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REVIEW

The Functions of the Orbitofrontal Cortex

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Abstract

The orbitofrontal cortex contains the secondary taste cortex, in which the reward value of taste is represented. It also contains the secondary and tertiary olfactory cortical areas, in which information about the identity and also about the reward value of odours is represented. The orbitofrontal cortex also receives information about the sight of objects from the temporal lobe cortical visual areas, and neurons in it learn and reverse the visual stimulus to which they respond when the association of the visual stimulus with a primary reinforcing stimulus (such as taste) is reversed. This is an example of stimulus–reinforcement association learning, and is a type of stimulus–stimulus association learning. More generally, the stimulus might be a visual or olfactory stimulus, and the primary (unlearned) positive or negative reinforcer a taste or touch. A somatosensory input is revealed by neurons that respond to the texture of food in the mouth, including a population that responds to the mouth feel of fat. In complementary neuroimaging studies in humans, it is being found that areas of the orbitofrontal cortex (and connected subgenual cingulate cortex) are activated by pleasant touch, by painful touch, by taste and by smell. Damage to the orbitofrontal cortex can impair the learning and reversal of stimulus–reinforcement associations, and thus the correction of behavioural responses when these are no longer appropriate because previous reinforcement contingencies change. The information which reaches the orbitofrontal cortex for these functions includes information about faces, and damage to the orbitofrontal cortex can impair face (and voice) expression identification. This evidence thus shows that the orbitofrontal cortex is involved in decoding and representing some primary reinforcers such as taste and touch; in learning and reversing associations of visual and other stimuli to these primary reinforcers; and in controlling and correcting reward-related and punishment-related behaviour, and thus in emotion.

Introduction

The prefrontal cortex is the cortex that receives projections from the mediodorsal nucleus of the thalamus and is situated in front of the motor and premotor cortices (areas 4 and 6) in the frontal lobe. Based on the divisions of the mediodorsal nucleus, the prefrontal cortex may be divided into three main regions (Fuster, 1996). First, the magnocellular, medial, part of the mediodorsal nucleus projects to the orbital (ventral) surface of the prefrontal cortex (which includes areas 13 and 12). It is called the orbitofrontal cortex, and receives information from the ventral or object-processing visual stream, and taste, olfactory and somatosensory inputs. Second, the parvocellular, lateral, part of the mediodorsal nucleus projects to the dorsolateral prefrontal cortex. This part of the prefrontal cortex receives inputs from the parietal cortex, and is involved in tasks such as spatial short-term memory tasks (Fuster, 1996; see Rolls and Treves, 1998). Third, the pars paralamellaris (most lateral) part of the mediodorsal nucleus projects to the frontal eye fields (area 8) in the anterior bank of the arcuate sulcus.

The functions of the orbitofrontal cortex are considered here. The cortex on the orbital surface of the frontal lobe includes area 13 caudally, and area 14 medially, and the cortex on the inferior convexity includes area 12 caudally and area 11 anteriorly (see Fig. 1; Carmichael and Price, 1994; Petrides and Pandya, 1994; Price, 1999). This brain region is poorly developed in rodents, but well developed in primates, including humans. To understand the function of this brain region in humans, the majority of the studies described were therefore performed with macaques or with humans.

Connections

Rolls *et al.* (1990) discovered an area with taste-responsive neurons in the lateral part of the orbitofrontal cortex, and showed that this was the secondary taste cortex in that it receives a major projection from the primary taste cortex and not from the thalamic taste relay nucleus (VPMpc)

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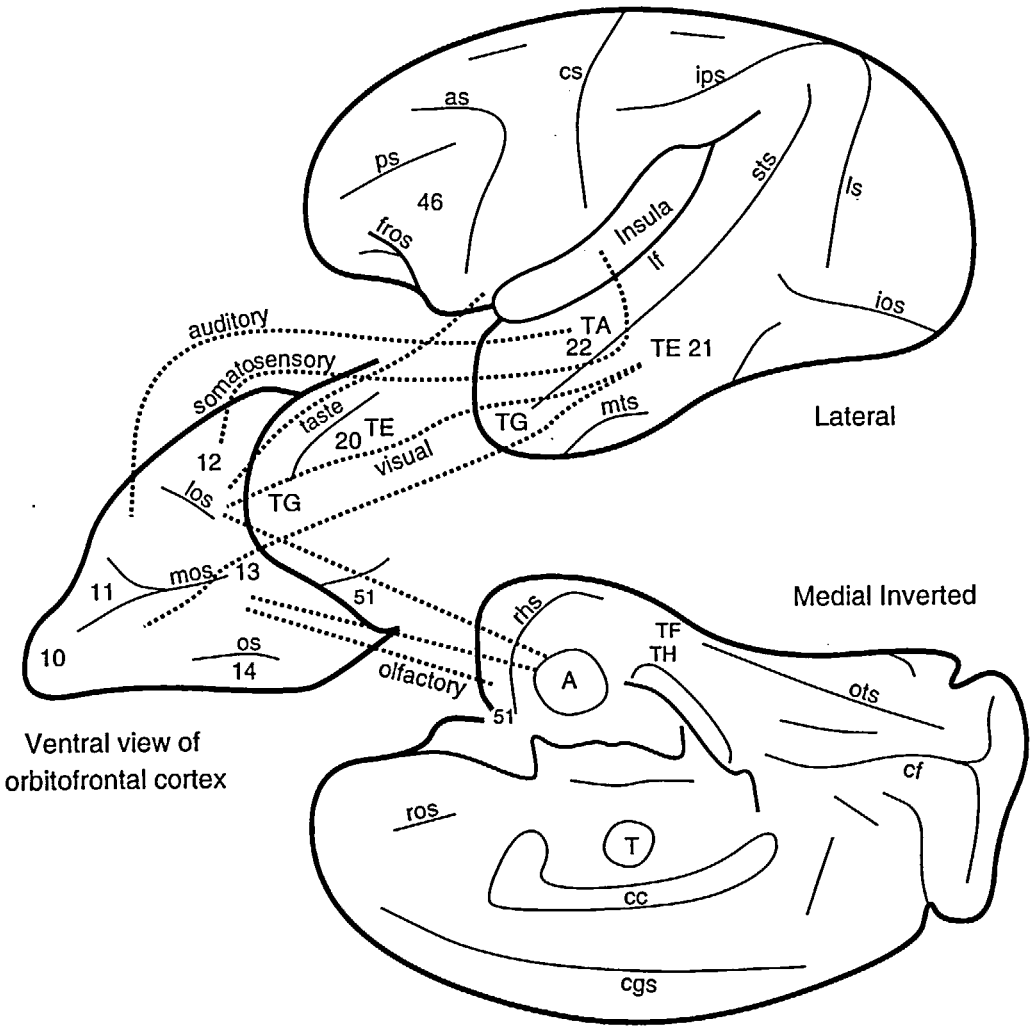

Fig. 1. Schematic diagram showing some of the gustatory, olfactory, visual and somatosensory pathways to the orbitofrontal cortex, and some of the outputs of the orbitofrontal cortex. The secondary taste cortex, and the secondary olfactory cortex, are within the orbitofrontal cortex. V1, primary visual cortex; V4, visual cortical area V4; as, arcuate sulcus; cc, corpus callosum; cf, calcarine fissure; cgs, cingulate sulcus; cs, central sulcus; ls, lunate sulcus; ios, inferior occipital sulcus; mos, medial orbital sulcus; os, orbital sulcus; ots, occipito-temporal sulcus; ps, principal sulcus; rhs, rhinal sulcus; sts, superior temporal sulcus; lf, lateral (or Sylvian) fissure (which has been opened to reveal the insula); A, amygdala; INS, insula; T, thalamus; TE (21), inferior temporal visual cortex; TA (22), superior temporal auditory association cortex; TF and TH, parahippocampal cortex; TG, temporal pole cortex; 12, 13, 11, orbitofrontal cortex; 35, perirhinal cortex; 51, olfactory (prepyriform and periamygdaloid) cortex.

(Baylis *et al.*, 1994). More medially, there is an olfactory area (Rolls and Baylis, 1994). Anatomically, there are direct connections from the primary olfactory cortex (pyriform cortex) to area 13a of the posterior orbitofrontal cortex, which in turn has onward projections to a middle part of the orbitofrontal cortex (area 11) (Price *et al.*, 1991; Morecraft *et al.*, 1992; Barbas, 1993; Carmichael *et al.*, 1994) (see Figs 1 and 2). Visual inputs reach the orbitofrontal cortex directly from the inferior temporal cortex, the cortex in the superior temporal sulcus and the temporal pole (see Barbas, 1988, 1993, 1995; Barbas and Pandya, 1989; Seltzer and Pandya, 1989; Morecraft *et al.*, 1992; Carmichael and Price, 1995). There are corresponding auditory inputs (Barbas, 1988, 1993), and somatosensory inputs from somatosensory cortical areas 1, 2 and SII in the frontal and pericentral operculum, and from the insula (Barbas, 1988; Carmichael and Price, 1995). The caudal orbitofrontal cortex receives strong inputs from the amygdala (e.g. Price *et al.*, 1991). The orbitofrontal cortex also receives inputs via the mediodorsal nucleus of the thalamus, pars magnocellularis, which itself receives afferents from temporal lobe structures such as the prepyriform (olfactory) cortex, amygdala and inferior temporal cortex (see Price, 1999). The orbitofrontal cortex projects back to temporal lobe areas such as the inferior temporal cortex, and, in addition, to the entorhinal cortex (or 'gateway to the hippocampus') and cingulate cortex (Insausti *et al.*, 1987). The orbitofrontal cortex also projects to the preoptic region and lateral hypothalamus, to the ventral tegmental area (Nauta, 1964; Johnson *et al.*, 1968), and to the head of the caudate nucleus (Kemp and Powell, 1970). Reviews of the cytoarchitecture and connections of the orbitofrontal cortex are provided by Petrides and Pandya (1994), Pandya

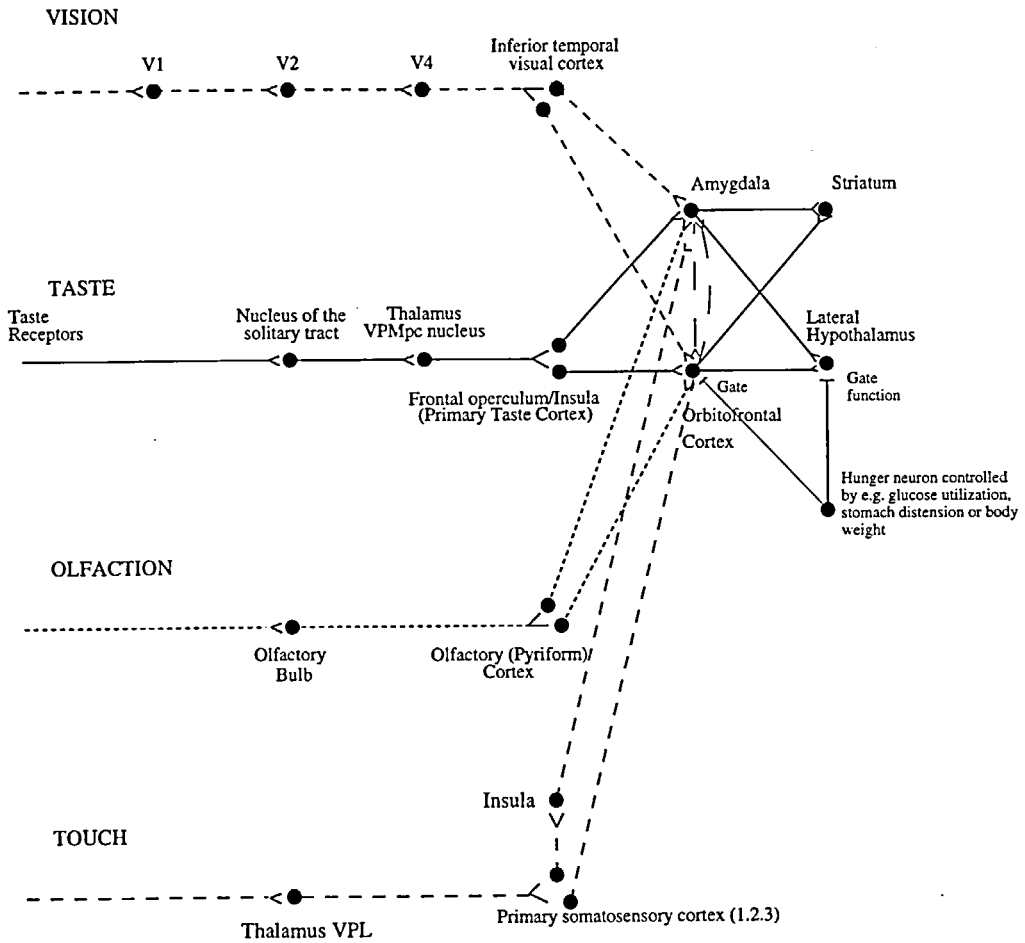

Fig. 2. Schematic diagram showing some of the gustatory, olfactory, visual and somatosensory pathways to the orbitofrontal cortex, and some of the outputs of the orbitofrontal cortex. The secondary taste cortex, and the secondary olfactory cortex, are within the orbitofrontal cortex. V1, primary visual cortex; V4, visual cortical area V4. The gate function refers to the fact that neurons in the orbitofrontal cortex and lateral hypothalamus only respond to the sight, taste or smell of food if hunger signals are present (see Rolls, 1997a, 1999a).

and Yeterian (1996), Carmichael and Price (1994, 1995), Barbas (1995) and Price (1999).

Effects of lesions of the orbitofrontal cortex

Macaques with lesions of the orbitofrontal cortex are impaired at tasks which involve learning about which stimuli are rewarding and which are not, and especially in altering behaviour when reinforcement contingencies change. The monkeys may respond when responses are inappropriate, e.g. no longer rewarded, or may respond to a non-rewarded stimulus. For example, monkeys with orbitofrontal damage are impaired on Go/NoGo task performance, in that they go on the NoGo trials (Iversen and Mishkin, 1970); in an object reversal task in that they respond to the object which was formerly rewarded with food; and in extinction in that they continue to respond to an object which is no longer rewarded (Butter, 1969; Jones and Mishkin, 1972). There is some evidence for dissociation of function within the orbitofrontal cortex, in that lesions to the inferior convexity produce the Go/NoGo and object reversal deficits, whereas damage to the caudal orbitofrontal cortex, area 13, produces the extinction deficit (Rosenkilde, 1979).

Lesions more laterally, in for example the inferior convexity, can influence working memory tasks in which objects must be remembered for short periods, e.g. delayed matching to sample and delayed matching to non-sample tasks (Passingham, 1975; Mishkin and Manning, 1978; Kowalska *et al.*, 1991), and neurons in this region may help to implement this visual object short-term memory by holding the representation active during the delay period (Rosenkilde *et al.*, 1981; Wilson *et al.*, 1993) by using the attractor properties of autoassociation networks (Rolls and Treves, 1998). Whether this inferior convexity area is specifically involved in a short-term object memory is not yet clear, and a medial part of the frontal cortex may also contribute to this function (Kowalska *et al.*, 1991). It should be noted that this short-term memory system for objects (which receives inputs from the temporal lobe visual cortical areas in which objects are represented) is different to the short-term memory system in the dorsolateral part of the prefrontal cortex, which is concerned with spatial short-term memories, consistent with

its inputs from the parietal cortex, but also probably operates using the attractor properties of autoassociation networks (see, for example, Rolls and Treves, 1998).

Damage to the caudal orbitofrontal cortex in the monkey also produces emotional changes (e.g. decreased aggression to humans and to stimuli such as a snake and a doll), and a reduced tendency to reject foods such as meat (Butter *et al.*, 1969, 1970; Butter and Snyder, 1972) or to display the normal preference ranking for different foods (Baylis and Gaffan, 1991). In humans, euphoria, irresponsibility and lack of affect can follow frontal lobe damage (see Damasio, 1994; Kolb and Whishaw, 1996; Rolls, 1999a), particularly orbitofrontal damage (Rolls *et al.*, 1994; Hornak *et al.*, 1996).

Neurophysiology of the orbitofrontal cortex

Taste

One of the recent discoveries that has helped us to understand the functions of the orbitofrontal cortex in behaviour is that it contains a major cortical representation of taste (see Rolls, 1989, 1995a, 1997a; cf. Fig. 2). Given that taste can act as a primary reinforcer, i.e. without learning as a reward or punishment, we now have the start for a fundamental understanding of the function of the orbitofrontal cortex in stimulus–reinforcement association learning. We know how one class of primary reinforcers reaches and is represented in the orbitofrontal cortex. A representation of primary reinforcers is essential for a system that is involved in learning associations between previously neutral stimuli and primary reinforcers, e.g. between the sight of an object and its taste.

The representation (shown by analysing the responses of single neurons in macaques) of taste in the orbitofrontal cortex includes robust representations of the prototypical tastes sweet, salt, bitter and sour (Rolls *et al.*, 1990), but also separate representations of the taste of water (Rolls *et al.*, 1990), of protein or umami as exemplified by monosodium glutamate (Baylis and Rolls, 1991) and inosine monophosphate (Rolls *et al.*, 1996a, 1998), and of astringency as exemplified by tannic acid (Critchley and Rolls, 1996c).

The nature of the representation of taste in the orbitofrontal cortex is that the reward value of the taste is represented. The evidence for this is that the responses of orbitofrontal taste neurons are modulated by hunger (as is the reward value or palatability of a taste). In particular, it has been shown that orbitofrontal cortex taste neurons stop responding to the taste of a food with which the monkey is fed to satiety (Rolls *et al.*, 1989). In contrast, the representation of taste in the primary taste cortex (Scott *et al.*, 1986; Yaxley *et al.*, 1990) is not modulated by hunger (Rolls *et al.*, 1988; Yaxley *et al.*, 1988). Thus, in the primary taste cortex, the reward value of taste is not represented, and instead the identity of the taste is represented. Additional evidence that the reward value of food is represented in the orbitofrontal cortex is that monkeys work for electrical stimulation of this brain region if they are hungry, but not if they are satiated (Mora *et al.*, 1979; Rolls, 1999a). Further, neurons in the orbitofrontal cortex are activated from many brain-stimulation reward sites (Mora *et al.*, 1980; Rolls *et al.*, 1980). Thus, there is clear evidence that it is the reward value of taste that is represented in the orbitofrontal cortex (see further Rolls, 1999a).

The secondary taste cortex is in the caudolateral part of the orbitofrontal cortex, as defined anatomically (Baylis *et al.*, 1994). This region projects onto other regions in the orbitofrontal cortex (Baylis *et al.*, 1994), and neurons with taste responses (in what can be considered as a tertiary gustatory cortical area) can be found in many regions of the orbitofrontal cortex (see Rolls *et al.*, 1990, 1996b; Rolls and Baylis, 1994). Neurons from these regions project to the hypothalamus, and it is probably by this route that hypothalamic neurons receive the inputs which make them respond to the taste and/or sight of food if the monkey is hungry [see Fig. 2 and Rolls (1999a), Chapter 2].

Convergence of taste and olfactory inputs in the orbitofrontal cortex: the representation of flavour

In these further parts of the orbitofrontal cortex, not only unimodal taste neurons, but also unimodal olfactory neurons, are found. In addition, some single neurons respond to both gustatory and olfactory stimuli, often with correspondence between the two modalities (Rolls and Baylis, 1994; cf. Fig. 2). It is probably here in the orbitofrontal cortex of primates that these two modalities converge to produce the representation of flavour (Rolls and Baylis, 1994). Evidence will soon be described which indicates that these representations are built by olfactory–gustatory association learning, an example of stimulus–reinforcement association learning.

An olfactory representation in the orbitofrontal cortex

Takagi, Tanabe and colleagues (see Takagi, 1991) described single neurons in the macaque orbitofrontal cortex that were activated by odours. A ventral frontal region has been implicated in olfactory processing in humans (Jones-Gotman and Zatorre, 1988; Zatorre and Jones-Gotman, 1991; Zatorre *et al.*, 1992). Rolls and colleagues have analysed the rules by which orbitofrontal olfactory representations are formed and operate in primates. For 65% of neurons in the orbitofrontal olfactory areas, Critchley and Rolls (1996a) showed that the representation of the olfactory stimulus was independent of its association with taste reward (analysed in an olfactory discrimination task with taste reward). For the remaining 35% of the neurons, the odours to which a neuron responded were influenced by the taste (glucose or saline) with which the odour was associated. Thus, the odour representation for 35% of orbitofrontal neurons appeared to be built by olfactory to taste association learning. This possibility was confirmed by reversing the taste with which an odour was associated in the reversal of an olfactory

discrimination task. It was found that 68% of the sample of neurons analysed altered the way in which they responded to odour when the taste reinforcement association of the odour was reversed (Rolls *et al.*, 1996b). [Twenty-five per cent showed reversal and 43% no longer discriminated after the reversal. The olfactory to taste reversal was quite slow, both neurophysiologically and behaviourally, often requiring 20–80 trials, consistent with the need for some stability of flavour representations. The relatively high proportion of neurons with modification of responsiveness by taste association in the set of neurons in this experiment was probably related to the fact that the neurons were pre-selected to show differential responses to the odours associated with different tastes in the olfactory discrimination task.] Thus, the rule according to which the orbitofrontal olfactory representation is formed is for some neurons by association learning with taste.

To analyse the nature of the olfactory representation in the orbitofrontal cortex, Critchley and Rolls (1996b) measured the responses of olfactory neurons that responded to food while they fed the monkey to satiety. They found that the majority of orbitofrontal olfactory neurons decreased their responses to the odour of the food with which the monkey was fed to satiety. Thus, for these neurons, the reward value of the odour is what is represented in the orbitofrontal cortex (cf. Rolls and Rolls, 1997). We do not yet know whether this is the first stage of processing at which reward value is represented in the olfactory system (although in rodents the influence of reward association learning appears to be present in some neurons in the pyriform cortex; Schoenbaum and Eichenbaum, 1995).

Although individual neurons do not encode large amounts of information about which of 7–9 odours has been presented, we have shown that the information does increase linearly with the number of neurons in the sample (Rolls *et al.*, 1996c). This ensemble encoding does result in useful amounts of information about which odour has been presented being provided by orbitofrontal olfactory neurons.

Visual inputs to the orbitofrontal cortex, and visual stimulus–reinforcement association learning and reversal

We have been able to show that there is a major visual input to many neurons in the orbitofrontal cortex, and that what is represented by these neurons is in many cases the reinforcement association of visual stimuli. The visual input is from the ventral, temporal lobe, visual stream concerned with 'what' object is being seen, in that orbitofrontal visual neurons frequently respond differentially to objects or images depending on their reward association (Thorpe *et al.*, 1983; Rolls *et al.*, 1996b). The primary reinforcer that has been used is taste. Many of these neurons show visual–taste reversal in one or a very few trials (see the example in Fig. 3). (In a visual discrimination task, they will reverse the stimulus to which they respond, from e.g. a triangle to a square, in one trial when the taste delivered for a behavioural response to that stimulus is reversed.) This reversal learning probably occurs in the orbitofrontal cortex, for it does not occur one synapse earlier in the visual inferior temporal cortex (Rolls *et al.*, 1977), and it is in the orbitofrontal cortex that there is convergence of visual and taste pathways onto the same neurons (Thorpe *et al.*, 1983; Rolls and Baylis, 1994; Rolls *et al.*, 1996b). The probable mechanism for this learning is Hebbian modification of synapses conveying visual input onto taste-responsive neurons, implementing a pattern association network (Rolls and Treves, 1998; Rolls, 1999a).

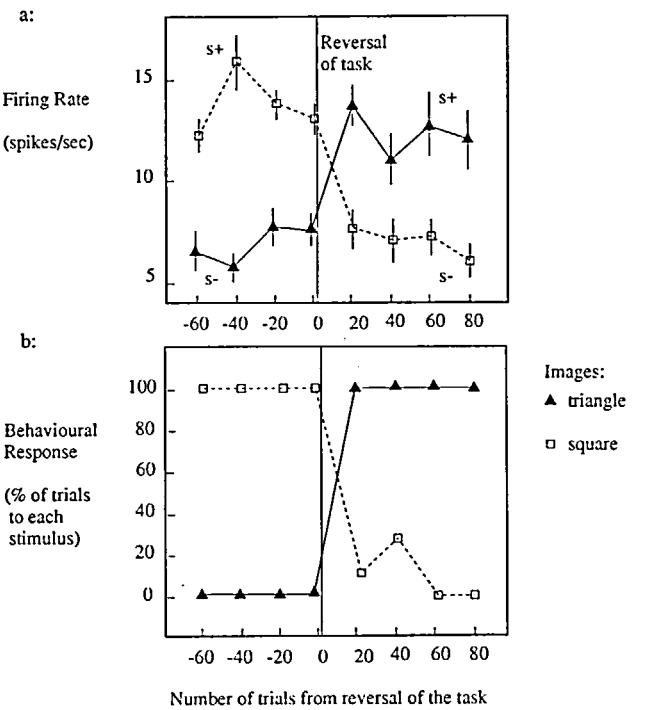

Fig. 3. Visual discrimination reversal of the responses of a single neuron in the macaque orbitofrontal cortex when the taste with which the two visual stimuli (a triangle and a square) were associated was reversed. Each point is the mean post-stimulus firing rate measured in a 0.5 s period over approximately 10 trials to each of the stimuli. (a) Before reversal, the neuron fired most to the square when it indicated (S+) that the monkey could lick to obtain a taste of glucose. After reversal, the neuron responded most to the triangle when it indicated that the monkey could lick to obtain glucose. The response was low to the stimuli when they indicated (S–) that if the monkey licked then aversive saline would be obtained. (b) The behavioural response to the triangle and the square, indicating that the monkey reversed rapidly. (After Rolls *et al.*, 1996b).

In addition to these neurons that encode the reward association of visual stimuli, other neurons in the orbitofrontal cortex detect non-reward, in that they respond, for example, when an expected reward is not obtained when a visual discrimination task is reversed (Thorpe *et al.*, 1983). Different populations of such neurons respond to other types of non-reward, including the removal of a formerly approaching taste reward, and the termination of a taste reward (Thorpe *et al.*, 1983). The presence of these neurons is fully consistent with the hypothesis that they are part of the mechanism by which the orbitofrontal cortex enables very rapid reversal of

behaviour by stimulus–reinforcement association relearning when the association of stimuli with reinforcers is altered or reversed (see Rolls, 1986a, 1990). Different orbitofrontal cortex neurons respond to different types of non-reward (Thorpe *et al.*, 1983), potentially enabling task or context-specific reversal to occur.

Another type of information represented in the orbitofrontal cortex is information about faces. There is a population of orbitofrontal neurons which respond in many ways similar to those in the temporal cortical visual areas [see Rolls (1984a, 1992a, 1994a, 1995b, 1996a, 1997b) and Wallis and Rolls (1997) for a description of their properties]. The orbitofrontal face-responsive neurons, first observed by Thorpe *et al.* (1983), then by Rolls *et al.* (1999 in preparation, see Booth *et al.*, 1998; Rolls, 1999a), tend to respond with longer latencies than temporal lobe neurons (140–200 ms typically, compared to 80–100 ms), also convey information about which face is being seen, by having different responses to different faces, and are typically rather harder to activate strongly than temporal cortical face-selective neurons, in that many of them respond much better to real faces than to two-dimensional images of faces on a video monitor (cf. Rolls and Baylis, 1986). Some of the orbitofrontal cortex face-selective neurons are responsive to face gesture or movement. The findings are consistent with the likelihood that these neurons are activated via the inputs from the temporal cortical visual areas in which face-selective neurons are found (see Fig. 2). The significance of the neurons is likely to be related to the fact that faces convey information that is important in social reinforcement. One way in which these neurons carry useful information in such situations is that by encoding face expression (cf. Hasselmo *et al.*, 1989) (e.g. a smile or a frown), their activation can act as a reinforcer. This may be partly innate, and partly by association with a primary reinforcer such as a pleasant touch or pain. Another way in which face-selective neurons may carry useful information in such situations is that they encode information about which individual is present (cf. Hasselmo *et al.*, 1989), which is also important in social situations as learned associations of particular individuals with reinforcers such as touch or pain can again guide behaviour.

Somatosensory inputs to the orbitofrontal cortex

Some neurons in the macaque orbitofrontal cortex respond to the texture of food in the mouth. Some neurons alter their responses when the texture of a food is modified by adding gelatine or methyl cellulose, or by partially liquefying a solid food such as apple (Critchley *et al.*, 1993). Another population of orbitofrontal neurons responds when a fatty food such as cream is in the mouth. These neurons can also be activated by pure fat such as glyceryl trioleate, and by non-fat substances with a fat-like texture such as paraffin oil (hydrocarbon) and silicone oil [$(Si(CH_3)_2O)_n$]. These neurons thus provide information by somatosensory pathways that a fatty food is in the mouth (Rolls *et al.*, 1999). These inputs are perceived as pleasant when hungry, because of the utility of ingestion of foods which are likely to contain essential fatty acids and to have a high calorific value (Rolls, 1999a,b). In addition to these oral somatosensory inputs to the orbitofrontal cortex, there are also somatosensory inputs from other parts of the body, and indeed a functional magnetic resonance imaging (fMRI) investigation we have performed in humans indicates that pleasant and painful touch stimuli to the hand produce greater activation of the orbitofrontal cortex relative to the somatosensory cortex than do affectively neutral stimuli (Rolls *et al.*, 1997a; Francis *et al.*, 1999; see below).

A neurophysiological basis for stimulus–reinforcement learning and reversal in the orbitofrontal cortex

The neurophysiological evidence and the effects of lesions described suggest that one function implemented by the orbitofrontal cortex is rapid stimulus–reinforcement association learning, and the correction of these associations when reinforcement contingencies in the environment change. To implement this, the orbitofrontal cortex has the necessary representation of primary reinforcers, including taste and somatosensory stimuli. It also receives information about objects, e.g. visual view-invariant information (Booth and Rolls, 1998), and can associate this at the neuronal level with primary reinforcers such as taste, and reverse these associations very rapidly. Another type of stimulus which can be conditioned in this way in the orbitofrontal cortex is olfactory, although here the learning is slower. It is likely that auditory stimuli can be associated with primary reinforcers in the orbitofrontal cortex, though there is less direct evidence of this yet. The orbitofrontal cortex also has neurons which detect non-reward, which are likely to be used in behavioural extinction and reversal. They may do this not only by helping to reset the reinforcement association of neurons in the orbitofrontal cortex, but also by sending a signal to the striatum which could be routed by the striatum to produce appropriate behaviours for non-reward (Rolls and Johnstone, 1992; Williams *et al.*, 1993; Rolls, 1994b). Indeed, the striatal route may be an important one through which the orbitofrontal cortex influences behaviour when the orbitofrontal cortex is decoding reinforcement contingencies and their changes (see Rolls, 1999a). Some of the evidence for this is that neurons with responses that reflect the output of orbitofrontal neurons are found in the ventral part of the head of the caudate nucleus and the ventral striatum, parts of the striatum that receive connections from the orbitofrontal cortex (Rolls *et al.*, 1983a, 1984b; Williams *et al.*, 1993; see Rolls and Treves, 1998; Rolls, 1999a, Chapter 6); and that lesions of the ventral part of the head of the caudate nucleus impair visual discrimination reversal (Divac *et al.*, 1967), which is also impaired by orbitofrontal cortex lesions.

Decoding the reinforcement value of stimuli, which involves for previously neutral (e.g. visual) stimuli learning their association with a primary reinforcer, often rapidly, and which may involve not only rapid learning, but also rapid

relearning and alteration of responses when reinforcement contingencies change, is then a function proposed for the orbitofrontal cortex. This way of producing behavioural responses would be important in, for example, motivational and emotional behaviour. It would be important, for example, for feeding and drinking by enabling primates to learn rapidly about the food reinforcement to be expected from visual stimuli (see Rolls, 1994c, 1999a). This is important, for primates frequently eat more than 100 varieties of food; vision by visual–taste association learning can be used to identify when foods are ripe; and, during the course of a meal, the pleasantness of the sight of a food eaten in the meal decreases in a sensory-specific way (Rolls *et al.*, 1983b), a function that is probably implemented by the sensory-specific satiety-related responses of orbitofrontal visual neurons (Critchley and Rolls, 1996b).

With respect to emotional behaviour, decoding and rapidly readjusting the reinforcement value of visual signals is likely to be crucial, for emotions can be described as responses elicited by reinforcing signals (Rolls, 1986a,b, 1990, 1995b, 1999a). [For the purposes of this paper, a positive reinforcer or reward can be defined as a stimulus which the animal will work to obtain, and a negative reinforcer or punishment as a stimulus that an animal will work to avoid or escape (see further, Rolls, 1990, 1999).] The ability to perform this learning very rapidly is probably very important in social situations in primates, in which reinforcing stimuli are continually being exchanged, and the reinforcement value of stimuli must be continually updated (relearned), based on the actual reinforcers received and given. Although the functions of the orbitofrontal cortex in implementing the operation of reinforcers such as taste, smell, tactile and visual stimuli, including faces, are most understood, in humans the rewards processed in the orbitofrontal cortex include quite general learned rewards (i.e. secondary reinforcers) such as working for 'points', as will be described shortly.

Although the amygdala is concerned with some of the same functions as the orbitofrontal cortex, and receives similar inputs (see Fig. 2), there is evidence that it may function less effectively in the very rapid learning and reversal of stimulus reinforcement associations, as indicated by the greater difficulty in obtaining reversal from amygdala neurons (see, for example, Rolls, 1992b, 2000), and by the greater effect of orbitofrontal lesions in leading to continuing choice of no longer rewarded stimuli (Jones and Mishkin, 1972). In primates, the necessity for very rapid stimulus–reinforcement re-evaluation, and the development of powerful cortical learning systems, may result in the orbitofrontal cortex effectively taking over this aspect of amygdala functions (see Rolls, 1992b, 1999a).

The human orbitofrontal cortex

It is of interest that a number of the symptoms of damage to some parts of the frontal lobes in humans appear to be related to this type of function, of altering behaviour when stimulus–reinforcement associations alter, as described next. Thus, some humans with frontal lobe damage can show impairments in a number of tasks in which an alteration of behavioural strategy is required in response to a change in environmental reinforcement contingencies (see Goodglass and Kaplan, 1979; Jouandet and Gazzaniga, 1979; Eslinger and Grattan, 1993; Kolb and Whishaw, 1996). For example, Milner (1963) showed that in the Wisconsin Card Sorting Task (in which cards are to be sorted according to the colour, shape or number of items on each card, depending on whether the examiner says 'right' or 'wrong' to each placement), some frontal patients either had difficulty in determining the first sorting principle, or in shifting to a second principle when required to. Also, in stylus mazes, frontal patients have difficulty in changing direction when a sound indicates that the correct path has been left (see Milner, 1982). It is of interest that, in both types of test, frontal patients may be able to verbalize the correct rules, yet may be unable to correct their behavioural sets or strategies appropriately. Some of the personality changes that can follow frontal lobe damage may also be related to a dysfunction in the alteration of stimulus–reinforcer associations. For example, the euphoria, irresponsibility, lack of affect and lack of concern for the present or future which can follow frontal lobe damage (see Hecaen and Albert, 1978; Damasio, 1994) may also be related to a dysfunction in altering behaviour appropriately in response to a change in reinforcement contingencies. Indeed, in so far as the orbitofrontal cortex is involved in the disconnection of stimulus–reinforcer associations, and such associations are important in learned emotional responses (see above), then it follows that the orbitofrontal cortex is involved in emotional responses by correcting stimulus–reinforcer associations when they become inappropriate.

These hypotheses, and the role in particular of the orbitofrontal cortex in human behaviour, have been investigated in recent studies in humans with damage to the ventral parts of the frontal lobe. (The description ventral is given to indicate that there was pathology in the orbitofrontal or related parts of the frontal lobe, and not in the more dorso-lateral parts of the frontal lobe.) A task which was directed at assessing the rapid alteration of stimulus–reinforcement associations was used, because the findings above indicate that the orbitofrontal cortex is involved in this type of learning. This was used instead of the Wisconsin Card Sorting Task, which requires patients to shift from category (or dimension) to category, e.g. from colour to shape, and clearly requires cognitive processing that is different from or additional to the stimulus–reinforcement association learning in which the orbitofrontal cortex is implicated. The task used was visual discrimination reversal, in which patients could learn to obtain points by touching one stimulus when it appeared on a video monitor, but had to withhold a response when a different visual stimulus appeared, otherwise a point was lost. After the subjects had acquired the visual discrimination, the reinforcement contingencies unexpectedly reversed. The patients with

Table 1. Vocal and face expression identification in patients with damage to the ventral parts of the frontal lobes and in control patients. Also shown are the number of reversals completed in 30 trials, and the number of the last trial on which an error occurred during reversal or extinction. Data are from Rolls *et al.* (1994) and Hornak *et al.* (1996)

	Behaviour Quest.	Subjective emotional change	Face expression % correct (SD)	Vocal expression % correct (SD)	No. of reversals	Last error reversal	Extinction
Ventral frontal							
Case no.							
1	6.0	–	29 (–6.5)[b]	42 (–3.7)[b]	0 (76%)	38F	–
2	4.0	2.0	84 (–0.4)	30 (–4.8)[b]	0 (83%)	50F	30F (93%)
3	6.0	7.5	60 (–3.1)[b]	36 (–4.9)[b]	0 (75%)	20F	–
4	7.5	4.5	60 (–3.0)[b]	54 (–2.5)[b]	0 (67%)	30F	–
5	8.5	7.0	58 (–3.2)[b]	39 (–4.0)[b]	–	–	34F
6	5.0	1.5	75 (–1.3)	67 (–1.3)	0 (54%)	51F	53F (38%)
7	6.0	5.0	67 (–2.3)[b]	58 (–2.1)[b]	2	4	30F (86%)
8	7.0	2.5	54 (–3.7)[b]	–	0 (100%)	50F	48F (93%)
9	4.0	1.5	83 (–0.4)	81 (+0.1)	2	5	36 (45%)
10	5.0	4.0	67 (–2.2)[b]	60 (–1.9)[a]	1	23	9
11	4.5	6.5	40 (–5.3)[b]	53 (–2.6)[b]			
12	3.0		38 (–5.6)[b]	43 (–3.5)[b]			
Medians	5.5	4.3	60	53	0	30	34
Non-ventral							
Case no.							
1	0.0	0.5	79 (–0.9)		2 (14%)	4	21 (43%)
2	2.5	1.0	83 (–0.4)		2 (46%)	11	12 (36%)
3	0.5	0.0	83 (–0.4)	61 (–1.8)[a]	2 (25%)	7	4 (7%)
4	0.0	2.0	75 (–1.4)	61 (–1.8)[a]	2 (8%)	4	3 (7%)
5	0.0	1.5	71 (–1.8)[a]	67 (–1.2)	1	14	13 (21%)
6	2.0	1.0	92 (+0.6)	75 (–0.5)	2 (42%)	13	100 (0%)
7	2.5	1.0	75 (–1.4)	61 (–1.8)[a]			
8	0.0	2.5	96 (+0.1)	78 (–0.2)			
9	0.5	1.0	67 (–2.3)[b]				
10	1.0	1.5	79 (–0.9)	72 (–0.7)			
11	0.5	1.0	83 (–0.4)	61 (–1.8)[a]			
12							4 (7%)
13					2 (8%)	4	4 (7%)
Medians	0.5	1.0	79	64	2	7	4

Behaviour Quest., Behaviour Questionnaire.
SD, number of standard deviations above (+) or below (–) the means for normal subjects.
[a]Scores which fall below the 5th centile of the normal distribution, i.e. SD < –1.64 (impaired).
[b]Scores which fall below the 1st centile of the normal distribution, i.e. SD < –1.96 (severely impaired).
The median values for reversal and extinction are for a larger group.
F, failed to reach criterion in reversal or extinction.
The % columns refer for reversal and extinction to the percentage of errors of commission, i.e. responses made to the stimulus that was before reversal or extinction the reward-related stimulus (old S+).

ventral frontal lesions made more errors in the reversal task (or in a similar extinction task in which the reward was no longer given), and completed fewer reversals, than control patients with damage elsewhere in the frontal lobes or in other brain regions (Rolls *et al.*, 1994; see Table 1). The impairment correlated statistically significantly with the socially inappropriate or disinhibited behaviour of the patients (assessed in a Behaviour Questionnaire) (see Table 1; Spearman $\rho = 0.76$), and also with their subjective evaluation of the changes in their emotional state since the brain damage [see Table 1 and Rolls *et al.* (1994); Spearman $\rho = 0.66$]. The patients were not impaired at other types of memory task, such as paired associate learning. The continued choice of the no longer rewarded stimulus in the reversal of the visual discrimination task is interpreted as a failure to reverse stimulus–reinforcer, i.e. sensory–sensory, associations, and not as motor response perseveration which may follow much more dorsal damage to the frontal lobes, and this is being investigated further in this type of patient. However, I note that one of the types of evidence which bears very directly on this comes from the responses of orbitofrontal cortex neurons. The evidence comes from the neurons which respond in relation to a sensory stimulus, such as a visual stimulus, when it is paired with another sensory stimulus to which the neuron responds, such as a taste stimulus. The taste stimulus is a primary reinforcer. These neurons do not respond to motor responses, and could not be involved in stimulus to motor response association learning. Bechara and colleagues also have findings which are consistent with these in patients with frontal lobe damage when they perform a gambling task (Bechara *et al.*, 1994, 1996, 1997; see also Damasio, 1994). The patients could choose cards from two piles. The patients with frontal damage were more likely to choose cards from a pile which did give rewards with a reasonable probability,

but also had occasional very heavy penalties, resulting in lower net gains than choices from the other pile. In this sense, the patients were not affected by the negative consequences of their actions: they did not switch from the pile of cards which was providing significant rewards even when large punishments were incurred.

It is of interest that in the reversal and extinction tasks, the patients can often verbalize the correct response, yet commit the incorrect action (Rolls *et al.*, 1994). This is consistent with the hypothesis that the orbitofrontal cortex is normally involved in executing behaviour when the behaviour is performed by evaluating the reinforcement associations of environmental stimuli (see below). The orbitofrontal cortex appears to be involved in this in both humans and non-human primates, when the learning must be performed rapidly, in for example acquisition, and during reversal.

An idea of how such stimulus–reinforcer learning may play an important role in normal human behaviour, and may be related to the behavioural changes seen clinically in these patients with ventral frontal lobe damage, can be provided by summarizing the behavioural ratings given by the carers of these patients. The patients were rated high in the Behaviour Questionnaire on at least some of the following: disinhibited or socially inappropriate behaviour, misinterpretation of other people's moods, impulsiveness, unconcern or underestimation of the seriousness of their condition, and lack of initiative (Rolls *et al.*, 1994). Such behavioural changes correlated statistically with the stimulus–reinforcer reversal and extinction learning impairment [see above, Table 1, and Rolls *et al.* (1994)]. The suggestion thus is that the insensitivity to reinforcement changes in the learning task may be at least part of what produces the changes in behaviour found in these patients with ventral frontal lobe damage. The more general impact on the behaviour of these patients is that their irresponsibility tended to affect their everyday lives. For example, if such patients had received their brain damage in a road traffic accident, and compensation had been awarded, the patients often tended to spend their money without appropriate concern for the future, sometimes, for example, buying a very expensive car. Such patients often find it difficult to invest in relationships too, and are sometimes described by their family as having changed personalities, in that they care less about a wide range of factors than before the brain damage. The suggestion that follows from this is that the orbitofrontal cortex may normally be involved in much social behaviour, and the ability to respond rapidly and appropriately to social reinforcers is of course an important aspect of primate (including human) social behaviour.

To investigate the possible significance of face-related inputs to orbitofrontal visual neurons described above, we also tested the responses of these patients to faces. We included tests of face (and also voice) expression decoding, because these are ways in which the reinforcing quality of individuals is often indicated. Impairments in the identification of facial and vocal emotional expression were demonstrated in a group of patients with ventral frontal lobe damage who had socially inappropriate behaviour (Hornak *et al.*, 1996; see Tables 1–3). The expression identification impairments could occur independently of perceptual impairments in facial recognition, voice discrimination or environmental sound recognition. The face and voice expression problems did not necessarily occur together in the same patients, providing an indication of separate processing. The impairment was found on most expressions apart from happy (which as the only positive face expression was relatively easy to discriminate from the others), with sad, angry, frightened and disgusted showing lower identification than surprised and neutral (see Table 2). Poor performance on both expression tests was correlated with the degree of alteration of emotional experience reported by the patients (Spearman $\rho = 0.88$). There was also a statistically strong positive (Pearson) correlation between the degree of altered emotional experience and the severity of the behavioural problems (e.g. disinhibition) found in these patients [see Hornak *et al.* (1996) and Table 1; Spearman $\rho = 0.66$]. A comparison group of patients with brain damage outside the ventral frontal lobe region, without these behavioural problems, was unimpaired on the face expression identification test, was significantly less impaired at vocal expression identification, and reported little subjective emotional change [see Hornak *et al.* (1996) and Table 1]. In current studies, these investigations are being extended, and it is being found that patients with face expression decoding problems do not necessarily have impairments at visual discrimination reversal, and vice versa. This is consistent with some topography in the orbitofrontal cortex (see, for example, Rolls and Baylis, 1994).

To elucidate the role of the human orbitofrontal cortex in emotion further, Rolls *et al.* (1997a) and Francis *et al.* (1999) performed an investigation to determine where the pleasant affective component of touch is represented in the brain. Touch is a primary reinforcer that can produce pleasure. They found with fMRI that a weak but very pleasant touch of the hand with velvet produced much stronger activation of the orbitofrontal cortex than a more intense but affectively neutral touch of the hand with wood. In contrast, the affectively neutral but more intense touch produced more activation of the primary somatosensory cortex than the pleasant stimuli. These findings indicate that part of the orbitofrontal cortex is concerned with representing the positively affective aspects of somatosensory stimuli. The significance of this finding is that a primary reinforcer that can produce affectively positive emotional responses is represented in the human orbitofrontal cortex. This provides one of the bases for the human orbitofrontal cortex to be involved in the stimulus–reinforcement association learning that provides the basis for emotional learning. In more recent studies, Rolls *et al.* (in preparation) are finding that there is also a representation of the affectively negative aspects of touch, including pain, in the human orbitofrontal cortex. This is consistent with the reports that humans with damage to the ventral part of the frontal lobe may report that they know that a stimulus is pain producing, but that the pain does not feel very bad to them (see Freeman and Watts, 1950; Valenstein, 1974; Melzack and Wall, 1996). It will be of interest to determine whether the regions of the human orbitofrontal cortex

Table 2. Facial expression identification. Group mean per cent correct on each emotion in normal subjects and in impaired ventral frontal patients. Data are from Hornak *et al.* (1996)

	Sad	Angry	Frightened	Disgusted	Surprised	Happy	Neutral
Normal subjects (N = 11)	68.6	94.7	77.6	81.8	92.0	100.0	93.9
Frontal patients (N = 9)	22.6	39.3	31.9	48.1	66.2	94.0	65.7

Table 3. Vocal expression identification. Group mean per cent correct on each emotion in normal subjects and in impaired ventral frontal patients. Data are from Hornak *et al.* (1996)

	Sad	Angry	Frightened	Disgusted	Puzzled	Contented
Normal subjects (N = 10)	80.8	66.1	88.1	95.0	78.9	68.9
Frontal patients (N = 7)	14.7	25.0	52.8	80.9	42.8	33.3

that represent pleasant touch and pain are close topologically or overlap. Even if fMRI studies show that the areas overlap, it would nevertheless be the case that different populations of neurons were being activated, for this is what recordings from single cells in monkeys indicate about positively versus negatively affective taste, olfactory and visual stimuli (see above).

It is also of interest that nearby, but not overlapping, parts of the human orbitofrontal cortex are activated by taste stimuli (such as glucose) and by olfactory stimuli (such as vanilla) (Rolls *et al.*, 1997b; Francis *et al.*, 1999). It is not yet known from human fMRI studies whether it is the reinforcing aspects of taste and olfactory stimuli that are represented here, but this is likely in view of the findings in non-human primates (see Rolls, 1999a).

Conclusions

The investigations described here show that the primate orbitofrontal cortex is involved in representing primary (unlearned) reinforcers such as taste and touch, and in learning associations of other stimuli, such as visual and olfactory stimuli, with these primary reinforcers. For these reasons, the orbitofrontal cortex has important functions in motivational behaviour such as feeding and drinking, and in emotion and social behaviour (see Rolls, 1999a). The type of learning in which the orbitofrontal cortex is involved is stimulus–reinforcer association learning, which is a particular case of stimulus–stimulus association learning. The model for the implementation is a pattern association between the conditioned stimulus, which activates the output neurons through associatively modifiable synapses, and the primary reinforcer, which activates the neurons through non-modifiable synapses [see Rolls and Treves (1998), Chapters 2 and 6]. Once learned, the same conditioned stimulus will activate the output neurons, with no need for ongoing activity. If the contingency reverses, the synapses from the previous conditioned stimulus are no longer active when the output neuron is active, and the synapses become weaker by a process of long-term depression.

This type of memory is distinct from the type of working memory implemented in the dorsolateral and inferior convexity prefrontal areas. The model for the implementation of such working memories is an autoassociation neural network in which the memory state is kept active by continuously recirculating neuronal activity. The dorsolateral part of the prefrontal cortex receives inputs particularly from area 7 of the parietal cortex, and may be especially involved in spatial response working memory, while the inferior convexity prefrontal cortex receives activity particularly from the inferior temporal visual cortex, and may be more involved in object working memory (Fuster, 1996; Goldman-Rakic, 1996; Rolls and Treves, 1998). The orbitofrontal stimulus–reinforcer pattern association memory is also very distinct from the episodic declarative memory in which the hippocampal system is implicated. This system may store memories by forming arbitrary associations between conjunctive events which need not be reinforcers and which typically include a spatial component. The storage may occur using an autoassociation network which does not operate in a continuous attractor mode in order to store a memory (see Rolls, 1996b; Rolls and Treves, 1998).

One set of output pathways by which the orbitofrontal cortex implements these functions for behaviour is via the striatum (Rolls, 1996a, 1999a). Another output of the orbitofrontal cortex is to the hypothalamus, and it is probably by this route that hypothalamic neurons in primates come to respond to the sight and taste of food when hunger is present [see Fig. 2 and for further evidence Rolls (1999a), Chapter 2]. The functions of this output system, and the orbitofrontal cortex connections which are directed further caudal in the brainstem, include autonomic and endocrine responses learned and updated to changing environmental stimuli [see Rolls (1999a), Chapter 4].

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References

Barbas H. Anatomic organization of basoventral and mediodorsal visual recipient prefrontal regions in the rhesus monkey. Journal of Comparative Neurology 1988; 276: 313–42.

Barbas H. Organization of cortical afferent input to the orbitofrontal area in the rhesus monkey. Neuroscience 1993; 56: 841–64.

Barbas H. Anatomic basis of cognitive-emotional interactions in the primate prefrontal cortex. Neuroscience and Biobehavioural Reviews 1995; 19: 499–510.

Barbas H, Pandya D N. Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. Journal of Computational Neurology 1989; 286: 353–75.

Baylis LL, Gaffan D. Amygdalectomy and ventromedial prefrontal ablation produce similar deficits in food choice and in simple object discrimination learning for an unseen reward. Experimental Brain Research 1991; 86: 617–22.

Baylis LL, Rolls ET. Responses of neurons in the primate taste cortex to glutamate. Physiology and Behavior 1991; 49: 973–9.

Baylis LL, Rolls ET, Baylis GC. Afferent connections of the orbitofrontal cortex taste area of the primate. Neuroscience 1994; 64: 801–12.

Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 1994; 50: 7–15.

Bechara A, Tranel D, Damasio H, Damasio AR. Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. Cerebral Cortex 1996; 6: 215–25.

Bechara A, Damasio H, Tranel D, Damasio AR. Deciding advantageously before knowing the advantageous strategy. Science 1997; 275: 1293–5.

Booth MCA, Rolls ET. View-invariant representations of familiar objects by neurons in the inferior temporal visual cortex. Cerebral Cortex 1998; 8: 510–23.

Booth MCA, Rolls ET, Critchley HD, Browning AS, Hernadi I. Face-selective neurons in the primate orbitofrontal cortex. Society for Neuroscience Abstracts 1998; 24: 898.

Butter CM. Perseveration in extinction and in discrimination reversal tasks following selective prefrontal ablations in *Macaca mulatta*. Physiology and Behavior 1969; 4: 163–71.

Butter CM, Snyder DR. Alterations in aversive and aggressive behaviors following orbitofrontal lesions in rhesus monkeys. Acta Neurobiologiae Experimentalis 1972; 32: 525–65.

Butter CM, McDonald JA, Snyder DR. Orality, preference behavior, and reinforcement value of non-food objects in monkeys with orbital frontal lesions. Science 1969; 164: 1306–7.

Butter CM, Snyder DR, McDonald JA. Effects of orbitofrontal lesions on aversive and aggressive behaviors in rhesus monkeys. Journal of Comparative and Physiological Psychology 1970; 72: 132–44.

Carmichael ST, Price JL. Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. Journal of Comparative Neurology 1994; 346: 366–402.

Carmichael ST, Price JL. Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. Journal of Comparative Neurology 1995; 363: 642–64.

Carmichael ST, Clugnet M-C, Price JL. Central olfactory connections in the macaque monkey. Journal of Comparative Neurology 1994; 346: 403–34.

Critchley HD, Rolls ET. Olfactory neuronal responses in the primate orbitofrontal cortex: analysis in an olfactory discrimination task. Journal of Neurophysiology 1996a; 75: 1659–72.

Critchley HD, Rolls ET. Hunger and satiety modify the responses of olfactory and visual neurons in the primate orbitofrontal cortex. Journal of Neurophysiology 1996b; 75: 1673–86.

Critchley HD, Rolls ET. Responses of primate taste cortex neurons to the astringent tastant tannic acid. Chemical Senses 1996c; 21: 135–45.

Critchley HD, Rolls ET, Wakeman EA. Orbitofrontal cortex responses to the texture, taste, smell and sight of food. Appetite 1993; 21: 170.

Damasio AR. Descartes' error. New York: Putnam, 1994.

Divac I, Rosvold HE, Szwarcbart M.K. Behavioral effects of selective ablation of the caudate nucleus. Journal of Comparative and Physiological Psychology 1967; 63: 184–90.

Eslinger PJ, Grattan LM. Frontal lobe and frontal-striatal substrates for different forms of human cognitive flexibility. Neuropsychologia 1993; 31: 17–28.

Francis S, Rolls ET, Bowtell R, McGlone F, O'Doherty J, Browning A *et al.* The representation of the pleasantness of touch in the human brain, and its relation to taste and olfactory areas. Neuroreport 1999; 10: 453–9.

Freeman WJ, Watts JW. Psychosurgery in the treatment of mental disorders and intractable pain. 2nd ed. Springfield, IL: Thomas, 1950.

Fuster JM. The prefrontal cortex. 3rd ed. New York: Raven Press, 1996.

Goldman-Rakic PS. The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. Philosophical Transactions of the Royal Society of London Series B 1996; 351: 1445–53.

Goodglass H, Kaplan E. Assessment of cognitive deficit in brain-injured patient. In: Gazzaniga MS, editor. Handbook of behavioral neurobiology. Vol. 2 Neuropsychology. New York: Plenum, 1979: 3–22.

Hasselmo ME, Rolls ET, Baylis GC. The role of expression and identity in the face-selective responses of neurons in the temporal visual cortex of the monkey. Behavioural Brain Research 1989; 32: 203–18.

Hecaen H, Albert ML. Human neuropsychology. New York: Wiley, 1978.

Hornak J, Rolls ET, Wade D. Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. Neuropsychologia 1996; 34: 247–61.

Insausti R, Amaral DG, Cowan WM. The entorhinal cortex of the monkey. II. Cortical afferents. Journal of Comparative Neurology 1987; 264: 356–95.

Iversen SD, Mishkin M. Perseverative interference in monkey following selective lesions of the inferior prefrontal convexity. Experimental Brain Research 1970; 11: 376–86.

Johnson TN, Rosvold HE, Mishkin M. Projections from behaviorally defined sectors of the prefrontal cortex to the basal ganglia, septum and diencephalon of the monkey. Experimental Neurology 1968; 21: 20–34.

Jones B, Mishkin M. Limbic lesions and the problem of stimulus-reinforcement associations. Experimental Neurology 1972; 36: 362–77.

Jones-Gotman M, Zatorre RJ. Olfactory identification in patients with focal cerebral excision. Neuropsychologia 1988; 26: 387–400.

Jouandet M, Gazzaniga MS. The frontal lobes. In: Gazzaniga MS, editor. Handbook of behavioral neurobiology. Vol. 2 Neuropsychology. New York: Plenum, 1979: 25–59.

Kemp JM, Powell TPS. The cortico-striate projections in the monkey. Brain 1970; 93: 525–46.

Kolb B, Whishaw IQ. Fundamentals of human neuropsychology. 4th ed. New York: Freeman, 1996.

Kowalska D-M, Bachevalier J, Mishkin M. The role of the inferior prefrontal convexity in performance of delayed nonmatching-to-sample. Neuropsychologia 1991; 29: 583–600.

Melzack R, Wall PD. The challenge of pain. Harmondsworth: Penguin, 1996.

Milner B. Effects of different brain lesions on card sorting. Archives of Neurology 1963; 9: 90–100.

Milner B. Some cognitive effects of frontal-lobe lesions in man. Philosophical Transactions of the Royal Society of London Series B 1982; 298: 211–26.

Mishkin M, Manning FJ. Non-spatial memory after selective prefrontal lesions in monkeys. Brain Research 1978; 143: 313–24.

Mora F, Avrith DB, Phillips AG, Rolls ET. Effects of satiety on self-stimulation of the orbitofrontal cortex in the monkey. Neuroscience Letters 1979; 13: 141–5.

Mora F, Avrith DB, Rolls ET. An electrophysiological and behavioural study of self-stimulation in the orbitofrontal cortex of the rhesus monkey. Brain Research Bulletin 1980; 5: 111–5.

Morecraft RJ, Geula C, Mesulam M-M. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. Journal of Comparative Neurology 1992; 323: 341–58.

Nauta WJH. Neural associations of the frontal cortex. Acta Neurobiologiae Experimentalis 1972; 32: 125–40.

Pandya DN, Yeterian EH. Comparison of prefrontal architecture and connections. Philosophical Transactions of the Royal Society of London Series B 1996; 351: 1423–31.

Passingham R. Delayed matching after selective prefrontal lesions in monkeys (*Macaca mulatta*). Brain Research 1975; 92: 89–102.

Petrides M, Pandya DN. Comparative architectonic analysis of the human and macaque frontal cortex. In: Boller F, Grafman J, editors. Handbook of neuropsychology 9. Amsterdam: Elsevier Science, 1994: 17–58.

Price JL. Networks within the orbital and medial prefrontal cortex. Neurocase 1999; 5: 231–41.

Price JL, Carmichael ST, Carnes KM, Clugnet M-C, Kuroda M, Ray JP. Olfactory input to the prefrontal cortex. In: Davis JL, Eichenbaum H, editors. Olfaction:

a model system for computational neuroscience. Cambridge, MA: MIT Press, 1991: 101–20.
Rolls ET. Neurons in the cortex of the temporal lobe and in the amygdala of the monkey with responses selective for faces. Human Neurobiology 1984a; 3: 209–22.
Rolls ET. Activity of neurons in different regions of the striatum of the monkey. In: McKenzie JS, Kemm RE, Wilcox LN, editors. The basal ganglia: structure and function. New York: Plenum, 1984b: 467–93.
Rolls ET. A theory of emotion, and its application to understanding the neural basis of emotion. In: Oomura Y, editor. Emotions. Neural and chemical control. Tokyo: Japan Scientific Societies Press; Basel: Karger, 1986a: 325–44.
Rolls ET. Neural systems involved in emotion in primates. In: Plutchik R, Kellerman H, editors. Emotion: theory, research, and experience. Vol. 3: Biological foundations of emotion. New York: Academic Press, 1986b: 125–43.
Rolls ET. Information processing in the taste system of primates. Journal of Experimental Biology 1989; 146: 141–64.
Rolls ET. A theory of emotion, and its application to understanding the neural basis of emotion. Cognition and Emotion 1990; 4: 161–90.
Rolls ET. Neurophysiological mechanisms underlying face processing within and beyond the temporal cortical visual areas. Philosophical Transactions of the Royal Society of London Series B 1992a; 335: 11–21.
Rolls ET. Neurophysiology and functions of the primate amygdala. In: Aggleton JP, editor. The amygdala. New York: Wiley-Liss, 1992b: 143–65.
Rolls ET. Brain mechanisms for invariant visual recognition and learning. Behavioural Processes 1994a; 33: 113–38.
Rolls ET. Neurophysiology and cognitive functions of the striatum. Revue Neurologique (Paris) 1994b; 150: 648–60.
Rolls ET. Neural processing related to feeding in primates. In: Legg CR, Booth DA, editors. Appetite: neural and behavioural bases. Oxford: Oxford University Press, 1994c: 11–53.
Rolls ET. Central taste anatomy and neurophysiology. In: Doty RL, editor. Handbook of olfaction and gustation. New York: Dekker, 1995a: 549–73.
Rolls ET. A theory of emotion and consciousness, and its application to understanding the neural basis of emotion. In: Gazzaniga MS, editor. The cognitive neurosciences. Cambridge, MA: MIT Press, 1995b: 1091–106.
Rolls ET. The orbitofrontal cortex. Philosophical Transactions of the Royal Society of London Series B 1996a; 351: 1433–44.
Rolls ET. A theory of hippocampal function in memory. Hippocampus 1996b; 6: 601–20.
Rolls ET. Taste and olfactory processing in the brain and its relation to the control of eating. Critical Reviews in Neurobiology 1997a; 11: 263–87.
Rolls ET. A neurophysiological and computational approach to the functions of the temporal lobe cortical visual areas in invariant object recognition. In: Jenkin M, Harris L, editors. Computational and psychophysical mechanisms of visual coding. Cambridge: Cambridge University Press, 1997b: 184–220.
Rolls ET. The brain and emotion. Oxford: Oxford University Press, 1999a.
Rolls ET. Taste, olfactory, visual and somatosensory representations of the sensory properties of foods in the brain, and their relation to the control of food intake. In: Seeley RJ, Berthoud H-R, editors. Neural control of macronutrient selection. Boca Raton, FL: CRC Press, 1999b.
Rolls ET. Neurophysiology and functions of the primate amygdala and connected structures. In: Aggleton JP, editor. The amygdala. Oxford: Oxford University Press, 2000.
Rolls ET, Baylis GC. Size and contrast have only small effects on the responses to faces of neurons in the cortex of the superior temporal sulcus of the monkey. Experimental Brain Research 1986; 65: 38–48.
Rolls ET, Baylis LL. Gustatory, olfactory and visual convergence within the primate orbitofrontal cortex. Journal of Neuroscience 1994; 14: 5437–52.
Rolls ET, Johnstone S. Neurophysiological analysis of striatal function. In: Vallar G, Cappa SF, Wallesch CW, editors. Neuropsychological disorders associated with subcortical lesions. Oxford: Oxford University Press, 1992: 61–97.
Rolls ET, Rolls JH. Olfactory sensory-specific satiety in humans. Physiology and Behavior 1997; 61: 461–73.
Rolls ET, Treves A. Neural networks and brain function. Oxford: Oxford University Press, 1998.
Rolls ET, Judge SJ, Sanghera M. Activity of neurones in the inferotemporal cortex of the alert monkey. Brain Research 1977; 130: 229–38.
Rolls ET, Burton MJ, Mora F. Neurophysiological analysis of brain-stimulation reward in the monkey. Brain Research 1980; 194: 339–57.
Rolls ET, Thorpe SJ, Maddison SP. Responses of striatal neurons in the behaving monkey. 1. Head of the caudate nucleus. Behavioural Brain Research 1983a; 7: 179–210.
Rolls ET, Rolls BJ, Rowe EA. Sensory-specific and motivation-specific satiety for the sight and taste of food and water in man. Physiology and Behavior 1983b; 30: 185–92.
Rolls ET, Scott TR, Sienkiewicz ZJ, Yaxley S. The responsiveness of neurones in the frontal opercular gustatory cortex of the macaque monkey is independent of hunger. Journal of Physiology 1988; 397: 1–12.
Rolls ET, Sienkiewicz ZJ, Yaxley S. Hunger modulates the responses to gustatory stimuli of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. European Journal of Neuroscience 1989; 1: 53–60.
Rolls ET, Yaxley S, Sienkiewicz ZJ. Gustatory responses of single neurons in the orbitofrontal cortex of the macaque monkey. Journal of Neurophysiology 1990; 64: 1055–66.
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.
Rolls ET, Critchley H, Wakeman EA, Mason R. Responses of neurons in the primate taste cortex to the glutamate ion and to inosine 5′-monophosphate. Physiology and Behavior 1996a; 59: 991–1000.
Rolls ET, Critchley H, Mason R, Wakeman EA. Orbitofrontal cortex neurons: role in olfactory and visual association learning. Journal of Neurophysiology 1996b; 75: 1970–81.
Rolls ET, Critchley HD, Treves A. The representation of olfactory information in the primate orbitofrontal cortex. Journal of Neurophysiology 1996c; 75: 1982–96.
Rolls ET, Francis S, Bowtell R, Browning D, Clare S, Smith E *et al.* Taste and olfactory activation of the orbitofrontal cortex. Neuroimage 1997a; 5: S199.
Rolls ET, Francis S, Bowtell R, Browning D, Clare S, Smith E *et al.* Pleasant touch activates the orbitofrontal cortex. Neuroimage 1997b; 5: S17.
Rolls ET, Critchley HD, Browning A, Hernadi I. The neurophysiology of taste and olfaction in primates, and umami flavor. In: Murphy C, editor. Olfaction and taste. Vol. XII. Annals of the New York Academy of Sciences 1998; 855: 426–37.
Rolls ET, Critchley HD, Browning AS, Hernadi I, Lenard L. Responses to the sensory properties of fat of neurons in the primate orbitofrontal cortex. Journal of Neuroscience 1999; 19: 1532–40.
Rosenkilde CE. Functional heterogeneity of the prefrontal cortex in the monkey: a review. Behavioural and Neural Biology 1979; 25: 301–45.
Rosenkilde CE, Bauer RH, Fuster JM. Single unit activity in ventral prefrontal cortex in behaving monkeys. Brain Research 1981; 209: 375–94.
Schoenbaum G, Eichenbaum H. Information encoding in the rodent prefrontal cortex. I. Single-neuron activity in orbitofrontal cortex compared with that in pyriform cortex. Journal of Neurophysiology 1995; 74: 733–50.
Scott TR, Yaxley S, Sienkiewicz ZJ, Rolls ET. Gustatory responses in the frontal opercular cortex of the alert cynomolgus monkey. Journal of Neurophysiology 1986; 56: 876–90.
Seltzer B, Pandya DN. Frontal lobe connections of the superior temporal sulcus in the rhesus monkey. Journal of Comparative Neurology 1989; 281: 97–113.
Takagi SF. Olfactory frontal cortex and multiple olfactory processing in primates. In: Peters A, Jones EG, editors. Cerebral cortex. 9. New York: Plenum Press, 1991: 133–52.
Thorpe SJ, Rolls ET, Maddison S. Neuronal activity in the orbitofrontal cortex of the behaving monkey. Experimental Brain Research 1983; 49: 93–115.
Valenstein ES. Brain control. A critical examination of brain stimulation and psychosurgery. New York: Wiley, 1974.
Wallis G, Rolls ET. Invariant face and object recognition in the visual system. Progress in Neurobiology 1997; 51: 167–94.
Williams GV, Rolls ET, Leonard CM, Stern C. Neuronal responses in the ventral striatum of the behaving monkey. Behaviour Brain Research 1993; 55: 243–52.
Wilson FAW, Scalaidhe SPO, Goldman-Rakic PS. Dissociation of object and spatial processing domains in primate prefrontal cortex. Science 1993; 260: 1955–8.
Yaxley S, Rolls ET, Sienkiewicz ZJ. The responsiveness of neurones in the insular gustatory cortex of the macaque monkey is independent of hunger. Physiology and Behavior 1988; 42: 223–9.
Yaxley S, Rolls ET, Sienkiewicz ZJ. Gustatory responses of single neurons in the insula of the macaque monkey. Journal of Neurophysiology 1990; 63: 689–700.
Zatorre RJ, Jones-Gotman M. Human olfactory discrimination after unilateral frontal or temporal lobectomy. Brain 1991; 114: 71–84.
Zatorre RJ, Jones-Gotman M, Evans AC, Meyer E. Functional localization of human olfactory cortex. Nature 1992; 360: 339–40.

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