to-sample case, choose the stimulus that feels familiar. There is some evidence for a natural relationship between familiarity and reward (or at least pleasantness). Zajonc has shown that subjects will prefer a familiar stimulus even in circumstances in which they are not aware that it is familiar (Zajonc, 1980). Thus, if familiarity is associated with intrinsic reward, in the delayed-matching-to-sample task the activity in the medial OFC may relate to the need to continuously monitor the reward value of the stimuli.

Language Tasks

Sentence Completion

We have also observed activation of the OFC in language-related tasks. One such task is sentence completion (i.e. generating the missing final word in sentences such as: 'Coming into the room he took off his . . .'). Performance of this task is known to be impaired by frontal lobe damage, especially in the version of the task in which a word that does NOT fit the sentence has to be generated (Burgess and Shallice, 1996). In a recent imaging study, Nathaniel-James and Frith (Frith, 1999) used a sentence completion task in which the level of constraint of the sentences was parametrically varied. Constraint was defined by the probability of the most frequent response listed in the Bloom and Fischler norms (Bloom and Fischler, 1980). Six levels of constraint, varying from low to high, were used during a PET neuroimaging study (high constraint: 'He posted the letter

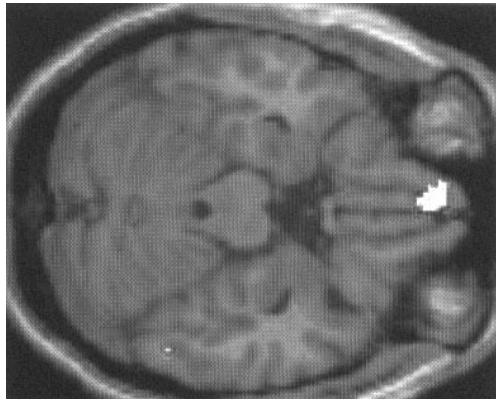


Figure 2. Areas in the OFC that were activated when a sentence had to be completed with a word that best fits the context. Areas where there were significant differences in activity between the two conditions are shown superimposed on a co-registered structural image. Activity is shown in a horizontal brain slice 28 mm below the plane defined by the anterior–posterior commissures (Frith, 2000).

without a . . . ; low constraint, ‘The police had never seen a man so . . .’). An additional factor in this study was whether subjects were told to give an appropriate or an inappropriate word to complete the sentence. The former condition requires response initiation, the latter requires response suppression. Anterior medial orbitofrontal activation was associated with making an appropriate rather than an inappropriate completion. This activation was enhanced in the lower constraint conditions. An open-ended sentence is an incompletely specified situation and the selection of an appropriate completion requires subjects to make associations. A strong mapping between the sentence stimuli and the chosen word ensures a correct outcome. The selection procedure becomes more difficult in less constrained sentences because there are more possible choices that could be associated with a successful outcome. As for the card-based guessing task discussed above, the presence of more possible responses predicts enhanced activation of the medial orbitofrontal region.

In the condition where subjects produced a word that did not fit there was much greater activation in the left DLPFC. This condition is also characterized by the requirement to choose between many possible responses. However, this choice can be made by deliberately selecting a word that breaks semantic and/or syntactic rules. When choosing a word that did fit, particularly in conditions of reduced constraint, more activity was observed in the OFC (see Fig. 2). When choosing a word that fits the subjective experience is of a feeling of ‘rightness’ or ‘closure’ when a suitable word is found, rather than of some rational consideration of why the word might be correct. Thus the activation of the OFC might be associated with the need to monitor this aspect of possible responses. With the less constrained sentences this need to monitor ‘rightness’ in order to choose the best response would be greater.

Story Comprehensibility

Another aspect of language processing, critically dependent on the formation of associations between stimuli and outcomes, is comprehension. Maguire and colleagues performed a PET study of the role of prior knowledge in comprehension and memory (Maguire *et al.*, 1999). There were a number of different cognitive conditions in this study, all involving subjects reading stories. Some of the stories were straightforward and readily

Tasks activating medial OFC

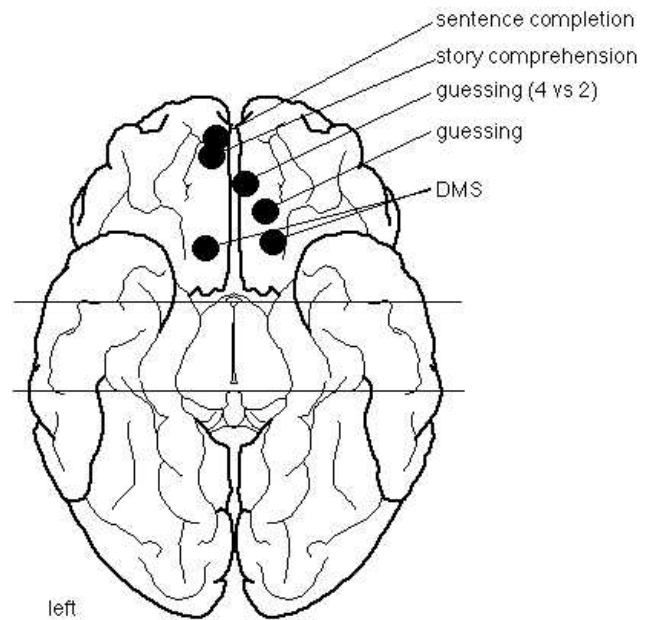


Figure 3. Schematic illustration of the locations of the peak of activation in the studies discussed in the previous section. The brain is viewed from below in the space defined by Talairach and Tournoux (Talairach and Tournoux, 1988).

comprehensible while others were unusual stories, that were difficult to comprehend without some prior knowledge to provide an explanatory theme. These stories were presented under different conditions, with and without a framework for comprehension provided by prior knowledge. Of the numerous comparisons made in this study, the one associated with activation of the OFC was a covariate analysis with subjective comprehension. After each story presentation, subjects rated their comprehension on a seven-point scale. The more subjectively comprehensible the stories, the greater the blood flow in an anterior region of the medial OFC, almost identical to the region involved in the sentence completion study described above. The unusual stories, in particular, are rather poorly specified and may even require a degree of guesswork to comprehend their meaning. Subjective comprehension, which is also likely to be intrinsically rewarding, depends on making associations between information and flexibly updating these associations in the light of incoming stimulus information.

To comprehend a story we must generate our own version in such a way as to capture the gist intended by the original storyteller. As with the sentence completion task discussed above, our experience of success in comprehension relates largely to a feeling of ‘rightness’ rather than any rational analysis of how our version relates to the original. In this experiment it would seem that the greater this feeling of rightness, the greater the activation in the medial OFC.

Summary

The medial OFC activation has been observed in various studies carried out in our laboratory (see Fig. 3). Although very different in some respects, all the studies discussed above shared a common requirement to make associations between stimuli and correct or rewarded responses. Further, these associations had to be updated in a flexible manner. The unifying feature of all the

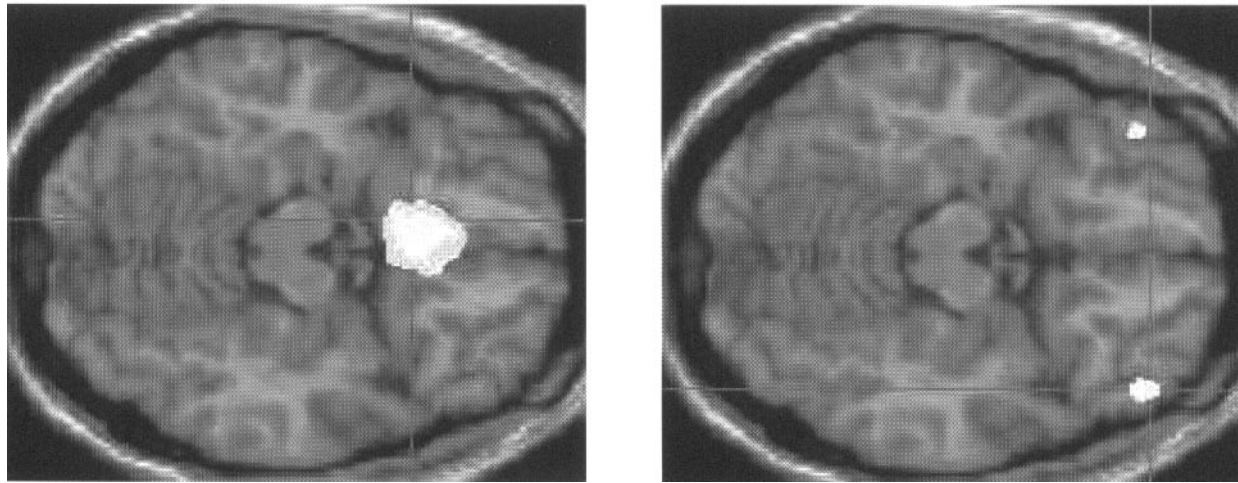


Figure 4. Contrasting areas in the OFC activated by delayed matching-to-sample and delayed non-matching-to-sample tasks. Areas where there were significant differences in activity between the two conditions are shown superimposed on a co-registered structural image. (A) Areas in the medial OFC that were more activated during delayed matching to sample in a horizontal slice 16 mm below the anterior–posterior cortex plane. (B) Areas in the lateral OFC that were more activated during delayed non-matching to sample in a horizontal slice 22 mm below the anterior–posterior cortex plane (Elliott and Dolan, 1999).

studies was the requirement to select stimuli and/or responses on the basis of their reward value. Subjects had to monitor or ‘hold in mind’ the reward value of previous stimuli and/or responses, and to contrast the possible reward values of future responses. We suggest, therefore, that the OFC has a function similar to other prefrontal regions in that it is involved in monitoring and in ‘holding things in mind’, but that this function is applied specifically to reward values (and related aspects such as familiarity and ‘rightness’). However, our experiments also suggest a distinction between the roles of the medial and the lateral OFC. In the next section we shall present evidence that the lateral OFC has a specific role in suppressing responses to previously rewarded stimuli.

Evidence for an Involvement of the Lateral OFC in Making Choices on the Basis of Response Suppression

Delayed Non-matching to Sample

As discussed above, we used fMRI to study differential responses in delayed matching and delayed non-matching to sample (Elliott and Dolan, 1999). In this study there was a double dissociation between lateral and medial activations. The comparison between matching and non-matching was associated with enhanced activity in medial orbitofrontal activation (see Fig. 4). However, the reverse comparison, between non-matching and matching, was associated with enhanced activity in a relatively anterior lateral region of the OFC, bilaterally. Both matching and non-matching involve short-term memory processes and the execution of a choice response. The medial activation associated with the matching condition was explained in terms of a need to monitor the familiarity and associated reward value of stimuli. The lateral activation associated with non-matching, however, can be explained in terms of a crucial difference between the tasks at the choice stage. In adult humans, unlike children and animals (Gaffan *et al.*, 1984; Diamond, 1991), matching is a more natural process than non-matching; the instinctive response at the choice stage is to the familiar rather than the novel stimulus. Thus, making the choice in non-matching involves inhibiting an instinctively preferred response in order to make a correct one. Inhibition can be seen as a particular feature of making choices,

especially in circumstances where an established or salient response may not always be appropriate. Such a role for the lateral OFC is consistent with previous studies implicating the OFC in response inhibition tasks, such as the classic go–no go tasks (Jones and Mishkin, 1972; Kowalska, 1991; Casey *et al.*, 1997). In particular, the lateral OFC seems to be involved when responses based upon the previous reward value have to be inhibited (Iversen and Mishkin, 1970).

Covert Orienting Task with Invalid Cues

A study looking more explicitly at response inhibition was a PET study using a variant of the Posner covert orienting task (Posner *et al.*, 1980) in which subjects are cued to orient spatial attention to a particular location prior to a response. Nobre *et al.* used a version of the task where cues were either spatial, directing subjects to a particular side of the screen, or temporal, indicating whether the target would appear 300 or 1500 ms after the cue (Nobre *et al.*, 1999). Subjects performed both the temporal and spatial tasks under two conditions: either with all cues valid or with 40% of the cues invalid (i.e. predicting the wrong location or interval). The presence of invalid cues in both the spatial and the temporal tasks was associated with activation of the lateral OFC bilaterally, with a relatively anterior focus, close to that seen in delayed non-matching to sample. This activation can be readily interpreted in terms of the requirement to inhibit a prepared motor sequence that the cue has (mis)led subjects to believe is correct. In this study, the invalid cues can also be seen as creating a situation of high unpredictability and the orbitofrontal activation is therefore also consistent with a wider role for this region in dealing with uncertainty.

Modulation of Hypothesis Testing by the Requirement to Make a Choice

A clear indication of a role for the lateral OFC in the expression of behavioural choice comes from a PET study of how the requirement to make a choice modulates cognitive performance (Elliott and Dolan, 1998). The paradigm used in this study was a visuospatial hypothesis-testing task under two conditions: with and without the requirement to make a choice. In the task, subjects were presented with a series of pairs of 6 × 6 checkerboards where the distribution of black and white squares was

randomly arranged. Subjects were told that on each trial one of the two checkerboards was 'correct' based upon a visuospatial rule. Their task was to try and work out this rule by hypothesis generation and testing across a number of trials (ten in each scanning block). In reality there was no rule, which obviated the possibility of subjects hitting on the right rule early on in the task and thereafter ceasing to generate and test hypotheses. In the 'choice' condition, subjects had to select which of each pair of stimuli they thought was correct on the basis of their current hypothesis, and were told whether the choice made was correct. In the 'no choice' condition, subjects were told which of the two stimuli was correct and were simply required to respond to this specified stimulus. In both cases, subjects obtained the same amount of information on each trial; namely, a knowledge of which of the two patterns was right such that their current hypothesis was either supported or disconfirmed. The only difference was that in the choice condition, their response represented commitment to a current hypothesis. A simple guessing control task was used where identical pairs of checkerboards were used as a signal for subjects to press either one of the response buttons ('choice' condition) or a specified button ('no choice' condition).

The comparison between the hypothesis-testing and guessing tasks was associated with the activation of a number of cortical and subcortical regions. There was no activation of the medial OFC, which may reflect that both tasks involve incompletely specified situations where stimulus–outcome associations are made and updated. However, the comparison between the choice and the no choice conditions was associated with activation of an anterior region of the lateral OFC bilaterally, as well as the ventral anterior cingulate. This is a clear demonstration that the lateral OFC is involved in the expression of behavioural choice in a situation where the outcome is uncertain. In the choice condition of both tasks subjects must select a response in a situation of extreme uncertainty. Because both tasks are insoluble there is a particular emphasis on rejecting previous hypotheses and thus a frequent need to suppress a previously rewarded response. This, we argue, is further evidence that the lateral OFC has a special role in suppressing previously rewarded responses.

Two- and Four-choice Guessing

Lateral orbitofrontal activation was also seen in the fMRI study of two-choice compared with four-choice guessing (Elliott *et al.*, 1999), described above. Guessing was associated with significant neural response in the lateral as well as the medial OFC, and this activity was also enhanced when the number of possible choices increased from two to four. Thus in this study, where the experimental but not the control task involved flexibly associating stimuli with outcomes and making a choice in the face of uncertainty, there was co-activation of both the medial and lateral OFC.

Another feature of these guessing tasks is that subjects will deliberately withhold previously rewarded responses from time to time because they know, due to the insoluble nature of such tasks, that their 'luck must change'. This is the 'gamblers fallacy' that leads us to believe that, if there have been five heads in a row, then the next toss is more likely to produce a tail. However, on this hypothesis we might also have expected to see activation of the lateral OFC in the guessing condition of the experiment described in Modulation of Cognitive Performance by Feedback. This difference may arise because the planning task used in this experiment was soluble and therefore there was less emphasis

on the need to reject hypotheses and suppress previously rewarded responses.

Response to Unstable Situations in a Reward Paradigm

A relatively posterior region of the lateral OFC was activated in a recent fMRI study of financial reward and punishment. We used a two-choice guessing task where subjects had to guess which of two playing cards was correct (a red card or a black card). The sequence of correct and incorrect choices had been predetermined. A bar at the side of the screen displayed the cumulative score across trials and this score had direct financial implications for subjects. Every time the subjects guessed correctly, the bar went up by a £1 increment; every time they were incorrect the bar went down by £1. The height of the bar, the rate of change of height and the interaction between the two were used to model the haemodynamic response. Orbitofrontal response was seen under a particular set of circumstances in the experiment, namely when the reward bar was either at a high level and rising quickly or at a low level and falling quickly. Subjectively, these were circumstances that were least stable, where subjects felt that their luck must be about to change. The orbitofrontal focus in these circumstances was accompanied by a response in the insula cortex and may represent the excitement associated with increased instability. The requirement to make choices between two responses was constant throughout this experiment but the subjective context in which these choices were made varied. Several studies suggest a role for the insula in processing emotionally relevant contexts (Casey *et al.*, 1995; Augustine, 1996), and the adjacent posterior lateral OFC may play a similar role. Thus the region may be implicated in a specific aspect of choice behaviour in uncertain situations, subsuming the emotional response to such choices. This experiment provides direct evidence of a link between the feeling that 'luck is going to change' and activation in the lateral OFC. This is the point in a guessing task when the subject must deliberately override response selection of the basis of previous rewards and try a new strategy.

Response to Angry Faces

Another study emphasizing the inhibitory role of the OFC was that of Blair *et al.*, who used PET to assess neural responses to facial expressions of sadness and anger (Blair *et al.*, 1999). Subjects were shown photographs of faces with sad, angry or neutral expressions and were required to make a behavioural response indicating whether the face was male or female. Activation of a region of the right lateral OFC (BA 47) was associated with responses to angry but not to sad or neutral faces (see Fig. 5). This orbitofrontal activation was correlated with the intensity of the angry expression and was close to that seen in the studies involving response inhibition: delayed non-matching to sample and the invalid cue task. This is consistent with the argument that angry expressions in others are a signal to us that our current behaviour is socially unsuitable or unacceptable. The anger of others should thus serve as a cue to cease the current behaviour. We propose that the orbitofrontal response to angry expressions may reflect this inhibitory effect.

Sentence Completion

The other task discussed above where lateral orbitofrontal activation occurred in the same comparison as more medial activation was the sentence completion study of Nathaniel-James and Frith. Again, the comparison between this task and its control involves not only making associations but also expressing

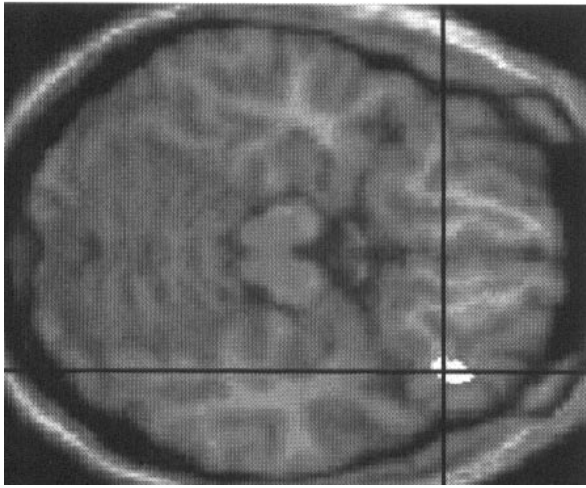


Figure 5. Areas in the lateral OFC that were more activated by the presentation of an angry face rather than a neutral face. Areas where there were significant differences in activity between the two conditions are shown superimposed on a co-registered structural image. Activity is shown in a horizontal brain slice 16 mm below the plane defined by the anterior–posterior commissures (Blair *et al.*, 1999).

responses in terms of a choice between alternatives. When the sentences were to be completed with appropriate words, and particularly, at a lower level of constraint, bilateral area 11 was activated, in regions extremely close to the lateral foci in the two choice guessing task of Elliott *et al.* (Elliott *et al.*, 1999). As in the card-playing task, the appropriate completion task requires subjects to select a response from a finite range of alternatives. Increasing the number of possible alternatives by lowering the level of constraint may place greater demands on the choice-making function subsumed by the lateral OFC.

We have suggested that finding a word that fits in this sentence completion task involves monitoring the possible responses for ‘how right’ they feel and that this is associated with activity in the medial OFC. However, it is also necessary to reject words have high local associations but do not fit the sentence as a whole. For example, ‘pepper’ would be an incorrect completion to the sentence, ‘the sea water tasted of salt and . . .’. It is possible that the activity in the lateral OFC seen in this study reflects suppression of these local associations (albeit, we admit, very forced).

Summary

Evidence from the experiments reviewed in this section suggests that the lateral OFC is particularly likely to be activated when the tendency to select previously rewarded responses has to be overridden (see Fig. 6).

Conclusions

The studies we have reviewed here suggest that the OFC is involved in making decisions and choosing responses, particularly in incompletely specified or uncertain situations. This observation is consistent with the wide range of deficits in patients with lesions to the OFC. The deficits in real-life decision making, as reported by Damasio and colleagues (Damasio, 1994), can certainly be thought of in these terms. Real life is uncertain and unpredictable, and decisions must be made on the basis of incomplete evidence, with uncertain outcomes. Decision making in uncertain situations is clearly an extremely complex process, involving a number of separable subprocesses,

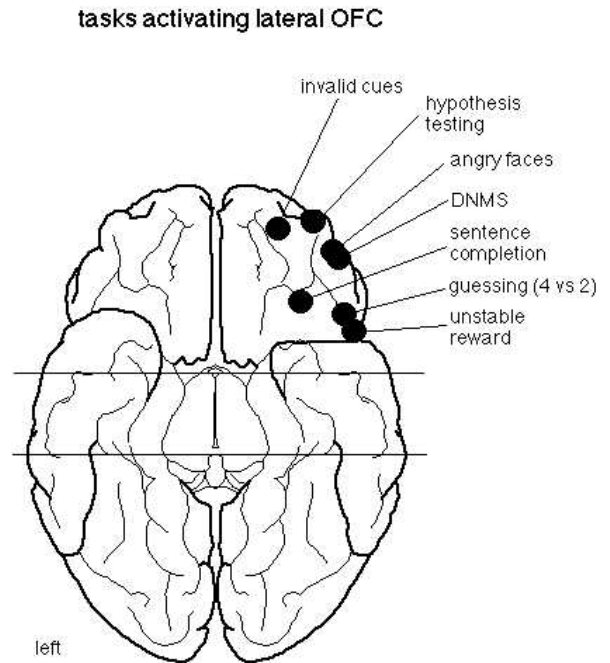


Figure 6. Schematic illustration of the locations of the peak activations in the studies discussed in the previous section. The brain is viewed from underneath in the space defined by Talairach and Tournoux (Talairach and Tournoux, 1988). For simplicity only the activations in the right hemisphere are shown although in nearly every study bilateral activations were observed. The tip of the right temporal lobe has been cut away to reveal the surface of orbital cortex above.

and the evidence presented above suggests some possible anatomical correlates of these functional distinctions.

A putative role for the OFC in coping with novel and uncertain situations does not distinguish it from other regions of the PFC. There is ample evidence that the prefrontal system has an executive function of this kind. However, we consider that the evidence we have presented here suggests that we can start to delineate a specific role for the OFC within the prefrontal executive system.

The Specific Role of the OFC

We have suggested that the OFC has a specific role in using the reward value associated with stimuli and responses in order to select actions. As a result, activity is seen in the OFC when tasks are performed that require monitoring of reward values and the holding in mind of reward values of past and future stimuli and responses. We suggest that the irrational sense of the rightness of a stimulus (which may relate to familiarity) is also associated with reward value. We derive these suggestions from the observation that the OFC is activated in tasks where the major determinant of the correct response is reward value or familiarity rather than sensory properties of the stimuli or motor properties of the response. Guessing tasks typify this situation. Our findings of a medial orbitofrontal involvement in simple guessing tasks is compatible with the findings of lesions studies that orbitofrontal damage impairs performance of gambling tasks (Bechara, 1994, 1996; Damasio, 1994; Rogers *et al.*, 1999). Finally we discussed two language tasks: sentence completion and comprehension of unusual stories, associated with anterior orbitofrontal activation. We suggest that performance of these language tasks depends upon monitoring possible responses on the basis of a feeling of rightness or familiarity rather than a

rational analysis of syntactic or semantic features. Our formulation is consistent with Rolls's suggestion that a key function of the OFC is rapid stimulus-reinforcement learning and reversal (Rolls, 1996). A flexible, rather than a 'hard-wired', system of this kind would require the monitoring and holding in mind of currently relevant reward values.

Specific Roles for the Medial and Lateral OFC

We suggest that, while the OFC in general is concerned with monitoring reward values, the lateral OFC is especially likely to be activated when a response previously associated with reward has to be suppressed. Response suppression is clearly involved in tasks such as delayed non-matching to sample and when responding to invalid cues in covert orienting tasks. We suggest that response suppression of this kind is also involved in gambling tasks, as when subjects decide that a response previously perceived as being lucky will probably cease to be so. This region is also responsive to angry facial expressions, which in social contexts may be an important signal to inhibit the current choice of behaviour. This anterior region corresponds to the isocortical section of the lateral OFC, the most significant connections of which include those to the dorsolateral PFC, a structure that has also been implicated in inhibitory processes (Fuster, 1997).

A more posterior and caudal region of the lateral OFC appears to be involved in the excitement engendered in making risky choices. This is the region that has strongest connections with the amygdala, insula and temporal pole – structures which are involved in emotional experience and expression (Aggleton, 1992; Augustine, 1996; Fink *et al.*, 1996). The making of risky choices may also elicit activity in this region since, when selecting risky responses, we allow knowledge that this choice may lead to an enhanced reward to override a wish to avoid such responses because they have previously been punished.

Contrast with the Role of Other Prefrontal Regions

In this article we have described a number of imaging studies in which activation has been seen in the OFC. On the basis of the nature of the tasks used in these studies we have suggested that the OFC has a specific role in monitoring the reward values of stimuli and responses so that reward value can be used to choose appropriate actions in a flexible and purposeful manner, particularly in situations of novelty and uncertainty. Although our account is somewhat speculative, it has the advantage of specifying a role for the OFC which accords with the idea that the PFC in general has an executive function while its various regions are concerned with different contextual aspects of executive control.

Notes

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