The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology

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Abstract

The human orbitofrontal cortex is an important brain region for the processing of rewards and punishments, which is a prerequisite for the complex and flexible emotional and social behaviour which contributes to the evolutionary success of humans. Yet much remains to be discovered about the functions of this key brain region, and new evidence from functional neuroimaging and clinical neuropsychology is affording new insights into the different functions of the human orbitofrontal cortex. We review the neuroanatomical and neuropsychological literature on the human orbitofrontal cortex, and propose two distinct trends of neural activity based on a meta-analysis of neuroimaging studies. One is a mediolateral distinction, whereby medial orbitofrontal cortex activity is related to monitoring the reward value of many different reinforcers, whereas lateral orbitofrontal cortex activity is related to the evaluation of punishers which may lead to a change in ongoing behaviour. The second is a posterior–anterior distinction with more complex or abstract reinforcers (such as monetary gain and loss) represented more anteriorly in the orbitofrontal cortex than simpler reinforcers such as taste or pain. Finally, we propose new neuroimaging methods for obtaining further evidence on the localisation of function in the human orbitofrontal cortex.
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1. Introduction

Over the last hundred years we have learned more about the localisation of function in the human brain than in the rest of recorded history. The early, poorly founded efforts of phrenology as practiced by Gall and his followers have been replaced by a corpus of solid neuroscientific evidence from experiments in other animals. Even so, with the advent of human neuroimaging over the last 15–20 years, there have been some who use this technique with its pretty pictures of coloured blobs on brain slices almost as a modern-day phrenology. It is crucial that we remember that these pretty pictures can easily mislead us, and that their interpretation needs to take into account the wealth of scientific evidence obtained with different methods from both humans and other animals.

The orbitofrontal cortex provides in many ways a good example of how functional neuroimaging can advance our understanding of the functional role of a human brain region but also how it needs to take into account other neuroscientific research. Some of the functions of the primate orbitofrontal cortex have been previously elucidated in a variety of experiments in non-human primates (for reviews, see Rolls, 2000a, 2002, 2004). Some of the conclusions of this research are that the orbitofrontal cortex represents the changing and relative reward value of many different primary (unlearned) reinforcers such as taste and somatosensory stimuli; of many different secondary (learned) reinforcers including olfactory and visual stimuli; and learns and rapidly reverses associations between secondary and primary reinforcers, that is it implements stimulus-reinforcement association learning, which is the type of learning that is involved in emotion (Rolls, 1999a, 2002).

This review demonstrates how recent neuroimaging (and neuropsychological) experiments have confirmed the important functional role of the human orbitofrontal cortex in emotion. Neuroimaging experiments have, however, more to offer than mere confirmation of the phylogenetic continuity of brain function in primates. One of the main premises of this review is that neuroimaging offers important new spatial information on neural activity in the human orbitofrontal cortex, which can serve to further elucidate the functional role of the subareas within this brain region. We should remember though that functional neuroimaging has limitations in that there are many sometimes quite small populations of neurons with different responses to different types of stimulus or event in the orbitofrontal cortex and other brain regions which may not all be revealed by neuroimaging, which reflects the average metabolic demands of a brain region (Deco et al., in preparation; Rolls, 1999a). Further, brain imaging does not address the issue of the information that is represented by virtue of the different tuning of individual neurons (which are the computing elements of the brain), and so does not provide the evidence on which computational models of brain function must be based (Rolls and Deco, 2002). It is thus very important to consider the results of human functional neuroimaging in the light of what is known from complementary studies using for example neurophysiology in primates, and the effects of brain damage.

The focus of this review is on elucidating the functional neuroanatomy of the human orbitofrontal cortex. We first review the neuroanatomical data on the cytoarchitecture and connections of the orbitofrontal cortex, which is based on relevant information from other primates and humans. We then review a number of relevant studies from the human neuropsychological literature. We then proceed to perform a meta-analysis of existing neuroimaging studies in the literature to determine to what extent it is possible to localise different functions in separate parts of the orbitofrontal cortex.

2. Neuroanatomy of the orbitofrontal cortex

The primate orbitofrontal cortex occupies the ventral surface of the frontal part of the brain (see Fig. 1) and can be defined as the part of the prefrontal cortex that receives projections from the magnocellular, medial, nucleus of the mediodorsal thalamus (Fuster, 1997). This is in contrast to other parts of the prefrontal cortex which receive projections from other parts of the mediodorsal thalamus, such the dorsolateral prefrontal cortex which receives projections from the parvocellular, lateral, part of the mediodorsal thalamic nucleus; and the frontal eye fields (Brodmann's area 8) in the anterior bank of the arcuate sulcus which receive projections from the paralamellar part of the mediodorsal nucleus of the thalamus.

2.1. Cytoarchitecture of the orbitofrontal cortex

Brodmann (1905, 1909) carried out one of the first comprehensive cytoarchitectural analyses of both the human and the primate (specifically that of the *Cercopithecus* monkey) brain and subsequently assigned unique numbers to different cytoarchitectonic areas (see Fig. 2). Unfortunately, Brodmann was less detailed in his investigations of the orbitofrontal cortex, and his cytoarchitectonical maps were restricted to mapping areas 10, 11 and 47 in the human brain. Moreover, the homologies between the human and primate regions were not fully worked out, in that in the primate map, area 11 is extended laterally and area 12 has taken over the medial area occupied by area 11 in the human map, while area 47 is not included at all in the non-human primate map.

Clarification was provided by Walker (1940), who investigated the monkey species *Macaca fascicularis* to try to resolve the inconsistencies present in Brodmann's maps. The orbitofrontal cortex turned out to be much less homogenous than specified by Brodmann. Walker therefore proposed to parcellate the primate orbital surface into five distinct areas
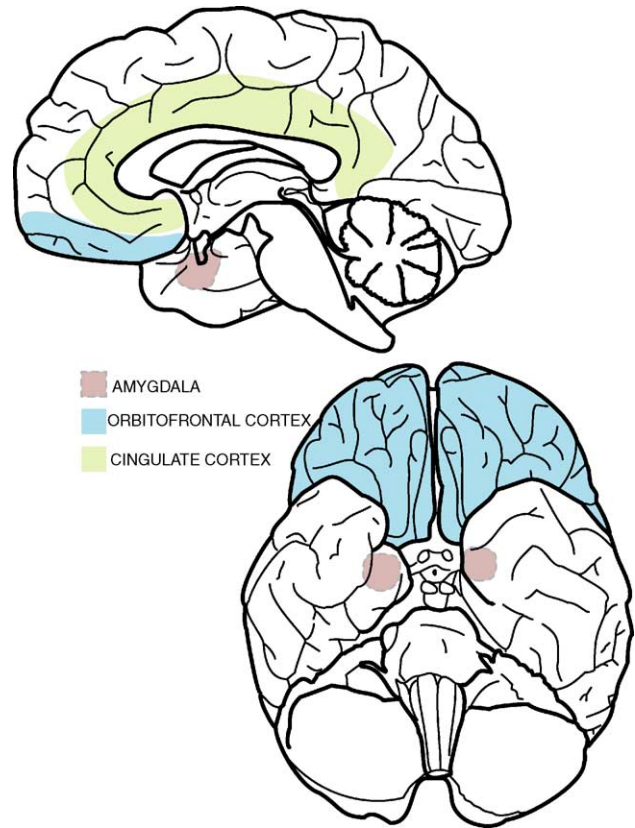
Fig. 1. Some of the key brain structures implicated in emotion. The position of the amygdala, orbitofrontal cortex and cingulate cortex are shown on a midsagittal view (top), and on a ventral view (bottom) of the human brain.

(areas 10, 11, 12, 13 and 14; see Fig. 3). Areas 12 and 13 occupy the lateral and medial orbital surface, respectively, while area 14 is on the ventromedial convexity near the gyrus rectus. Further anterior, area 10 occupies the frontal pole, while area 11 occupies the remaining anterior orbital surface.
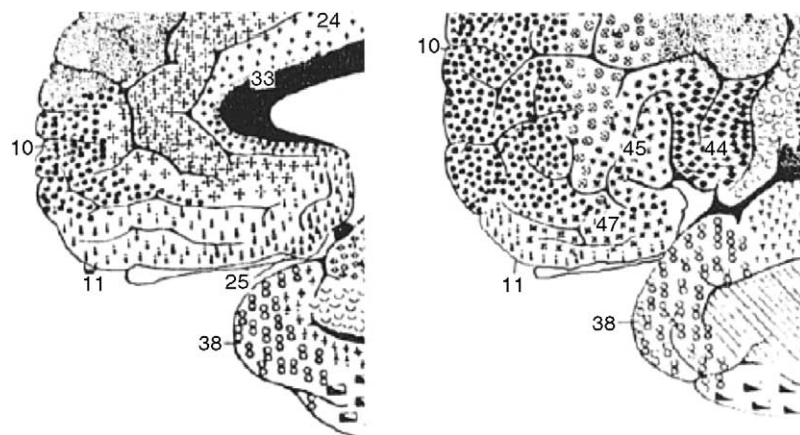
Fig. 2. Brodmann's original cytoarchitectonic maps of the human brain. On the left is shown a medial view of the cortical areas on the medial wall of the human brain, and on the right is shown a ventral view of the human brain. Notice how the cytoarchitecture of the orbitofrontal cortex is reduced to three areas 10, 11 and 47. Later investigations found it necessary to further subdivide the orbitofrontal cortex in order to reflect its heterogeneity.

Fig. 3. Progressive refinements in cytoarchitectonic maps in non-human primates. In (a) on the far left, the map of Walker (1940) of the areas in the monkey *Macaca fascicularis* is shown on views of the medial wall and the ventral surface. The orbitofrontal cortex is now parcelled into five areas (areas 10, 11, 12, 13 and 14) as an improvement to Brodmann's primate (and human) map. In the middle in (b) is shown the map of Petrides and Pandya (1994) where the differences in Brodmann's primate and human brain were reconciled with Walker's ma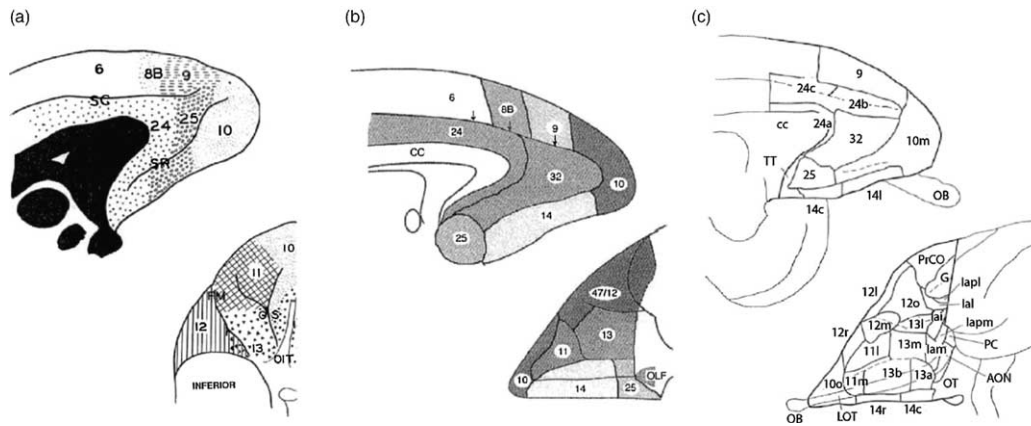p by naming the lateral parts of the orbitofrontal cortex area 47/12. On the far right in (c) is shown the redrawn map of Carmichael et al. (1994) where the orbitofrontal cortex was further subdivided into smaller subareas.

Area 47 from the human map was still not included in Walker's map, and subsequently Petrides and Pandya (1994) tried to reconcile the remaining inconsistencies between the human and monkey cytoarchitectonic maps by proposing to label the lateral parts of the orbitofrontal gyri as 47/12 (see Fig. 4). Another study (see Fig. 3) used nine different histochemical and immunohistochemical stains to further subdivide the orbitofrontal cortex into smaller subareas (Carmichael et al., 1994).

It has also been proposed that cytoarchitecturally and functionally the orbitofrontal cortex should be considered to be part of what is collectively called the orbital and medial prefrontal cortex (OMPFC, Öngür and Price, 2000). This network includes both the orbitofrontal cortex and

parts of the anterior cingulate cortex and has distinct connections to other parts of the brain. The orbital network receives input from all the sensory modalities including visceral afferents and is proposed to be important for the regulation of food intake, while the medial network has extensive visceromotor outputs (see Figs. 5 and 6, where the available anatomical information from monkeys has been extrapolated to humans). The two networks were therefore proposed, in the light also of neurophysiological studies (Rolls, 1997), to serve as a crucial sensory-visceromotor link for consummatory behaviours.

Another crucial cytoarchitectonic feature of the orbitofrontal cortices is the considerable variability between individuals. A recent study mapped the various orbital sulci
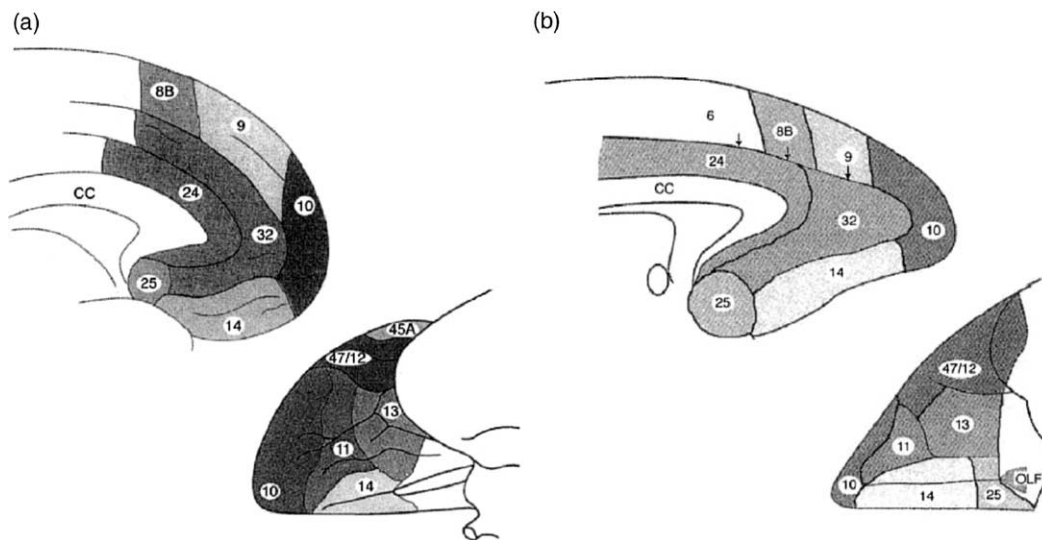

Fig. 4. Comparable monkey and human cytoarchitectonic maps. In (a) on the left are shown the cytoarchitectonic areas on the medial wall and on the ventral surface of the human brain proposed by Petrides and Pandya (1994). In (b) on the right are shown the homologous areas in the primate.

Fig. 5. Networks in the primate orbitofrontal cortex. The figures show the cytoarchitectonic areas and subareas on the medial wall on the left and on the orbital surface on the right. In (a) at the top of the figure are shown the areas and the spatial locations of some of the sensory inputs to the orbitofrontal cortex. In (b) is shown the orbital network, and in (c) is shown the medial network in the orbitofrontal cortex. From the medial network there are direct connections to various parts of the hypothalamus to influence the internal system (figure modified from Öngür and Price, 2000).

in both humans and monkeys (*Macaca mulatta*) using magnetic resonance imaging of 50 right-handed humans (22 women and 28 men) and photographs of 50 post-mortem monkey brains (Chiavaras and Petrides, 2000). Three main types of sulcal patterns were found in humans (see Fig. 7), with considerable variability even within each subtype. Generally, four main sulci were identified on the orbital surface: the olfactory, medial, lateral and transverse orbital sulci. These four sulci essentially subdivided the orbitofrontal cortex into four main gyri. The gyrus rectus (posteriorly area 14 and anteriorly parts of area 11) on the ventromedial convexity is delineated laterally by the olfactory sulcus and medially by the anterior sulcus on the ventromedial

surface. The medial and the lateral sulci run parallel (over areas 11, 13 and 47/12), and are connected by the transverse sulcus (usually forming the border between areas 13 and 11). This arrangement typically forms an 'H', 'K' or 'X' but is occasionally augmented by further orbitofrontal sulci such as the intermediate orbital sulci, the posterior orbital sulci and the sulcus fragmentosus. In 81% of the data the intermediate orbital sulci were observed anterior to the transverse orbital sulci. In 77% of the hemispheres either one or two longitudinal sulci were found posterior to the transverse orbital sulcus. This posterior orbital sulcus most often runs the entire extent of the posterior orbital region. In 10% of the hemispheres a small sulcus was

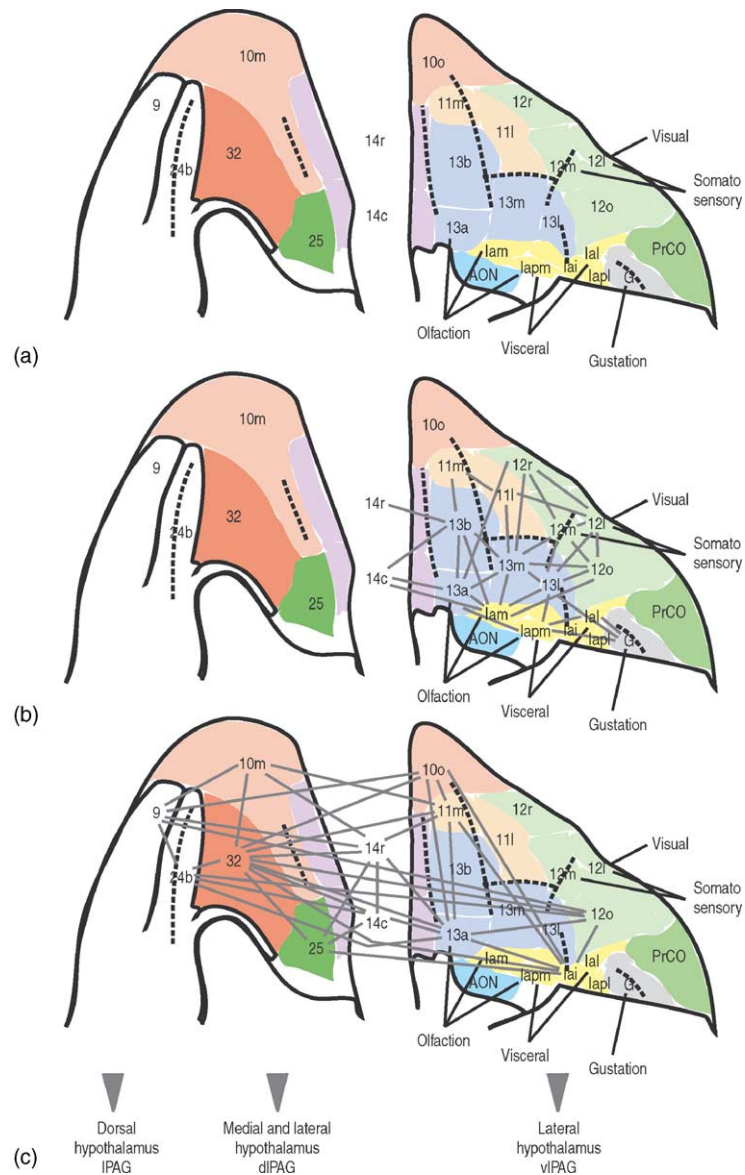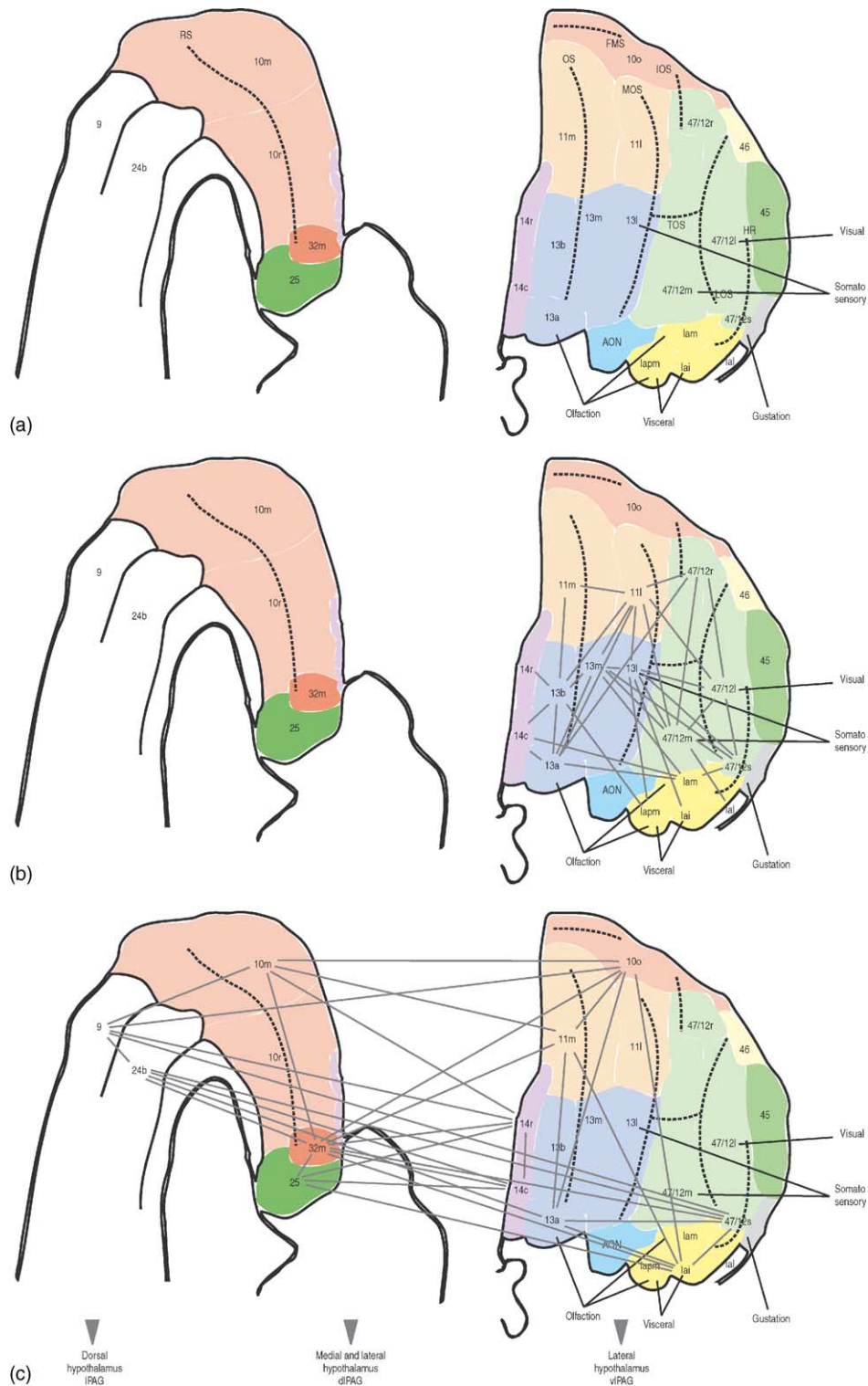Fig. 6. Putative networks in the human orbitofrontal cortex. The figures show the cytoarchitectonic areas and subareas on the medial wall on the left and on the orbital surface on the right of the human brain. The cytoarchitectonic maps of the human orbitofrontal cortex shown are based on the maps from Öngür and Price (2000), but extended to use the functional connectivity from studies in primates. In (a) at the top of the figure are shown the areas and the spatial locations of some of the sensory inputs to the orbitofrontal cortex. In (b) is shown the orbital network, and in (c) is shown the medial network with direct connections to various parts of the hypothalamus. Modified and extended with putative functional connectivity from Öngür and Price (2000).
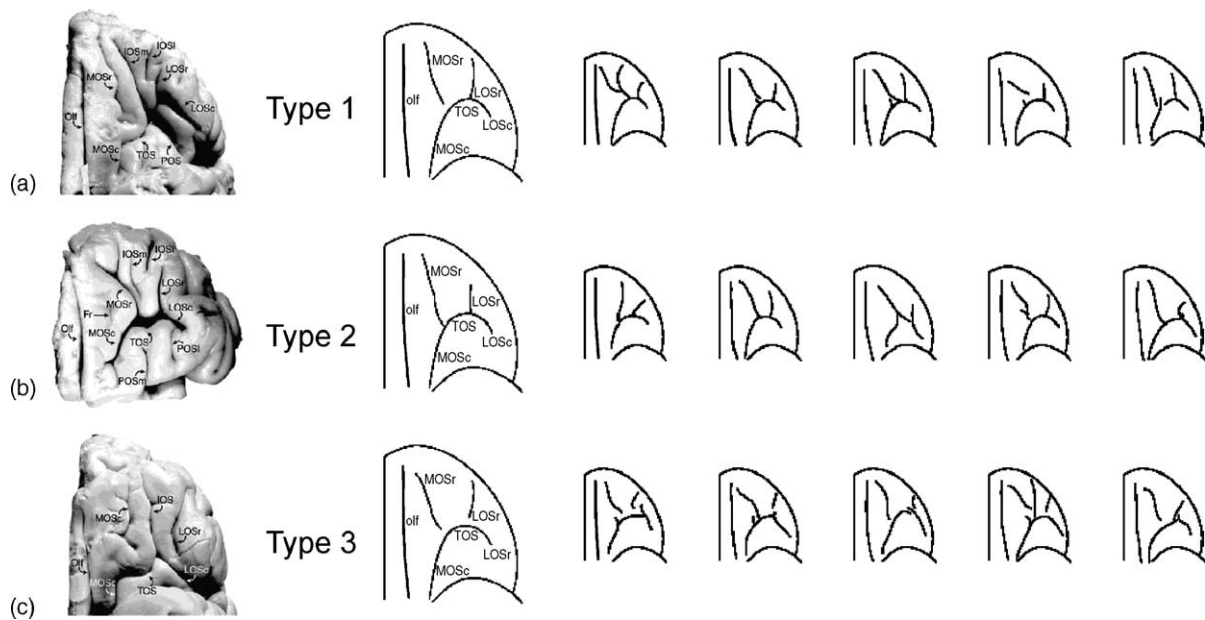
Fig. 7. Sulcal variability. The figure demonstrates the considerable variability of the sulcal patterns in the human orbitofrontal cortex. The three main types of sulcal types with the various subtypes are shown in a, b and c. On the left of the figure are shown ventral of views of the left hemispheres of human brains and on the right are shown schematic drawings of the three sulcal types and their subtypes (modified from Chiavaras and Petrides, 2001). Abbreviations used: Fr, sulcus fragmentosus; IOS, intermediate orbital sulcus; IOSl, lateral intermediate orbital sulcus; IOSm, medial intermediate orbital sulcus; LOS, lateral orbital sulcus; LOSc, caudal portion of lateral orbital sulcus; LOSr, rostral portion of lateral orbital sulcus; MOS, medial orbital sulcus; MOSc, caudal portion of medial orbital sulcus; MOSr, rostral portion of medial orbital sulcus; Olf, olfactory sulcus; POS, posterior orbital sulcus; POSl, lateral posterior orbital sulcus; POSm, medial posterior orbital sulcus; TOS, transverse orbital sulcus.

present between the olfactory sulcus and the medial orbital sulcus.

Similar variability was observed for the orbital surfaces in the monkeys, with only three major sulci: the olfactory sulcus, the medial orbital sulcus and the lateral orbital sulcus, which gave rise to three subtypes.

The considerable variability found in the orbitofrontal cortex can be further expressed in sulcal probability maps in standardised stereotaxic proportional space (Chiavaras and Petrides, 2001). The pattern of sulcal variability is also reflected in sulcal development (Chi et al., 1977), which follows two main trends, where sulci appearing in early gestation are much less variable than those sulci appearing later in development (see Fig. 8). In the mediolateral trend the sulcal variability increases from the medial to the lateral part of the orbital sulcus, while in the posterior–anterior trend the sulcal variability increases from posterior regions to anterior regions.

The mediolateral trend starts with the olfactory sulcus, which is the least variable of the orbital sulci with a large area common to over 90% of subjects. The olfactory sulcus is first visible after only 16 weeks which is thus comparable to other major sulci in the human brain such as the interhemispheric and transverse cerebral fissures (at 8 weeks), the Sylvian fissure and callosal sulcus (at 14 weeks), the calcarine fissure (at 16 weeks) and the central sulcus (at 20 weeks).

As one progresses further lateral the variability increases with only a small area of the medial orbital sulcus common to

90% of the subjects, which fits well with its first appearance at 28–31 weeks after gestation. The lateral orbital sulcus does not contain an area common to 90% of the subjects, but instead only a small area common to 75%. Again, what could well be the lateral orbital sulcus appears rather late after gestation (at 32–35 weeks).

A similar pattern is seen with the posterior–anterior trend where the posterior part of the olfactory sulcus is less variable than parts located further anterior. This is mirrored by the first appearance of the olfactory sulcus after 16 weeks, which gradually extends anteriorly until the 25th week. Likewise for the transverse orbital sulcus that first appears after 36 weeks and for the intermediate orbital sulci that appear at 40–44 weeks after gestation.

Overall, the considerable variability of human orbitofrontal cortex anatomy shows that there are significant differences between individuals. It also poses interesting methodological challenges for those who hope to normalise individual brains to a template brain in order to generalise about the functional anatomy of the human orbitofrontal cortex (see meta-analysis later and the section on possible improvements to current methods).

2.2. Inputs

The orbitofrontal cortex receives inputs from all the sensory modalities: gustatory, olfactory, somatosensory, auditory and visual (see Fig. 9 and Rolls, 1999a,b). Visceral
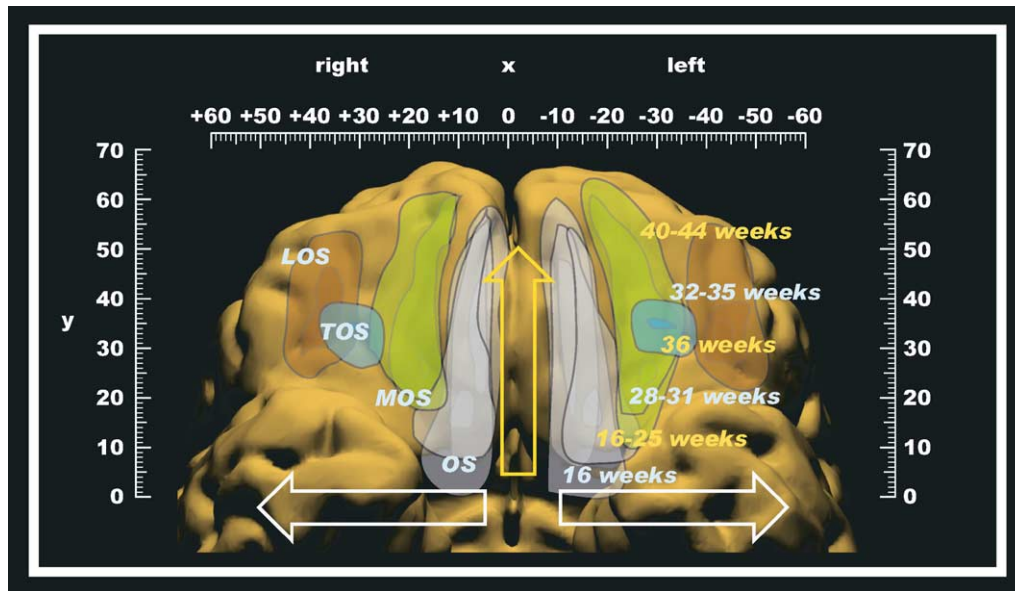
Fig. 8. Sulcal probability and development. The figure shows a ventral view of the orbital surface with a sulcal probability map superimposed. Furthermore, the two developmental trends of the orbital sulci after gestation are indicated by arrows and indications of the weeks for the first appearance of the sulci based on Chi et al. (1977). In the mediolateral trend the sulcal variability increases from the medial to the lateral part of the orbitofrontal cortex, while in the posterior–anterior trend the sulcal variability increases from posterior to anterior regions. Abbreviations used OS, olfactory sulcus; MOS, medial orbital sulcus; TOS, transverse orbital sulcus; LOS, lateral orbital sulcus. Sulcal probability modified from Chiavaras and Petrides (2001).

information is also received by the orbitofrontal cortex and all this sensory information makes the orbitofrontal cortex the perhaps most polymodal region in the entire cortical mantle with the possible exception of the rhinal regions of the temporal lobes (Barbas, 1988). The orbitofrontal cortex
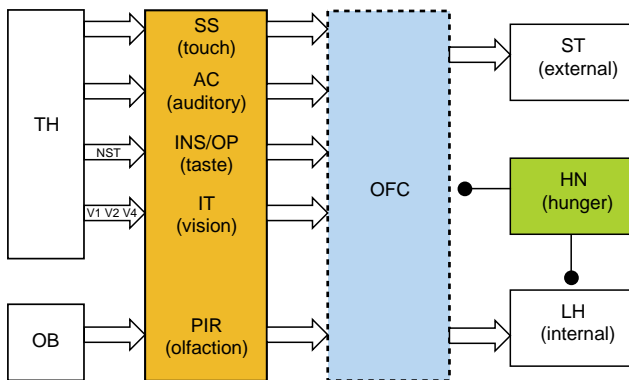

Fig. 9. Schematic diagram of sensory input to the orbitofrontal cortex. The orbitofrontal cortex receives input from all the sensory modalities: gustatory, olfactory, somatosensory, auditory and visual. This information is then represented and available for pattern-association between primary (e.g. taste, touch and pain) and secondary (e.g. visual) reinforcers. The reward value of this representation can be modulated by hunger neurons (HN). The output from the orbitofrontal cortex to both striatum (external) and lateral hypothalamus (internal) can then lead to behaviour. Abbreviations utilised: TH, thalamus; OB, olfactory bulb; NST, nucleus of the solitary tract; V1, V2, V4, primary and secondary visual areas; SS, somatosensory cortex (3, 1, 2); AC, auditory cortex; INS/OP, insula cortex/frontal operculum; IT, inferior temporal visual cortex; PIR, piriform cortex; OFC, orbitofrontal cortex; HN, hunger neurons; ST, striatum; LH, lateral hypothalamus (figure modified from Rolls, 1999a,b).

may be conceptualised as receiving the outputs of all the "what" processing systems, including those that specify primary reinforcers including those produced by taste and somatosensory input (Rolls, 1999a; Rolls and Deco, 2002). In this respect, the orbitofrontal cortex is a unique cortical area.

The orbitofrontal cortex is thus well placed for multimodal stimulus-reinforcement association learning (Rolls, 1990; Rolls, 1999a). Taste information is received from the ventral posteromedial nucleus of the thalamus by the primary taste cortex in the anterior insular and adjoining frontal operculum, which then projects to the primate caudolateral orbitofrontal cortex (area 13 and Ial) which then by definition contains the secondary taste cortex (Baylis et al., 1994; Rolls et al., 1990). Olfactory information is also processed in the orbitofrontal cortex, with the secondary (areas Iam, Iapm and 13) and tertiary olfactory cortex (area 11) located in the orbitofrontal cortex (Carmichael et al., 1994; Critchley and Rolls, 1996b; Rolls et al., 1996). Object-processed visual information is received from the inferior temporal cortex in lateral areas of the orbitofrontal cortex (area 47/12) (Barbas, 1988; Morecraft et al., 1992; Rolls and Deco, 2002; Thorpe et al., 1983). Further visual information is received from the temporal pole and from the anterior part of the superior temporal sulcus where face-responsive neurons are found (Hasselmo et al., 1989a; Hasselmo et al., 1989b). Auditory information is received in area 11 and 47/12 from area TA and area TAa in the cortex in the superior temporal cortex (Barbas, 1988; Morecraft et al., 1992; Romanski et al., 1999).

Somatosensory information is conveyed primarily to area 47/12 (47/12m) in projections from the somatosensory areas

2, 1 and SII in the frontal and pericentral operculum and from the insula (Barbas, 1988; Carmichael and Price, 1995b; Morecraft et al., 1992; Rolls et al., 1999; Verhagen et al., 2003).

Visceral information is received in the caudal orbitofrontal cortex (areas Ial and Iapm) from a region of the ventrolateral posteromedial thalamic nucleus, which is distinct from the parvocellular part involved in taste processing (Öngür and Price, 2000).

There are also direct inputs from other brain structures. The most prominent of these brain structures is the amygdala, where a number of its nuclei including the lateral, basal and accessory basal, anterior, periamygdaloid and medial nuclei all project extensively to widespread areas of the orbitofrontal cortex (mostly to areas 13a, 13b, 47/12l and less densely to areas 14 and 10, e.g. Amaral and Price, 1984; Carmichael and Price, 1995a). Some of these projections and especially those from the basal nucleus of the amygdala are topographically organised. The connections are in almost all cases reciprocal, and there is some evidence that the orbitofrontal cortex projects more widely to the amygdala than vice versa (Cavada et al., 2000). In addition, as described above, the insula projects taste, olfactory, visceral, and somatosensory information widely to the caudal part of orbitofrontal cortex (Mesulam and Mufson, 1982).

The projections from the anterior cingulate cortex to the orbitofrontal cortex are dense, with projections from nearly all parts of the anterior cingulate cortex (Van Hoesen et al., 1993). Parts of the posterior cingulate cortex (areas 23 and 30) also project to the orbitofrontal cortex (Van Hoesen et al., 1993). There are substantial reciprocal projections to areas 10o, 11m, Iai, 14r and 14c from the rostral part of the anterior cingulate cortex (Öngür and Price, 2000). The motor cingulate area, 23c, also has strong reciprocal connections with the orbitofrontal cortex (Carmichael and Price, 1996; Cavada et al., 2000). Premotor area F5 contains the representation of distal arm movement with neurons responding to goal-related motor acts and motivational visual stimuli (Rizzolatti et al., 1988), and has reciprocal connections with the lateral and caudal orbitofrontal cortex (Barbas and Pandya, 1989; Morecraft et al., 1992).

There are reciprocal connections with other prefrontal areas (areas 9 and 46) in extensive parts of the orbitofrontal cortex including areas 10, 11, 12 and 14 (Barbas and Pandya, 1989; Carmichael and Price, 1995b). The posterior hypothalamus also projects to the prefrontal cortex (Rempel-Clower and Barbas, 1998).

The hippocampus has direct extensive ipsilateral topographic projections to primarily the medial orbitofrontal cortex (Cavada et al., 2000). The prosubiculum adjacent to CA1 also projects to the orbitofrontal cortex.

The orbitofrontal cortex is innervated by cholinergic and aminergic subcortical fibres (Morecraft et al., 1992). The cholinergic innervation principally comes from the nucleus basalis of Meynert, and it is interesting to note that the orbitofrontal cortex projects into the nucleus basalis and thus has the possibility of controlling cholinergic input to the entire cerebral cortex (Mesulam and Mufson, 1984). The other regions projecting to the nucleus basalis are other interconnected structures including the hypothalamus, nucleus accumbens, piriform cortex, entorhinal cortex, temporal pole, anterior insula, septal nuclei and posterior parahippocampal cortex, and neurons in the region of the nucleus basalis/substantia innominata/lateral hypothalamus have responses to the sight, smell and taste of food (Rolls, 1999a).

Finally, as mentioned above, the orbitofrontal cortex receives indirect information via projections from the mediodorsal thalamic nucleus pars magnocellularis which itself receives afferents from temporal structures such as the amygdala, the prepyrifom cortex and inferior temporal cortex (Öngür and Price, 2000).

2.3. Outputs

Most of the input connections to the orbitofrontal cortex mentioned above are reciprocal unless specifically stated. This means that the orbitofrontal cortex projects back to temporal lobe areas such as the amygdala, entorhinal cortex, hippocampus and the inferior temporal cortex. Other efferent projection regions include the cingulate cortex, caudate nucleus, preoptic region, lateral hypothalamus and ventral tegmental area (Rolls, 1999a).

Of special interest are the heavy interconnections of the orbitofrontal cortex with the hypothalamus and in particular the posterior hypothalamus (Rempel-Clower and Barbas, 1998). Interestingly, the efferent projections from the prefrontal cortex come from more selective areas than those that receive inputs from the hypothalamus/substantia innominata, with the medial prefrontal cortex sending the densest projections, followed by those from the orbitofrontal cortex, with only very weak projections from the lateral prefrontal cortex (Öngür and Price, 1998; Rempel-Clower and Barbas, 1998).

Also interesting in view of the role of the orbitofrontal cortex in emotion are the strong reciprocal connections with the periaqueductal grey (Rempel-Clower and Barbas, 1998). There are strong connections with the striosomal compartment of the anterior and ventromedial striatum, mainly the caudate nucleus (Eblen and Graybiel, 1995). This pathway could be involved in goal-directed behaviour and may control dopaminergic substantia nigra pars compacta neurons (Rolls, 1999a). There is evidence of direct ascending and descending pathways to dopaminergic cell groups in the mesencephalon (Öngür and Price, 1998; Porrino and Goldman-Rakic, 1982) and some evidence for a direct link to the nucleus accumbens (Haber et al., 1995).

2.4. Phylogeny

The orbitofrontal cortex forms part of the prefrontal cortex and it has long been a cherished idea of neuroscience that the volume of the prefrontal cortex has increased with respect to

brain size through mammalian evolution (Brodmann, 1912; Papez, 1929). This proposed increase in the volume of prefrontal cortex could then be linked to the progressive increase in cognitive sophistication reached by primates. More recent studies have, however, largely failed to replicate the early findings, and instead found a linear relationship between overall brain size and prefrontal size (Semendeferi et al., 1997; Uylings and van Eden, 1990). One study found a very small increase when comparing the human prefrontal cortex with that of a baboon, but an increase from 9.8% in baboons to 11.5% in humans hardly constitutes strong evidence (McBride et al., 1999). The increase in cognitive abilities for higher primates is therefore more likely to be linked to the well-established finding that overall brain size has increased with respect to body size through evolution. The human brain, for instance, is about three times bigger than what would be expected for a primate of comparable size (Passingham, 1982).

Size is, of course, not everything when it comes to brains, and the extrinsic and intrinsic neural connections within and between brain areas are just as important for regulating the functional properties of the brain. Indeed, because of the great development of the temporal visual cortical areas, with respect to rodents, the macaque orbitofrontal cortex is much easier to compare with the human orbitofrontal cortex. Perhaps because of the emphasis this visual processing places on cortical computation (Rolls and Deco, 2002), even the taste system has been connected differently in primates than in rodents, with a much greater emphasis on the direct route to the taste cortex, with few connections in primates from brainstem taste nuclei to other subcortical structures (see Rolls and Scott, 2003). Moreover, the homologies between the human and non-human primate orbitofrontal cortical areas can be surmised based on architectonic data as described above, but clear comparisons are very difficult to make with rodents.

It has also long been argued that the orbitofrontal cortex constitutes an evolutionarily rather older brain structure than the rest of the prefrontal cortex (though certainly not than the amygdala), and cytoarchitectonic analysis of the different regions of the prefrontal cortex clearly demonstrates differences in cortical organisation. Whereas the dorsolateral prefrontal cortex consists of fully laminated six-layered granular cortex, the orbitofrontal cortex consists (except for the most anterior parts) of five-layered agranular cortex (posterior and medial parts), and transitional dysgranular cortex (central parts) (Öngür and Price, 2000). This could be taken as indirect evidence for these parts of the orbitofrontal cortex being phylogenetically older than other prefrontal areas. These differences in cytoarchitecture and cortical organisation are likely to correspond to functional differences for different parts of the prefrontal cortex and especially for the orbitofrontal cortex, e.g. when comparing the functions of anterior versus posterior parts.

More indirect evidence consistent with this phylogenetic hypothesis comes from the relative increase in size of the different parts of the mediodorsal thalamus when ascending the phylogenetic scale (Fuster, 1997). The parvocellular part (which projects to the dorsolateral prefrontal cortex) has progressively increased in size when compared to the magnocellular part (which projects to the orbitofrontal cortex), although it is not yet clear whether this is reflected in the relative sizes across species of the dorsolateral and orbitofrontal cortex (Semendeferi et al., 1997).

Similar arguments regarding the phylogenetic status of the orbitofrontal cortex have been advanced with respect to the relatively late myelination of the orbitofrontal cortex by invoking the common assumption that phylogeny reflects ontogeny (Fuster, 1997). The evidence is, however, not very strong given that myelination investigation techniques are imprecise, and subsequent studies have failed to find sequential myelination in the cortex including the prefrontal cortex (Goldman-Rakic et al., 1997).

Different strands of indirect evidence are thus converging on the claim that parts of the orbitofrontal cortex are phylogenetically older than other parts of the prefrontal cortex. Such phylogenetic arguments do not, however, translate into a diminution in the functional role of the orbitofrontal cortex. On the contrary, the evidence presented in this review points to a crucial role of the orbitofrontal cortex in flexibly processing rewards and punishments, and thus being implicated in almost all aspects of human behaviour and especially goal-directed behaviour.

3. The functional role of the orbitofrontal cortex

Converging evidence from lesions of the orbitofrontal cortex in both non-human primates and humans as well as neurophysiological recordings in non-human primates has led to a number of theories on the functional role of this brain region. Foremost this evidence has linked the orbitofrontal cortex to the study of emotion. In this section, first the orbitofrontal cortex is placed within the context of the current state of emotional research. Then follows a review of the evidence from lesions to the human orbitofrontal cortex, and from neurophysiological recordings and lesions to non-human primates. Finally, three influential theories on the functional orbitofrontal cortex are discussed.

3.1. Emotion and the orbitofrontal cortex

Emotion has for many years remained an elusive scientific topic, but recent years have seen a significant increase in research on emotion, leading to important new discoveries of the brain mechanisms involved. The main problem with scientific investigations of emotion has been one of definition. Ancient Greek and later Western philosophers have discussed emotion extensively, but with the emphasis almost exclusively on its cognitive evaluation, and a definition of emotion useful for scientific inquiry did not emerge.

The field of emotion research began slowly to make headway with advances made by pioneering individuals such as Charles Darwin (1872), who examined the evolution of emotional responses and facial expressions. In the 1880s, William James and Carl Lange independently proposed the idea that rather than emotional experience being a response to a stimulus, it is the perception of the ensuing physiological bodily changes which results in the emotional feelings (James, 1890; Lange, 1887). The James–Lange theory suggests that we do not run from the bear because we are afraid but that we become afraid because we run.

These ideas, however, still did not address the question of what brain structures were involved in emotion, which only began with the detailed critique of the James–Lange theory by William Cannon (1927) showing that surgical disruption of the peripheral nervous system in dogs did not eliminate emotional responses as would have been predicted by the James–Lange theory. Further investigations by Schachter and Singer (1962) and others (Reisenzein, 1983) provided evidence that cognitive factors were essential for emotion, and that bodily states may merely modulate to some extent the intensity of whatever emotion is being produced by cognitive inputs. Nevertheless, the James–Lange theory was resurrected by Antonio Damasio (1994) in the form of his somatic marker hypothesis, in which feedback from the peripheral nervous system controls the 'decision' about the correct behavioural response rather than the 'emotional feelings' as postulated in the James–Lange theory.

An alternative to such bodily theories of emotions has been proposed by Larry Weiskrantz (1968), Jeffrey Gray (1975) and Edmund Rolls (1990, 1999a) who instead regard emotions as states elicited by rewards and punishments, i.e. by instrumental reinforcers. Emotional stimuli (primary and secondary reinforcers) are represented by different brain structures depending on the kind of reinforcer. The subsequent evaluation is a multistage process mediated by a number of specific brain structures, and the results of this evaluation then influence which behaviour is selected, which feelings are produced, and which autonomic responses are elicited.

The early pioneering theories were built on a paucity of experimental data, and with the recent flourishing of emotion research, and especially given the ever increasing amount of primate neurophysiological and human neuroimaging data, we are finally in a much better position to evaluate which brain structures are crucial to emotion. The evidence points to the amygdala and the cingulate cortex as necessary for the proper emotional functioning of the primate brain (see Figs. 1 and 9). Furthermore, it has also become clear that in humans and other higher primates a very significant role is played by the orbitofrontal cortex. Some of the first evidence for this came from the case of Phineas Gage (Harlow, 1848; Macmillan, 2000). As described in this review, recent studies have shed further light on the functioning of the orbitofrontal cortex, and shown that the reward and punishment values of primary (unlearned) reinforcers such as taste, touch and pain, and visual and olfactory stimuli which become secondary (learned) reinforcers by association with a primary reinforcer, are represented in the orbitofrontal cortex. Strong reciprocal connections are found between the orbitofrontal cortex and the amygdala, and the evidence suggests a similar role for the two brain areas, although the orbitofrontal cortex appears to be the more important for rapid emotion-related learning, and becomes relatively more important in humans and higher primates (Rolls, 1999a).

A number of other brain structures have been found to contribute to emotional processing in primates, including the hypothalamus, insula, nucleus accumbens, and various brainstem nuclei such as the periaqueductal grey (Rolls, 1999a). These brain regions are closely linked with the orbitofrontal cortex, amygdala and anterior cingulate cortex, and are crucial for correct emotional processing. They are not, however, primarily concerned with decoding reinforcers and with stimulus-reinforcement association learning, but instead provide some of the necessary input and output systems for the multi-modal association regions such as the amygdala and the orbitofrontal cortex which are involved in representing and learning about reinforcers (see Fig. 9).

3.2. Lesions of the human orbitofrontal cortex

In humans, damage to the orbitofrontal cortex causes major changes in emotion, personality, behaviour and social conduct. Patients often show lack of affect, social inappropriateness and irresponsibility (Hornak et al., 2003; Rolls et al., 1994). It has been shown that patients are impaired at correctly identifying social signals including for example face and voice expression identification (Hornak et al., 1996, 2003). A classic case of orbitofrontal damage is that of Phineas Gage, whose medial frontal lobes were penetrated by a metal rod (Harlow, 1848). Miraculously Gage survived but his personality and emotional processing was changed completely (although care should be taken because our information is sparse; Macmillan, 2000).

Later cases of patients such as EVR have confirmed this brain structure's importance in social behaviour. EVR had a successful resection of an orbitofrontal meningioma involving a bilateral excision of the orbital and lower mesial cortices (Eslinger and Damasio, 1985). After the operation EVR still had normal performance on the Wisconsin Card Sorting Test and performed in the 97th percentile on IQ tests, but lost his job and wife as a consequence of his complete change in personality and general irresponsibility.

Analyses of the effects of lesions to the human orbitofrontal cortex show that they impair the patients in a variety of important ways related to emotion, stimulus-reinforcement association and reversal, and decision-making. The severity of these changes can be measured by performance on neuropsychological tests including gambling (Bechara et al., 1994), visual discrimination reversal learning (Hornak et al., 2004; Rolls et al., 1994), and decision-making (Rogers et al., 1999a), as described next.

Bechara and colleagues developed a gambling task to bring out cognitive deficits in patients with orbitofrontal cortex lesions such as EVR. Subjects were asked to select cards from four decks of cards and maximise their winnings. During the task electrodermal activity (skin conductance responses, SCR) of the subject was measured as an index of somatic state activation. After each selection of a card, facsimile money is lost or won. Two of the four packs produce large payouts with larger penalties (and can thus be considered high-risk), while the other two packs produce small payouts but smaller penalties (low-risk). The most profitable strategy is therefore to consistently select cards from the two low-risk decks, which is the strategy adopted by normal control subjects. Patients with damage to the ventromedial part of orbitofrontal cortex, but not the dorsolateral prefrontal cortex, would persistently draw cards from the high-risk packs, and lack anticipatory SCRs while they pondered risky choices. The task was designed to mimic aspects of real-life decision-making that patients with orbitofrontal cortex lesions find difficult. Such decisions typically involve choices between actions associated with differing magnitudes of reward and punishment where the underlying contingencies relating actions to relevant outcomes remain hidden.

Bechara et al. (1998) have since reported a dissociation between subjects with different frontal lobe lesions. All subjects with orbitofrontal cortex lesions were impaired on the gambling task, while only those with the most anteriorly placed lesions were normal on working memory tasks. Other subjects with right dorsolateral/high mesial lesions were impaired on working memory tasks but not on the gambling task.

Bechara et al. (1999) went on to compare subjects with bilateral amygdala but not orbitofrontal cortex lesions, and subjects with orbitofrontal cortex but not amygdala lesions, and found that all subjects were impaired in the gambling task and all failed to develop anticipatory SCRs. However, while subjects with orbitofrontal cortex lesions still, in general, produced SCRs when receiving a monetary reward or punishment, the subjects with bilateral amygdala lesions failed to do so.

Most known cases of human orbitofrontal damage have occurred in adulthood, but recently two cases of damage acquired in very early life were reported (Anderson et al., 1999). The two patients showed lifelong behavioural problems, which were resistant to corrective influences. But more importantly, the patients appeared completely to lack knowledge with about moral and societal conventions. Interestingly, other patients with late acquired orbitofrontal lesions have retained knowledge of such matters, even if they do not always act in accordance with this explicit knowledge. The lack of this moral knowledge and subsequent reckless behaviour in the two patients with early life damage to the orbitofrontal cortex is consistent with the hypothesis that the orbitofrontal cortex is crucial for stimulus-reinforcement learning (Rolls, 1990). The implication would seem to be that the orbitofrontal cortex is necessary for the development of personal moral-based knowledge based on the processing of rewards and punishments (Dolan, 1999).

Rolls et al. (1994) used a visual discrimination reversal task, which is aimed to capture the fundamental type of learning involved in emotion, making associations with a previously neutral (e.g. visual) stimulus with a (typically primary) reinforcer, and then rapidly reversing these associations when the reinforcement contingencies alter (Rolls, 1990; Thorpe et al., 1983). In a simple go/no-go task, subjects were required to learn to obtain points by touching one visual stimulus when it appeared on a video monitor, but not to touch a different visual stimulus when it appeared or they would lose points. When the patients had acquired the visual discrimination, the reinforcement contingencies suddenly reversed. Rolls et al. (1994) found that patients with lesions to the ventral part of the orbital surface were severely impaired on this reversal task (and on a similar extinction task) compared to control patients with damage elsewhere in the frontal or other brain regions. The patients with orbitofrontal lesions were unable to change their behaviour appropriately, but were nevertheless able to verbally report the change. The perseveration of the patients with orbitofrontal lesions in touching a previously rewarded stimulus is consistent with the literature for non-human primates with lesions of the orbitofrontal cortex (see Rolls, 1999a). Furthermore, high correlations were found between the performance on the reversal and extinction tests by patients with orbitofrontal lesions and the degree of disinhibited and socially inappropriate behaviour (measured with a Behaviour Questionnaire completed by the carers of the patients). Interestingly, the patients with orbitofrontal lesions achieved normal levels of performance on a standard planning task, the Tower of London task (Shallice, 1982).

A new version of the reversal-learning task has since been developed to clarify a number of points. The deficits shown in the original task with patients perseverating in touching the previously rewarded, now unrewarded stimulus on no-go trials were probably at the level of a failure to reverse stimulus-reinforcement learning, which involves stimulus–stimulus learning, as would be consistent with the neurophysiology of the primate orbitofrontal cortex in which sensory-reinforcement association learning is represented but motor responses are not (Rolls, 1999a,b). However, there could have been a contribution from a type of motor disinhibition, in which the patients could not inhibit a previously learned response. In order to be able to discriminate between the two possibilities in patients, a concurrent discrimination object reversal design has been adopted for the new reversal-learning task (Hornak et al., 2004) in which both the currently rewarded and the currently unrewarded stimulus are shown simultaneously on each trial, and the correct stimulus must be selected. Given that subjects must make motor responses on every trial, any deficits found cannot be attributed to motor response inhibition.

The new version of the reversal-learning task also employs probabilistic reward and punishment schedules such

that the selection of both the currently rewarded stimulus and the unrewarded stimulus can lead to a monetary gain or loss but only consistent selection of the currently rewarded stimulus results in overall monetary gain (Hornak et al., 2004). This probabilistic design minimises the possibility for patients to use other cognitive strategies such as explicit verbal strategies rather than affective (i.e. direct stimulus-reinforcement) learning. The reversal task shares the probabilistic reinforcement schedules and subsequent stimulus-reinforcement associations with the gambling task of Bechara described above, but adds the key element of reversal, and thus the affective learning and rapid reversal of stimulus-reinforcement associations.

In another innovation used in this investigation to seek positive confirmation that effects on stimulus-reinforcement association learning and reversal were related to orbitofrontal cortex damage rather than to any other associated pathology, the new reversal-learning task was used with a group of patients with discrete, surgically produced, lesions of the orbitofrontal cortex. It was found that a group of patients with bilateral orbitofrontal cortex lesions were severely impaired at the reversal task, in that they accumulated less money (Hornak et al., 2004). These patients often failed to switch their choice of stimulus after a large loss; and often did switch their choice even though they had just received a reward. The investigation showed that the impairment was only obtained with bilateral orbitofrontal cortex damage, in that patients with unilateral orbitofrontal cortex (or medial prefrontal cortex) lesions were not impaired in the reversal task.

It is of interest that the patients with bilateral orbitofrontal cortex damage who were impaired at the visual discrimination reversal task had high scores on parts of a Social Behaviour Questionnaire in which the patients were rated on behaviours such as emotion recognition in others (e.g. their sad, angry or disgusted mood); in interpersonal relationships (such as not caring what others think, and not being close to the family); emotional empathy (e.g. when others are happy, is not happy for them); interpersonal relationships (e.g. does not care what others think, and is not close to his family); public behaviour (is uncooperative); antisocial behaviour (is critical of and impatient with others); impulsivity (does things without thinking); and sociability (is not sociable, and has difficulty making or maintaining close relationships) (Hornak et al., 2003), all of which could reflect less behavioural sensitivity to different types of punishment and reward. Further, in a Subjective Emotional Change Questionnaire in which the patients reported on any changes in the intensity and/or frequency of their own experience of emotions, the bilateral orbitofrontal cortex lesion patients with deficits in the visual discrimination reversal task reported a number of changes, including changes in sadness, anger, fear and happiness (Hornak et al., 2003). As described later, these results are complemented by neuroimaging results with fMRI in normal subjects, which showed that in the same task, activation of the medial orbitofrontal cortex was correlated with how much money was won on single trials, and activation of the lateral orbitofrontal cortex was correlated with how much money was lost on single trials (O'Doherty et al., 2001). It has also been found that impulsive behaviour as measured by making unusually rapid responses on a matching familar figures task is produced by orbitofrontal cortex damage (Berlin et al., 2004). Together, these results on the effects of brain damage to the orbitofrontal cortex, and these and other complementary neuroimaging results described later, provide evidence that at least part of the function of the orbitofrontal cortex in emotion, social behaviour, and decision-making (see Hornak et al., 2003, 2004) is related to representing reinforcers, detecting changes in the reinforcers being received, using these changes to rapidly reset stimulus-reinforcement associations, and rapidly changing behaviour as a result.

Another important example of dysfunction of the orbitofrontal cortex is frontotemporal dementia which is a progressive neurodegenerative disorder attacking the frontal lobes and producing major and pervasive behavioural changes in personality and social conduct resembling those produced by orbitofrontal lesions (Rahman et al., 1999). Patients appear either socially disinhibited with facetiousness and inappropriate jocularity, or apathetic and withdrawn. Many patients show mental rigidity and inability to appreciate irony or other subtle aspects of language. They tend to engage in ritualistic and stereotypical behaviour, and their planning skills are invariably impaired. The dementia is accompanied by gradual withdrawal from all social interactions. Memory is usually intact but patients have difficulties with working memory and concentration. Interestingly, given the anatomy and physiology of the orbitofrontal cortex, frontotemporal dementia causes profound changes in eating habits, with escalating desire for sweet food coupled with reduced satiety, which is often followed by enormous weight gain.

In summary, lesions to the human orbitofrontal cortex quite severely impair the detection of some reinforcers such as voice or face expression, responses to changing reinforcers, subjective emotion, emotional behaviour, social behaviour, and, as a consequence, some types of decision-making. This makes the orbitofrontal cortex a region of primary interest in the elucidation of the functional neuroanatomy of human emotion.

3.3. Neurophysiological studies in non-human primates

Much evidence from neurophysiological studies supports the hypothesis that the reward and punishment value of stimuli are represented in the orbitofrontal cortex, and that rapid stimulus-reinforcement association learning is implemented in the orbitofrontal cortex (Rolls, 1999a, 2004). Electrical stimulation of the primate orbitofrontal cortex acts like a food reward in that it is rewarding when the monkey is hungry, but not after feeding to satiety (Mora et al., 1979). Neurons have been found that code for taste and olfactory

stimuli (Rolls and Baylis, 1994; Takagi, 1991; Tanabe et al., 1975). Orbitofrontal cortex taste, olfactory, and visual neurons only respond to food when hunger is present, that is when the taste, smell and sight of the food are rewarding (Critchley and Rolls, 1996a; Rolls et al., 1989). Evidence for stimulus-reinforcement learning has also been found in the macaque orbitofrontal cortex, where neurons can reverse the visual stimuli to which they respond in as little as one trial in a visual discrimination reversal task (Thorpe et al., 1983). Similarly, neurons with olfactory responses can reverse their responses in an olfactory discrimination task where the taste reward contingencies of two odours are reversed once they have been successfully acquired (Rolls et al., 1996). The reversal of odour–taste reward associations is much slower and inflexible than visual-taste associations, which could be important for forming the stable odour–taste associations needed for the formation and perception of flavours. Further, there is a separate population of primate orbitofrontal cortex neurons that respond only when there is a mismatch between the expected reward value of a visual stimulus and the reward value that is actually obtained (Thorpe et al., 1983). These error detection neurons are likely to play an important role in the behavioural changes that are required when reinforcement contingencies change (Deco and Rolls, 2004). In addition, there is evidence that some macaque orbitofrontal cortex neurons respond to faces, and this is likely to be important because face-reinforcement associations need to be learned and reversed for social interactions, and because face expression can itself be a reinforcer (Rolls, 1999a; Rolls et al., in preparation).

Lesion studies in non-human primates support the hypothesis that reward value is represented in the orbitofrontal cortex. One lesion study has found that lesions to the orbitofrontal cortex alter food preferences in monkeys (Baylis and Gaffan, 1991). Another lesion study has used unilateral crossed lesions to show that the orbitofrontal cortex and the amygdala are important for the alteration of stimulus–reward associations (Baxter et al., 2000).

3.4. Theories of the functional role of the orbitofrontal cortex

The orbitofrontal cortex is a key player in emotion, but the exact role of this brain region is still being discussed. In the following we will briefly discuss three different proposed roles of the orbitofrontal cortex in the literature: a role in inhibition, as a contributor to the so-called somatic markers and a role in representing the reward and punishment value of primary (unlearned) reinforcing stimuli and in rapid reversal of stimulus-reinforcement associations.

3.4.1. Inhibition and the orbitofrontal cortex

The impairments seen on neuropsychological tasks after lesions to the orbitofrontal cortex have sometimes been interpreted in terms of lack of inhibition. The main argument for the response inhibition hypothesis is the fact that hu-

man and other higher primates continue to choose a previously rewarded, but now no longer rewarded, stimulus in object-reversal learning tasks (Dias et al., 1996; Rolls et al., 1994). There are, however, at least four lines of evidence against the idea of simple response inhibition. Neurophysiological recordings in monkeys have only shown activity to the stimuli presented and the rewards received, and not to the motor responses being made (Rolls, 1999a,b, 2002, 2004). Lesion studies in monkeys have also shown that errors on reversal-learning tasks may not be caused by perseverative responses, but can be caused by failure to learn to respond to the currently rewarded stimulus (Iversen and Mishkin, 1970). Neuroimaging studies in humans have found that a different area, part of the lateral prefrontal cortex within the inferior frontal sulcus, was active during response inhibition in both a go/no-go task and in a Wisconsin card sorting task (Konishi et al., 1999). Fourth, Hornak et al. (2004) found in an object-reversal learning task in which one of two simultaneously presented stimuli in random locations had to be chosen on every trial so that response perseveration could not account for the results, that patients with discrete, surgical, orbitofrontal cortex lesions were impaired at the reversal part of the task.

Similarly, Bechara et al. (1998) have claimed that the primary reason why subjects with orbitofrontal cortex lesions show poor performance on their gambling task is not because of failure of inhibitory control. Just as normal controls, subjects with orbitofrontal cortex lesions switch decks when they receive punishment, but they return more often to high-risk decks. However, these claims are hard to quantify due to the nature of the gambling task. This interpretation is, however, supported by the data from patients with frontal variant frontotemporal dementia tested on a decision-making task (Rahman et al., 1999; Rogers et al., 1999b). The patients showed much longer deliberation times and did not consistently choose early bets in either ascending or descending sequence. Furthermore, they were generally able to adjust their bets according to the given odds, though nevertheless at a lower level than normals.

3.4.2. The somatic marker hypothesis

In an alternative approach, Bechara et al. (1997) have instead argued that the poor performance by subjects with orbitofrontal cortex lesions on their gambling task is due to a failure to anticipate future outcomes. Damasio further interprets the results in terms of his somatic marker hypothesis (described earlier), whereby somatic markers would presumably link previous behaviours and situations with contingent affective consequences (Damasio, 1994).

The decision-making theory put forward by Damasio to account for the impairments in patients with orbitofrontal cortex lesions shares most of the weaknesses of the James–Lange theory. The Damasio theory is not, however, concerned primarily with emotion but with decision-making, and it is not at all clear why the peripheral feedback route is needed, as this will inevitably introduce noise into the

system. When this issue is raised, Damasio retreats to his 'as-if' loop that leaves out the body loop altogether. However, the most problematic aspect of the theories of both James–Lange and Damasio is that they do not specify which classes of stimuli can elicit emotion, and are as such seriously underspecified (see Rolls, 1999a).

3.4.3. Representations of reward and punishment

Rolls (1990, 1999a) proposes a different hypothesis, according to which the orbitofrontal cortex is involved in emotion because it represents the reward and punishment value of primary (unlearned) reinforcing stimuli, and because it is involved in the rapid relearning and reversal of associations between previously neutral stimuli and primary reinforcers. According to Rolls this means that the impairments in patients with orbitofrontal cortex lesions are related to deficits in responding to primary reinforcers, and in reversing reinforcement-related associations when the contingencies change (a type of stimulus–stimulus learning), and not to the inability to inhibit a previously learnt motor response. This theory is well supported by the neurophysiological evidence from non-human primates as described above.

Overall, the orbitofrontal cortex does appear to be crucially involved in representing and altering the reward value of primary and secondary reinforcers as incorporated into the theory of emotion and its brain mechanisms put forward by Rolls (1999a). It should, however, be noted that this approach to emotion starts with an operational definition of the conditions under which emotion is elicited, and that the theory has been developed beyond this to account for complexity in emotion, and for the experiential aspects of human emotion (see Rolls, 1999a, 2000b and commentaries to Rolls, 2000b).

4. Meta-analysis of neuroimaging data

The aim of this section is to elucidate the functions of the human orbitofrontal cortex and its subareas by presenting a meta-analysis of the findings from a large portion of the published neuroimaging studies in which activations in the orbitofrontal cortex have been investigated.

4.1. Meta-analysis methods

The meta-analysis is based on the results from 87 published neuroimaging papers in the literature (listed in Table 1, of which there were 48 PET studies and 39 fMRI studies). Only studies ranging from years of publication 1994 to the beginning of 2003 were used, in which reliable activation of the human orbitofrontal cortex was found at the group level and where stereotaxic coordinates (in MNI space, see Collins et al., 1994) were made available exclusively for tasks submitted to nonpathological subjects.

A relational database with a total of 267 data points was built to store information about these neuroimaging studies.

Table 1 list all the studies and Table 2 lists all the activations. For reference, the cytoarchitecture of the human orbitofrontal cortex as described by Öngür and Price (2000) is shown superimposed on the orbital surface in standard stereotactic space in Fig. 10.

In addition to standard bibliographical information uniquely identifying each study (including authors, year, title of article, journal etc.), other information was stored including the number of subjects, gender-ratio, a short description of the study, notes on the statistics employed, and the stimulus type. The reported activations were then categorised according to activation type and attached with their unique attributes including stereotaxic coordinates, significance level (z-value, t-value or other statistic, depending on the study) and comparison condition.

Although these database attributes for each study and its activations are quite accurate in describing each study, and as such come a long way to standardise the findings for further meta-analysis, it is important to remember that at least three factors could potentially cause problems: differences in imaging methods, differences in stimuli and differences in statistical analysis.

'The differences in imaging methods' arise because PET is quite different from fMRI. As described later, there are certain challenges when imaging the orbitofrontal cortex with fMRI. Perhaps reflecting these initial challenges, most of the studies in the neuroimaging literature that have reported activations of the orbitofrontal cortex are PET studies. PET studies have, however, their own problems including quite poor temporal and spatial resolution.

'The differences in stimuli include' problems with inadequate control stimuli such as using water as a control stimulus in taste experiments. It is not clear that a contrast between taste and water would be especially meaningful given that water is known to be rewarding in its own right in a thirsty animal, and activates neurons in taste cortical areas (De Araujo et al., 2003b; Rolls et al., 1989, 1990).

'The differences in statistical analysis' could be the cause of the most important problems for a meta-analysis given that statistics can be used in many diverse ways on large datasets such as those obtained by neuroimaging. There are pertinent questions with regards to how datasets were preprocessed, normalised and subsequently used for inter-subject averages. The level of statistical significance and the possible inferences to larger parts of the population are also important issues to remember in a meta-analysis.

If all these questions and potential obstacles were fully resolved, which unfortunately is not possible at the present time, performing meta-analysis of neuroimaging data would become more of a science and less of an art. Even if this came true, it would still be prudent to remember the cautionary words of Francis Crick who is reputed to have said "...a theory that accounts for all the facts is bound to be wrong, because some of the facts are bound to be wrong".

Table 1
List of published papers reviewed in meta-analysis

Reference	Type	Total	Men	Women	Short description
Aharon et al., 2001	fMRI	10	10	0	Facial beauty
Anderson et al., 2003	fMRI	16	8	8	Odour intensity and valence
Bantick et al., 2002	fMRI	8	6	2	Attentional modulation of pain
Berns et al., 2001	fMRI	25	25	0	Fruit juice
Berthoz et al., 2002	fMRI	12	12	0	Social norm violations
Blair et al., 1999	PET	13	13	0	Varying angry faces (also sad and neutral)
Blood et al., 1999	PET	10	5	5	Music
Blood and Zatorre, 2001	PET	5	5	5	Pleasurable music
Cabeza et al., 2001	fMRI	12	12	0	Distinguishing true from false
Cerf-Ducastel and Murphy, 2001	fMRI	6	3	3	Retronasal odours
Chua et al., 1999	PET	10	10	0	Anticipatory anxiety
Coghill et al., 1994	PET	–	–	–	Phasic heat pain
Coghill et al., 1999	PET	16	9	7	Thermal stimulation of hands
Coghill et al., 2001	PET	9	4	5	Thermal stimulation of hands
Craig et al., 2000	PET	10	7	3	Thermosensory stimuli
Critchley et al., 2000b	fMRI	6	3	3	Neural activity and SCR
Critchley et al., 2000a	PET	6	6	0	Effects of low and high stress, MAP and HR
Critchley et al., 2002	fMRI	17	9	8	Fear conditioning and autonomic arousal
Dade et al., 2001	PET	12	6	6	Odour and working memory
De Araujo et al., 2003a	fMRI	10	6	4	Umami and synergism
De Araujo et al., 2003c	fMRI	11	6	5	Crossmodal convergence of taste and smell
De Araujo et al., 2003b	fMRI	11	5	6	Water in the mouth
Derbyshire et al., 1997	PET	12	6	6	Phasic laser pain (left)
Elliott and Dolan, 1998a	PET	6	6	0	Hypothesis testing
Elliott and Dolan, 1998c	PET	9	9	0	Subliminally presented
Elliott and Dolan, 1999	fMRI	10	6	4	DMTS and DNMTS
Elliott et al., 1999	PET	5	5	0	Guessing
Elliott et al., 2000b	fMRI	9	−1	−1	Winning monetary streaks
Elliott et al., 2003	fMRI	12	6	6	Financial reward
Farrow et al., 2001	fMRI	10	7	3	Social, empathic and forgivability judgments
Frey et al., 2000	PET	11	0	11	Auditory crashes
Frey and Petrides, 2000	PET	12	12	0	Memory encoding
Ghatan et al., 1995	PET	8	4	4	Maze task
Ghatan et al., 1998	PET	6	6	0	Serial cognitive tasks during auditory interference
Gorno-Tempini et al., 2001	fMRI	10	5	5	Happy vs. disgusted faces
Gottfried et al., 2002b	fMRI	15	6	9	Olfactory learning
Gottfried et al., 2002a	fMRI	15	6	9	Olfaction
Gusnard et al., 2003	fMRI	12	0	12	Individual differences in persistence
Hobday et al., 2001	fMRI	8	8	0	Ano-rectal stimulation
Hsieh et al., 1995	PET	–	–	–	Ongoing neuropathic pain
Iwase et al., 2002	PET	12	6	6	Pleasant facial expression
Janata et al., 2002	fMRI	8	4	4	Tracking activation in tonal space
Kringelbach et al., 2003	fMRI	9	5	4	Whole food sensory specific satiety
Kringelbach and Rolls, 2003	fMRI	9	3	6	Reversal learning
Lafleur et al., 2002	PET	9	5	4	Sequential foot movements
Lorenz et al., 2002	PET	14	14	0	Heat allodynia
Lorenz et al., 2003	PET	14	14	0	Pain modulation
Lotze et al., 2001	fMRI	8	4	4	Anal and rectal stimulation
Maratos et al., 2001	fMRI	12	5	7	Memory for emotional content
Moll et al., 2002	fMRI	7	3	4	Emotional moral and non-moral judgment
Morris et al., 1998	PET	5	4	1	Emotional (happy/fear) vs. neutral faces
Morris et al., 1999	PET	6	6	0	Emotional voices
Morris and Dolan, 2001	PET	10	9	1	Memory for food
Nathaniel-James and Frith, 2002	PET	6	6	0	Sentence completion
Nobre et al., 1999	PET	7	7	0	Breaches of expectation
O'Doherty et al., 2001	fMRI	9	3	6	Reversal task monetary
O'Doherty et al., 2002	fMRI	8	5	3	Anticipation of taste reward
O'Doherty et al., 2003a	fMRI	25	13	12	Facial beauty
O'Doherty et al., 2003b	fMRI	13	4	9	Temporal differences in human reward learning
Patterson et al., 2002	fMRI	7	5	2	Correlation with skin conductance
Petrovic et al., 2000	PET	7	7	0	Pain with distractor
Petrovic et al., 2002a	PET	9	9	0	Placebo and opiod analgesia
Petrovic et al., 2002b	PET	17	0	0	Pain regression analysis

Table 1 (*Continued*)

Reference	Type	Total	Men	Women	Short description
Phillips et al., 1999	fMRI	5	–	0	Neutral-angry faces
Rainville et al., 1999	PET	8	5	3	Pain modulated vs. not modulated during hypnosis
Rilling et al., 2002	fMRI	36	0	36	Social cooperation
Rogers et al., 1999a	PET	8	8	0	Monetary reward
Rolls et al., 2003b	fMRI	9	4	5	Pleasant, painful and neutral touch
Rolls et al., 2003a	fMRI	11	5	6	Pleasantness of odours
Royet et al., 2000	PET	12	12	0	Emotional responses to olfaction, vision, audition
Royet et al., 2001	PET	12	12	0	Odour-control (conjunction analysis)
Savage et al., 2001	PET	8	4	4	Verbal memory
Schnider et al., 2000	PET	8	8	0	Learning of new memories
Small et al., 1997	PET	10	5	5	All smell-odourless
Small et al., 1999	PET	–	–	–	Review
Small et al., 2001	PET	9	5	4	Chocolate "beyond" satiety
Sobel et al., 1998	fMRI	12	6	6	Odour sniffing and smelling
Thut et al., 1997	PET	10	10	0	Monetary reward
Völlm et al., 2004	fMRI	7	3	4	Met-amphetamine effects
Wicker et al., 2003	PET	10	10	0	Gaze and emotion
Winston et al., 2002	fMRI	16	8	8	Trustworthiness of faces
Zald and Pardo, 1997	PET	12	0	12	Aversive odours—absence
Zald et al., 1998	PET	9	0	9	Saline, choc and water stimuli
Zald et al., 2002a	PET	9	5	4	Quinine and sugar
Zald et al., 2002b	PET	51	28	23	Correlation with negative affect
Zatorre et al., 1992	PET	11	5	6	Odours
Zatorre et al., 2000	PET	12	6	6	Pleasantness and intensity judgments

For each study is stated the full reference, type of imaging, total number of subjects (men and women), and a short description.

4.2. Results of the meta-analysis

It is clear from all the nine neuroimaging studies conducted in our laboratory which have explored the representation of many different reinforcers in the orbitofrontal cortex that the resulting activations can be categorised into at least three groups as follows. In the first category, the identity and intensity of a stimulus are represented independently of its hedonic or affective value. A primary reinforcer like taste has a representation of the identity of the stimulus in the primary taste cortex in the insula/operculum, and in the most anterior, agranular, part of the insula where it is topologically
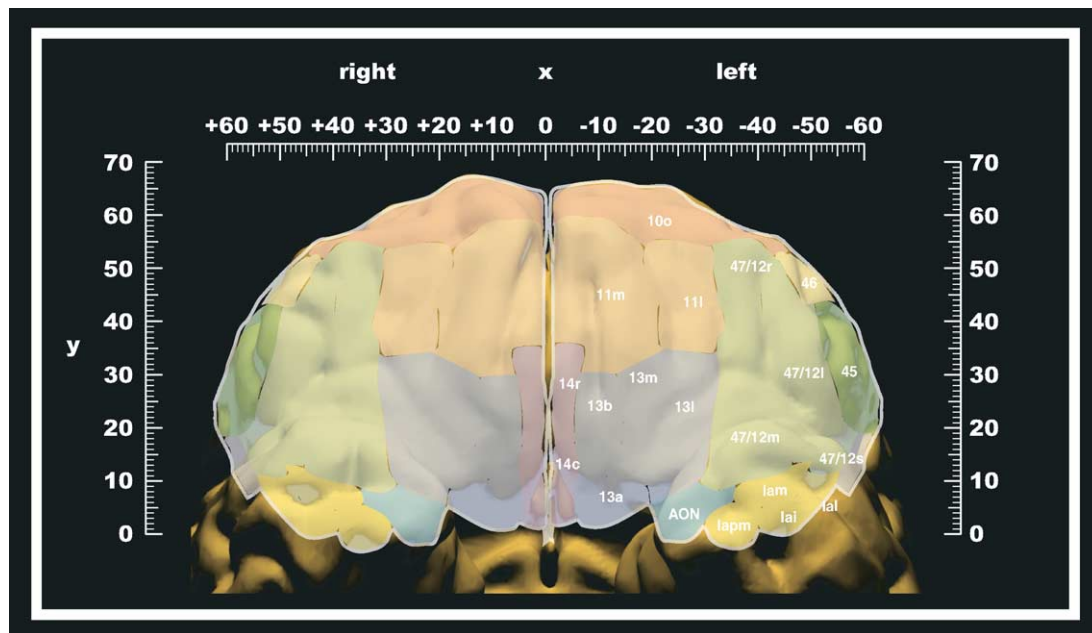

Fig. 10. Cytoarchitectonic maps in stereotaxic space. The human cytoarchitectonic maps of the orbitofrontal cortex rendered on the orbital surface. Modified and extended from Öngür and Price (2000).

Table 2
A full list of all 267 activations included in the meta-analysis

Table of all activations included in meta-analysis

Aharon et al., 2001: [−18, 45, −5, $P < 0.0001$], [19, 48, −11, $P < 0.0001$], [−21, 33, −8, $P < 0.0001$], [−21, 45, −5, $P < 0.0001$], [34, 42, −2, $P < 0.0001$], [13, 54, −8, $P < 0.0001$], [22, 51, −2, $P < 0.0001$], [−21, 18, −8, $P < 0.0001$], [16, 45, −11, $P < 0.0001$], [28, 45, −5, $P < 0.0001$]

Anderson et al., 2003: [−18, 51, −19, $P < 0.002$], [12, 17, −18, $P < 0.0005$], [8, 65, −17, $P < 0.003$]

Bantick et al., 2002: [18, 44, 2, 3.8]

Berns et al., 2001: [20, 36, −12; 7.31], [32, 16, −16; 4.22]

Berthoz et al., 2002: [−36, 28, −22, 3.47, $P < 0.001$], [−42, 26, −14, 4.21, $P < 0.001$]

Blair et al., 1999: [42, 42, −16, 3.32]

Blood and Zatorre, 2001: [17, 32, −23, 3.52]

Blood et al., 1999: [12, 32, −17, 5.76], [13, 30, −18, 6.84], [−24, 32, −14, 4], [−5, 41, −21, 3.75]

Cabeza et al., 2001: [16, 53, −19, 5.4, $P < 0.05c$]

Cerf-Ducastel and Murphy, 2001: [−32, 21, −10, $P < 0.0125$], [48, 39, −6, $P < 0.0125$]

Chua et al., 1999: [−32, 60, −10, 4.84], [−40, 44, −18, 3.63], [34, 60, −4, 5.27], [−42, 52, −12, 4.47]

Coghill et al., 1999: [36, 52, −8, 4.07]

Coghill et al., 2001: [44, 50, −10, $r = 2.07$], [32, 42, −14, $r = 1.91$], [38, 46, −12, $r = 2.04$]

Coghill et al., 1994: [20, 67, −11, n/a]

Craig et al., 2000: [24, 38, 0, 4.8]

Critchley et al., 2000a: [30, 34, −8, 3.26], [−38, 28, −12, 3.73], [44, 54, −4, 3.23], [6, 46, −28, 3.23], [−6, 36, −18, 3.38], [−34, 28, −12, 3.4]

Critchley et al., 2000b: [36, 26, −12, 4.88], [28, 24, −22, 4.47], [10, 52, −10, 4.63]

Critchley et al., 2002: [−24, 40, −6, 9.75, $P < 0.05$]

Dade et al., 2001: [−27, 30, −17, 3.4, $P < 0.001$], [−46, 41, −11, 3.1, $P < 0.001$], [−51, 34, −9, 3.9, $P < 0.001$], [32, 44, −18, 3, $P < 0.001$], [−47, 39, −11, 2.9, $P < 0.01$]

De Araujo et al., 2003c: [2, 52, −15, 4.14, $P < 0.05svc$], [0, 46, −17, 5.09, $P < 0.05c$], [−32, 50, −10, 3.92, $P < 0.05svc$], [36, 25, −6, 3.2, $P < 0.001u$], [38, 23, −7, 3.1, $P < 0.001u$], [10, 22, −12, 3.64, $P < 0.05svc$], [14, 26, −6, 3.94, $P < 0.05svc$]

De Araujo et al., 2003a: [−34, 26, −6, 4.84, $P < 0.05c$], [−44, 34, −18, 3.46, $P < 0.05svc$]

De Araujo et al., 2003b: [9, 19, −16, 3.7, $P < 0.05svc$], [−3, 45, −16, 3.92, $P < 0.05svc$], [16, 46, −16, 3.42, $P < 0.001u$], [2, 30, −18, 4.53, $P < 0.05c$], [6, 22, −7, 3.1, $P < 0.005u$], [−1, 35, −16, 3.9, $P < 0.03svc$]

Derbyshire et al., 1997: [−10, 40, −8, n/a]

Elliott et al., 2003: [−51, 27, 12, 3.99, $P < 0.05svc$], [−33, 42, −15, 3.79, $P < 0.001$], [48, 33, −12, 3.41, $P < 0.05svc$], [−3, 60, −9, 4.28, $P < 0.05svc$]

Elliott and Dolan, 1998a: [30, 52, −14, 3.2], [−34, 54, −12, 3.78]

Elliott and Dolan, 1998b: [42, 38, −16, 3.29]

Elliott and Dolan, 1999: [−10, 18, −16, 4.79], [46, 44, −22, 4.28], [12, 20, −16, 4.7], [−48, 36, −22, 3.45]

Elliott et al., 1999: [3, 39, −12, 3.59], [−30, 24, −30, 3.67], [45, 21, −36, 3.87], [−30, 24, −30, 4.73], [9, 42, −12, 4.58], [15, 27, −12, 3.27]

Elliott et al., 2000b: [−33, 15, −12, 5.2], [51, 15, −12, 4.16]

Farrow et al., 2001: [2, 49, −19, 5.22], [4, 50, −19, 5.22]

Frey and Petrides, 2000: [34, 46, −17, 3.07]

Frey et al., 2000: [−24, 15, −21, 3.46], [27, 22, −20, 2.69]

Ghatan et al., 1995: [−50, 25, −8, 3.17], [30, 20, −12, 3.88]

Ghatan et al., 1998: [−24, 20, −20, 2.74]

Gorno-Tempini et al., 2001: [24, 32, −16, 3.2], [−40, 32, −20, 5.5], [36, 28, −24, 4.2]

Gottfried et al., 2002a: [18, 16, −16, 3.54, $P < 0.001$], [20, 30, −20, 3.76, $P < 0.001$], [−26, 36, −16, 3.15, $P < 0.001$], [−24, 34, −16, 3.31, $P < 0.001$], [−22, 24, −20, 3.22, $P < 0.001$]

Gottfried et al., 2002b: [18, 44, −16, 4.03, $P < 0.05svc$], [30, 42, −10, 3.6, $P < 0.001$], [10, 36, −14, 3.56, $P < 0.001$], [16, 50, −10, 3.8, $P < 0.001$], [14, 46, −18, 3.88, $P < 0.001$], [−32, 52, −12, 4.19, $P < 0.05svc$], [−28, 50, −12, 4.36, $P < 0.05svc$], [14, 46, −18, 5.85, $P < 0.05c$], [28, 46, −8, 4.79, $P < 0.05c$]

Gusnard et al., 2003: [45, 15, −4, $P < 0.001$]

Hobday et al., 2001: [−45, 15, −3, $P < 0.001$], [44, 22, −3, $P < 0.001$], [45, 15, −3, $P < 0.001$], [−44, 22, −3, $P < 0.001$]

Hsieh et al., 1995: [42, 56, −9, 4.55], [−46, 47, −8, 3.13], [40, 55, −8, 4.36]

Iwase et al., 2002: [−2, 22, −24, 6.14, $P < 0.05c$]

Janata et al., 2002: [49, 41, −10, $P < 0.001$]

Kringelbach et al., 2003: [−26, 45, −8, 3.83, $P < 0.05svc$], [16, 38, −22, 5.48, $P < 0.05c$], [2, 30, −22, 4.64, $P < 0.05c$], [−22, 34, −8, 4.06, $P < 0.05svc$], [−33, 44, −12, 3.22, $P < 0.001u$], [−24, 42, −12, 3.37, $P < 0.001u$], [12, 26, −28, 2.85, $P < 0.005u$]

Kringelbach and Rolls, 2003: [−46, 30, −8, 5.51, $P < 0.05c$], [42, 42, −8, 4.94, $P < 0.05c$]

Lafleur et al., 2002: [−4, 10, −24, 5.94]

Lorenz et al., 2002: [−24, 53, −4, 4.7, $P < 0.05c$]

Lorenz et al., 2003: [28, 53, −2, $P < 0.001$], [28, 46, −4, $P < 0.001$],],

Lotze et al., 2001: [51, 24, −9, 4.01, $P < 0.05svc$], [51, 27, −9, 4.18, $P < 0.05svc$]

Maratos et al., 2001: [6, 48, −18, 3.45, $P < 0.001$], [−4, 46, −14, 3.51, $P < 0.001$]

Moll et al., 2002: [−10, 46, −12, $P < 0.0002$]

Morris et al., 1998: [12, 12, −20, 3.35]

Morris et al., 1999: [34, 36, −12, 2.71], [28, 40, −24, 2.8], [−36, 30, −14, 2.98]

Morris and Dolan, 2001: [30, 42, −16, $P < 0.05$, corr]

Table 2 (*Continued*)

Table of all activations included in meta-analysis

Nathaniel-James and Frith, 2002: [−8, 56, −22, 3.9, *P* < 0.001], [−4, 48, −28, 3.7, *P* < 0.001], [0, 50, −20, 3.5, *P* < 0.001], [28, 28, −28, 3.9, *P* < 0.001]

Nobre et al., 1999: [32, 50, −22, 3.33], [−34, 48, −2, 3.68], [42, 52, −16, 3.21], [−36, 50, −16, 3.57], [22, 52, −24, 3.86], [−32, 54, −8, 3.72]

O'Doherty et al., 2002: [32, 46, −6, 3.77, *P* < 0.001], [28, 38, −16, 3.55, *P* < 0.001], [24, 18, −16, 3.5, *P* < 0.001], [10, 44, −22, 3.58, *P* < 0.001]

O'Doherty et al., 2003b: [−21, 45, −9, 3.38, *P* < 0.001], [−24, 54, −18, 3.17, *P* < 0.001]

O'Doherty et al., 2003a: [45, 45, −9, 3.26, *P* < 0.001], [−3, 36, −18, 4.57, *P* < 0.05svc]

O'Doherty et al., 2001: [34, 52, −12, *Z* > 2.56], [28, 60, −6, *Z* > 2.56], [−6, 34, −28, *Z* > 2.56], [−28, 64, −8, *Z* > 2.56], [0, 44, −26, *Z* > 2.56]

Patterson et al., 2002: [3, 39, −10, 4.06, *P* < 0.001]

Petrovic et al., 2002b: [12, 16, −22, 3.26, *P* < 0.001], [20, 20, −18, 3.65, *P* < 0.001], [−22, 14, −14, 4.04, *P* < 0.001], [22, 20, −16, 3.89, *P* < 0.001], [−22, 14, −14, 4.05, *P* < 0.001]

Petrovic et al., 2002a: [18, 12, −18, 4.05, *P* < 0.001], [30, 30, −6, 3.54, *P* < 0.001], [−24, 42, −16, 3.09, *P* < 0.001], [30, 46, −14, 3.49, *P* < 0.001]

Petrovic et al., 2000: [30, 30, 0, 3.11]

Phillips et al., 1999: [38, 39, −2, *P* < 0.0004]

Rainville et al., 1999: [−34, 56, −2, 6.84], [−47, 39, −11, 7.1], [46, 32, −17, 6.06], [36, 25, −8, 5.22]

Rilling et al., 2002: [6, 51, −18, 3.26, *P* < 0.01], [3, 48, −12, 4.03, *P* < 0.01], [4, 36, −12, 4.39, *P* < 0.01]

Rogers et al., 1999b: [22, 40, −32, 4.42], [42, 50, −8, 4.24], [−4, 54, −20, 4.54], [−14, 34, −32, 3.28], [18, 48, −28, 3.81], [36, 56, −12, 3.92]

Rolls et al., 2003b: [−22, 52, −10, 4.48, *P* < 0.05svc], [16, 32, −24, 5.14, *P* < 0.05c], [−8, 58, −12, 4.1, *P* < 0.05svc], [−26, 40, −20, 4.88, *P* < 0.05c]

Rolls et al., 2003a: [−40, 26, −10, 4.53, *P* < 0.05c], [0, 54, −12, 5.23, *P* < 0.05c], [−2, 52, −10, 4.28, *P* < 0.01svc], [−20, 54, −14, 4.26, *P* < 0.01svc], [−36, 27, −8, 4.23, *P* < 0.05svc], [−16, 28, −18, 4.08, *P* < 0.05svc]

Royet et al., 2001: [36, 48, −6, 3.84], [28, 26, −16, 3.61], [28, 28, −10, 3.66], [−26, 24, −10, 4.28], [−28, 26, −6, 3.85], [26, 30, −12, 3.95], [−26, 22, −10, 4.84]

Royet et al., 2000: [28, 26, −14, 3.91], [26, 30, −12, 3.95], [−24, 30, −8, 4.34]

Savage et al., 2001: [2, 54, −4, 4.31], [14, 54, −12, 4.38]

Schnider et al., 2000: [−16, 24, −28, 3.42], [10, 36, −32, 3.76], [14, 22, −20, 3.55], [−16, 28, −32, 4.73]

Small et al., 1997: [9, 37, −26, 3.85], [21, 49, −5, 3.75], [34, 29, −21, 6.63], [43, 51, −17, 4.27], [−36, 60, −14, 5.41], [34, 24, −17, 4.56], [−3, 60, −14, 3.6], [27, 37, −20, 4.71], [−8, 37, −20, 3.05], [−17, 42, −12, 4.45], [19, 65, −15, 3.62]

Small et al., 1999: [−44, 39, −9, n/a], [21, 41, −14, n/a], [−15, 44, −11, n/a], [−17, 30, −22, n/a], [26, 28, −16, n/a], [−17, 41, −17, n/a], [17, 37, −20, n/a], [25, 24, −23, n/a], [−26, 29, −18, n/a], [−21, 36, −12, n/a], [28, 23, −18, n/a]

Small et al., 2001: [16, 27, −19, 4.8], [44, 27, −5, 4.2], [−18, 25, −18, 5.3], [41, 34, −19, 4.3]

Sobel et al., 1998: [30, 45, −10, 2.49]

Thut et al., 1997: [−30, 18, −16, 3]

Völlm et al., 2004: [12, 42, −14, 5.1, *P* < 0.05c], [0, 54, −8, 3.66, *P* < 0.001]

Wicker et al., 2003: [1, 34, −18, 4.13, *P* < 0.001], [18, 57, −8, 4, *P* < 0.001]

Winston et al., 2002: [−28, 42, −10, 3.73, *P* < 0.001]

Zald et al., 2002a: [−24, 50, −11, 4.6, *P* < 0.001], [−24, 55, −11, 3.5, *P* < 0.001], [−24, 44, −16, 3.5, *P* < 0.001], [26, 26, −18, 3.9, *P* < 0.001], [19, 35, −20, 4.1, *P* < 0.001]

Zald et al., 2002b: [−7, 46, −11, *P* < 0.05], [3, 55, −9, *P* < 0.005], [−3, 44, −9, *P* < 0.05]

Zald and Pardo, 1997: [−42, 35, −14, 4.7]

Zald et al., 1998: [−24, 41, −7, 3.4], [−21, 39, −7, 3.5]

Zatorre et al., 1992: [17, 29, −13, 3.66], [−7, 5, −11, 3.5]

Zatorre et al., 2000: [24, 34, −11, 3.83], [23, 36, −14, 4.41]

For each study is listed the (*x*, *y*, *z* statistic), where statistic is the peak *z*-value where available, or, if not available, the *t*-value or the *P*-value.

continuous with the caudal orbitofrontal cortex (De Araujo et al., 2003a, 2003c; Kringelbach et al., 2003, 2004). Similarly, the intensity and identity of olfactory stimuli but not their pleasantness is represented in the primary olfactory cortical areas (Rolls et al., 2003a). A second category of sites in a medial part of the orbitofrontal cortex is activated in relation to the pleasantness of stimuli, such as the pleasantness of the taste or smell of stimuli (De Araujo et al., 2003b; Rolls et al., 2003a), how consonant taste and olfactory stimuli are (De Araujo et al., 2003c), or after the administration of amphetamine (Völlm et al., 2004). A third category of sites in more lateral parts of the orbitofrontal cortex is activated when punishing stimuli which may lead to a change in behaviour are delivered, such as monetary loss (O'Doherty et al., 2001), painful touch (Rolls et al., 2003b), and a face

expression (which instead of the expected smile in a visual discrimination task is an angry expression) which signals that behaviour should change (Kringelbach and Rolls, 2003).

Our data can thus be interpreted as revealing two distinct trends: a mediolateral trend and a posterior–anterior trend, as shown in Fig. 11. The mediolateral trend was clearly seen in our monetary gambling experiment (O'Doherty et al., 2001), where monetary gain which did not lead to behavioural change activated the medial–anterior parts of the orbitofrontal cortex, while monetary losses signalled that the subjects needed to change their behaviour activated lateral and anterior parts of the orbitofrontal cortex. The posterior–anterior trend was clearly seen in our whole food sensory-specific satiety experiment (Kringelbach et al., 2003), where having food in the mouth activated caudal
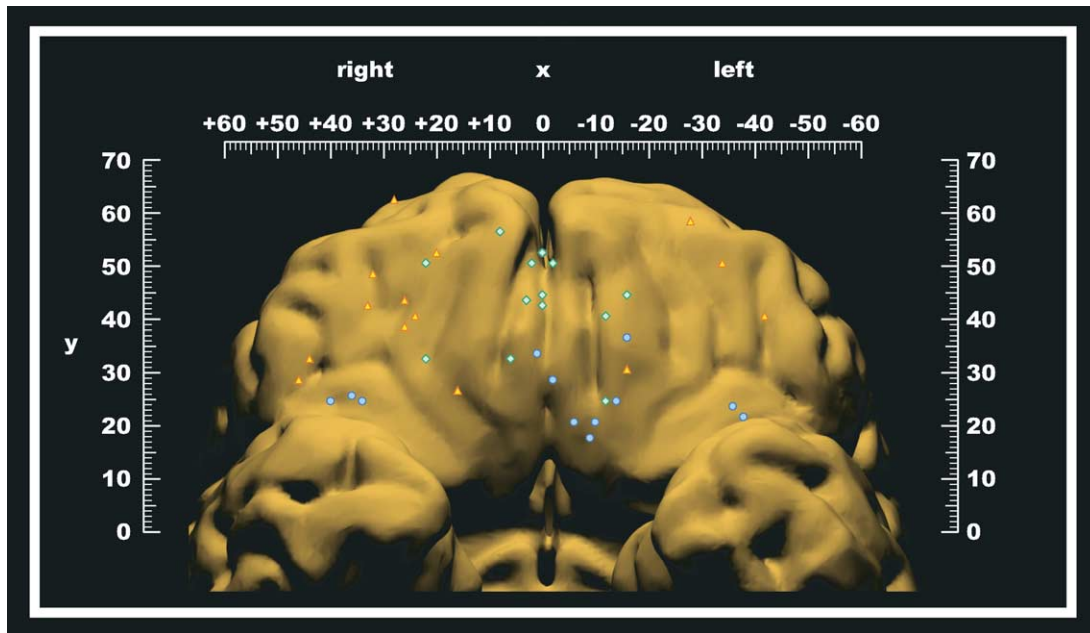
Fig. 11. Activations from studies from Rolls' Lab. Primary reinforcers (blue circles) tend to be represented in posterior regions of the orbitofrontal cortex. The activations related to monitoring the reward value of reinforcers are mainly represented in more anterior and medial regions of the orbitofrontal cortex (shown as light green diamonds), while those activations related to impending change in behaviour are mainly located in lateral regions (shown as yellow triangles). This separation in a medial–lateral distinction and a posterior–anterior distinction was found in individual studies.

parts of the orbitofrontal cortex close to the junction with the agranular insula independently of whether the food was pleasant at the start of a meal or less pleasant at the end of the meal, whereas the pleasantness of the food (in a sensory-specific satiety design) was related to activation in more anterior parts of the orbitofrontal cortex.

However, it is not clear from just a limited number of studies whether these trends are consistent. For example, in another study (Rolls et al., 2003a), we found the main effects of odour irrespective of valence to be located more anterior than would be expected from the prediction of the two trends. To test this, we classified all 267 activations from the meta-analysis according to the very same criteria as those used for our own studies. The different activations within studies were thus either classified as: (1) representations of reinforcers such as taste and smell which were independent of the reward/punishment value (17.6%); (2) representations which reflected the hedonic value or pleasantness of the stimuli (26.2%); (3) punishers leading to behavioural change (43.8%); or (4) other, which did not fit the above criteria (12.4%). When performing a cluster analysis on these groups it was found that the motivation-independent reinforcer representations (category 1) were best described by two clusters (one in each hemisphere) with coordinates ($\pm$standard error mean): [-23.5 ± 2.4, 31.0 ± 2.2] and [16.2 ± 2.1, 30.8 ± 1.9] (hereafter called RP_L and RP_R). A single cluster with coordinates [2.8 ± 1.6, 41.0 ± 1.4] (hereafter called M) was found to best describe the activations classified as pleasantness/monitoring positive hedonic value (category 2). Two clusters (one in each hemisphere) were found to best

describe the activations classified as punishers leading to a behavioural change (category 3): [-32.5 ± 1.4, 41.7 ± 1.7] and [33.6 ± 1.3, 40.5 ± 1.5] (hereafter called PBC_L and PBC_R). The centres of mass for all clusters are superimposed on the representation of all of the activations in Fig. 12.

We then performed t-tests to compare all the activations for each of the individual clusters. Clearly demonstrating the posterior–anterior trend, significant differences were found between the y-coordinates of the activations in the two RP clusters and the M cluster (RP_Ly versus My: $t = 3.91$, $P < 0.0002$; RP_Ry versus My: $t = 4.27$, $P < 0.00006$; one-tailed). Likewise significant differences were found between y-coordinates of the activations in the two RP clusters and the PBC clusters (RP_Ly versus PBC_Ly: $t = 4.08$, $P < 0.0002$; RP_Ly versus PBC_Ry: $t = 3.68$, $P < 0.0005$; RP_Ry versus PBC_Ly: $t = 4.41$, $P < 0.00005$; RP_Ry versus PBC_Ry: $t = 3.98$, $P < 0.0002$). No significant differences were found between the y-coordinates of the activations in the M cluster and the PBC clusters.

Similarly, clearly demonstrating the mediolateral trend, very significant differences were found between the x-coordinates of the activations in the M cluster (category 2) and the PBC clusters (category 3) (Mx versus PBC_Lx: $t > 8$; Mx versus PBC_Rx: $t > 8$). Likewise, significant differences were found between the x-coordinates of the activations in the M cluster (category 2) and in the RP clusters (category 1) (Mx versus RP_Lx: $t = 4.6$; Mx versus RP_Rx: $t = 4.03$). There were also significant differences between the x-coordinates of the activations in the RP cluster and in
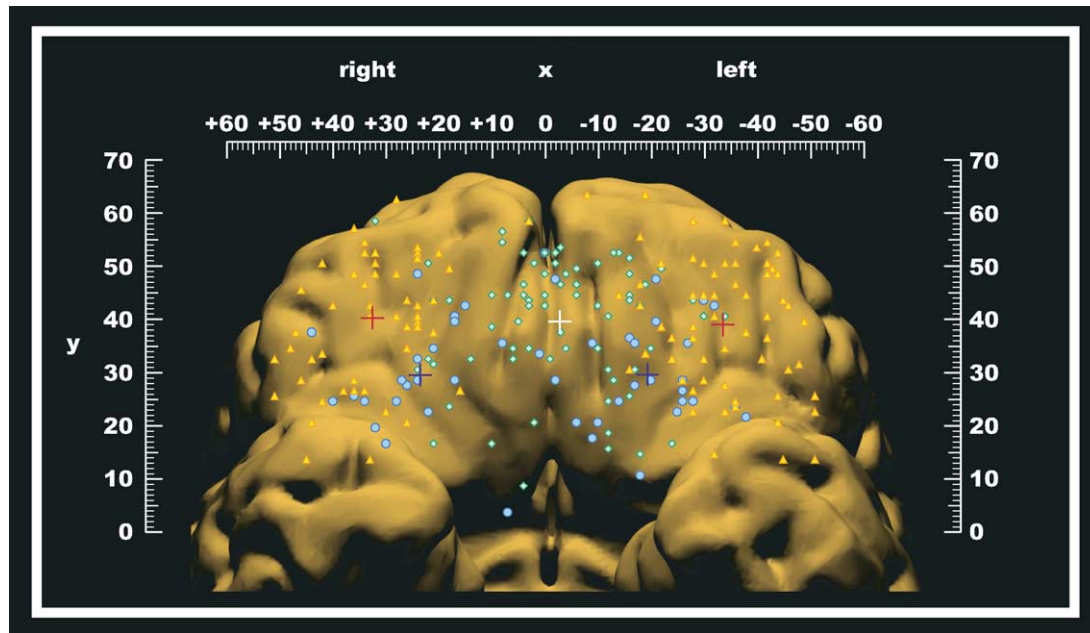
Fig. 12. Meta-analysis. The 267 activations in stereotaxic space from all the reviewed studies are shown rendered on the orbital surface of the human brain. The two centres of mass of the clusters for activations related to motivation-independent reinforcer representation (blue circles) are marked with a dark blue cross, while the centre of mass of the cluster of activations related to monitoring of reward value (light green diamonds) is marked with a white cross. Similarly, the two centres of mass of the clusters related to punishers leading to changes in behaviour (yellow triangles) are marked with a red cross. Statistical analysis of the activations in these clusters confirms that the clusters are significantly separated in a medial–lateral and anterior–posterior trend (see Section 4.2).

the PBC clusters (RP_Lx versus PBC_Lx: $t = 3.43$; RP_Rx versus PBC_Rx: $t > 8$).

Not surprisingly and testifying to the lack of clear lateralisation in the orbitofrontal cortex, there were no significant differences between the y-coordinates of the activations in the RP_L and RP_R clusters, or between the y-coordinates of the activations in the PBC_L and PBC_R clusters.

This statistical analysis of activation peaks should of course be taken cautiously as the 87 studies reviewed here employed very different statistical methods, and it is of considerable interest to note that only some of the 87 published papers reviewed here have used the more stringent group analyses such as random effects or conjunction analysis, which would allow generalisation to significant proportions of the population. It is also interesting to note that the majority of the studies used a threshold of statistical significance of $P < 0.001$ uncorrected for multiple comparisons, and this choice may reflect the substantial variability in the orbitofrontal cortex between different individuals.

4.3. Discussion of the meta-analysis

The meta-analysis revealed a distinction between the functions of medio versus lateral and posterior versus anterior areas in the sample of the 87 reviewed papers. The results of the meta-analysis thus confirm that there is some localisation of function within the orbitofrontal cortex in terms of its functional neuroanatomy.

4.3.1. Medial versus lateral trend

The clearest indication of a differentation in function between medial versus lateral areas of the human orbitofrontal cortex was found in a study from our laboratory investigating visual discrimination reversal learning, which showed a clear dissociation between the medial areas correlating with monetary gain and the lateral areas correlating with monetary loss (O'Doherty et al., 2001). This result, and some of the other studies included in the meta-analysis, can be interpreted as evidence for a difference between medial orbitofrontal cortex areas involved in decoding and monitoring the reward value of reinforcers, and lateral areas involved in evaluating punishers which when detected may lead to a change in current behaviour. A good example of a study showing the latter involved a visual discrimination reversal task in which face identity was associated with a face expression (Kringelbach and Rolls, 2003). When the face expression associated with one of the faces reversed and the face expression was being interpreted as a punisher and indicated that behaviour should change, then lateral parts of the orbitofrontal cortex became activated.

Further support for this medial–lateral distinction comes from a recent neuropsychological study using patients with circumscribed surgical lesions (Hornak et al., 2004). It was found that only patients with bilateral lesions to the anterior lateral regions of the human orbitofrontal cortex (and not unilateral lesions or lesions to other parts of the orbitofrontal cortex) were significantly impaired on a

probabilistic reversal-learning task. This fits very well with the evidence from neuroimaging where specifically the lateral parts (and not the medial parts) of the orbitofrontal cortex are engaged when reversing stimulus contingencies (Kringelbach and Rolls, 2003; O'Doherty et al., 2001).

As reviewed earlier there is neuroanatomical evidence from non-human primates (macaques) that supports a distinction between medial and lateral areas of the orbitofrontal cortex. As depicted in Fig. 5, it has been shown that the connectivity of the orbital network encompassing lateral areas of the primate orbitofrontal cortex is primarily within these areas with weak connections to medial parts (Carmichael and Price, 1996). As shown in Fig. 4b, anatomical evidence shows that within the lateral region, the taste input is lateral and posterior, the visual input is lateral and a little more anterior, and the somatosensory input is towards the middle of the lateral area. Anatomical evidence indicates that the medial areas receive olfactory inputs (see Fig. 4a), and have many connections with the cingulate cortex (see Fig. 4c), including area 25 which has autonomic outputs. This has led Carmichael and Price (1996) and Öngür and Price (2000) to propose a distinction between a medial prefrontal network providing a viscero-motor link, and a lateral orbital network providing multimodal sensory processing. Similarly, the differences described earlier in the cytoarchitecture, phylogeny, sulcal variability and maturity rate between medial and lateral parts of the orbitofrontal cortex may account for the functional difference.

However, it must be said that neurophysiological findings which allow one to test that actual inputs to each neuron do not support great segregation into areas dominated by any one sensory modality, with considerable intermixing of orbitofrontal cortex neurons with inputs from each modality, and many neurons responding to inputs from several modalities, as shown by Rolls and Baylis (1994) and by later studies in the reference list from Rolls' lab (Rolls, 2004). The findings from the meta-analysis, and emphasised particularly in the papers of O'Doherty et al. (2001) and Rolls et al. (2003a), that more medial areas of the human orbitofrontal cortex have responses especially related to rewards, and the lateral areas to punishers, is an interesting result of the human neuroimaging that is not predicted based on a simple topological comparison of medial versus lateral in the macaque anatomical or neurophysiological literature. In macaques, for each primary reinforcer type (e.g. taste, somatosensory input), neurons with responses to rewards and punishers tend to be intermingled. However, it is the case that medial parts of the macaque orbitofrontal cortex (more medial than approximately 5 mm from the midline) have been relatively little explored, and it will be of interest to record now in these areas to help understand what has been found in the human neuroimaging studies. If neurons that respond to for example olfactory and somatosensory rewarding stimuli are not found in this medial part of the macaque orbitofrontal cortex, then it is likely that areas found more laterally in macaques are present more medi-

ally in humans, perhaps because the more dorsal and lateral parts of the human prefrontal cortex have expanded greatly, pushing the orbitofrontal areas generally more towards the middle and medial parts of the orbitofrontal cortex in humans.

Elliott et al. (2000a) have also proposed a distinction between medial and lateral orbitofrontal cortex based on both published and unpublished studies from their laboratory. These authors propose that the orbitofrontal cortex is activated when there is insufficient information available to determine the appropriate course of action and when this information is related to the reward value of stimuli and the response. This is in contrast to stimulus identity or location, which activate different parts of the prefrontal cortex. Specifically, they propose that the lateral regions of orbitofrontal cortex are activated when the action selected requires the inhibition of previously rewarded responses, while they propose that the medial regions are concerned with monitoring reward value. However, as discussed earlier, the evidence for a role of the orbitofrontal cortex in motor response inhibition is not very strong. Instead, we believe that a more parsimonious description of the role of the lateral and anterior regions of the orbitofrontal cortex is to regard them as concerned with evaluating the punishment (versus reward values) of stimuli and thus providing a signal that can lead to a change in current behaviour.

4.3.2. Posterior versus anterior trend

The bulk of the published experiments we have reviewed suggest that an increase in complexity of the representation and processing of rewards and punishers is mirrored by the posterior–anterior location of activation in the orbitofrontal cortex. Very abstract reinforcers such as loss of money appear to be represented further anterior towards the frontal pole (e.g. O'Doherty et al., 2001) than posterior areas representing simple reinforcers such as taste (e.g. De Araujo et al., 2003b,c) or thermal intensity (Craig et al., 2000). This posterior–anterior trend is clearly demonstrated in the statistical results from the meta-analysis and is likely to reflect some kind of hierarchical processing in the orbitofrontal cortex.

One trend is that the main effects of primary reinforcers such as odour and taste tend to be located in relatively more posterior areas of the orbitofrontal cortex, whereas correlations with subjective pleasantness and unpleasantness ratings tend to be more anterior, as exemplified by findings in a number of studies (Blood et al., 1999; De Araujo et al., 2003b, 2003c; Kringelbach et al., 2003; O'Doherty et al., 2001, 2003a; Rolls et al., 2003a; Völlm et al., 2004). This is consistent with higher level processing more anteriorly which is on a route to parts of the brain involved in making processing available to conscious experience (Rolls, 1999a). Another finding is that areas that have supralinear responses to combinations of sensory inputs, for example taste and smell (De Araujo et al., 2003c), or the umami taste stimuli MSG and inosine 5′-monophosphate (De Araujo et al.,

2003a), tend to be more anterior than the areas where the components of the combinations are represented in the orbitofrontal cortex. This could easily reflect hierarchy in the system, with convergence tending to increase from more posterior to more anterior orbitofrontal cortex areas, and thus effects of combinations of inputs becoming more evident anteriorly. Supporting evidence of such hierarchical processing comes from a recent paper which found activation of posterior regions of the orbitofrontal cortex to unimodal odour but further multimodal integration of olfactory–visual stimuli in anterior parts of the medial orbitofrontal cortex (Gottfried and Dolan, 2003).

The diagrams published on the intricate connectivity of the different areas of the primate orbitofrontal cortex (see Figs. 5 and 6) do suggest that the processing within the orbitofrontal cortex could well be hierarchical (Carmichael and Price, 1995a,b, 1996). Moreover, as shown in Fig. 6, where the primate connectivity diagrams are extended to the known anatomy of the human orbitofrontal cortex, the possibility for hierarchical processing and thus support for a posterior–anterior trend becomes somewhat clearer (Öngür and Price, 2000).

The meta-analysis thus demonstrates that the published studies do appear to show a posterior–anterior trend in the orbitofrontal cortex. Some authors have claimed posterior–anterior trends correlating with increases in sophistication in cortical processing in other areas of the prefrontal cortex (Christoff and Gabrieli, 2000; Petrides, 1994). To our knowledge, however, this is the first time that a similar trend for the areas on the orbital surface of the human brain has been proposed.

4.4. Challenges of neuroimaging the human orbitofrontal cortex

A challenge for most studies investigating the human orbitofrontal cortex using functional magnetic resonance imaging is that this brain region is in close proximity to the air-filled sinuses, which potentially means that signal dropout, geometric distortion and susceptibility artefacts are common when using EPI at higher magnetic field strengths. In collaboration with physicists, first at the University of Nottingham (Drs. R. Bowtell and S. Francis) and then at FMRIB, University of Oxford (Drs. P. Jezzard and J. Wilson), we worked to maximise the signal obtained from the orbitofrontal cortex using a number of methods. One method is to optimise the local shim for the orbitofrontal cortex. Such methods for optimisation of the local shim over one part of the brain come at a price, however, whereby the signal obtained from other parts of the brain is degraded. Specifically, while it is possible to either obtain a good signal in the orbitofrontal cortex or in the amygdala in the temporal lobes, current methods do not allow for a good signal to be obtained in both brain structures at the same time when scanning at 3T. Recently, however, physicists J. Wilson and P. Jezzard from FMRIB have come up with

an ingenious solution (patent pending) that dramatically improves the signal (Wilson et al., 2002).

Until such new methods become available for general use, the following main five steps are recommended for the optimisation of the signal from the orbitofrontal cortex:

4.4.1. Use coronal slicing
Susceptibility artefacts are minimised by using a coronal slicing direction rather than the more commonly used axial slicing direction, as the slices are aligned perpendicular to the predominant direction of the susceptibility induced field gradients. This limits the amount with which a single slice includes areas with markedly different field properties (Ojemann et al., 1997).

4.4.2. Minimise in-plane voxel resolution
The probability of brain tissue within a voxel having different precession frequencies due to susceptibility induced field inhomogeneities is increased with larger voxel sizes, and thus the use of smaller voxels leads to less phase cancellation.

4.4.3. Increase the gradient switching frequency
The geometric distortion occurring in the data can be minimised by increasing the gradient switching frequency, which is dependent on the hardware characteristics of the gradient coils. We use a higher gradient switching frequency than is normally used in conventional EPI sequences: 1.9 kHz at the 3T scanner at the University of Nottingham and 960 Hz at the 3T scanner at the University of Oxford.

4.4.4. Utilise short echo time (TE)
Shorter echo times give less phase dispersion across the voxel as phase coherence is preserved. The standard echo time for EPI is 30 ms, while the studies from our laboratory utilised 23 and 25 ms echo times.

4.4.5. Employ higher order shimming
Shimming using the shim coils was carried out on each individual subject to optimise the static magnetic field in order to minimise field homogeneities. In particular we weighted the orbitofrontal cortex using an automatic shimming method (Wilson et al., 2002).

4.5. Improvements to neuroimaging methods

As alluded to earlier, performing a meta-analysis of published studies in the neuroimaging literature is difficult. The problems with the large variety of methods have been mentioned, particularly those arising from comparing imaging studies using different imaging methods (PET versus fMRI), different stimuli, and analysed with different statistical methods.

In addition to these general problems with meta-analyses of neuroimaging studies, there are further problems quite unique to the orbitofrontal cortex. As described in Section 1
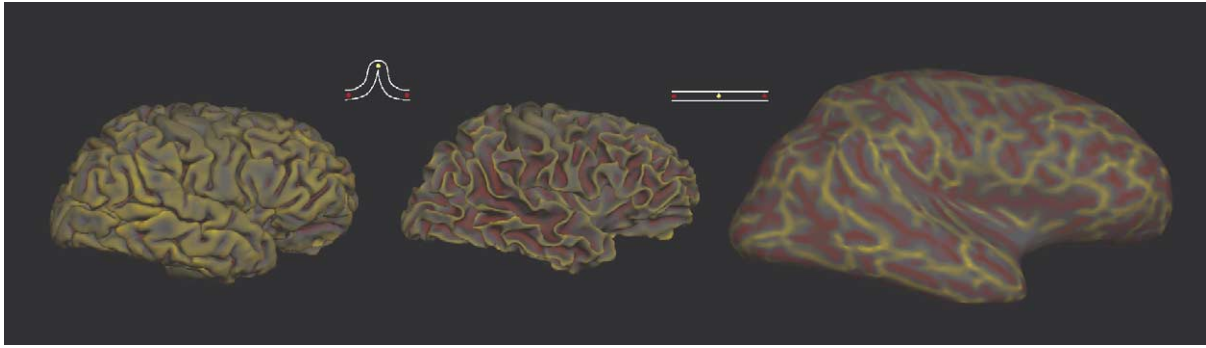
Fig. 13. Inflation of hemisphere. From left to right in the figure it is demonstrated how the highly convoluted cortex of a right hemisphere of the human brain (far left) can be reduced to white matter (middle) and then subsequently inflated to show the patterns of sulci and gyri. Data was partly prepared and processed with the Freesurfer-software package (Dale et al., 1999; Fischl et al., 1999).

there is substantial individual variability in the orbitofrontal cortex as expressed for example in the variability of sulcal patterns. The inter-subject variability raises a number of additional problems when normalising individual data to standard stereotaxic space. Even when taken into account as a result of the spatial smoothing applied as part of the normal preprocessing of functional data, individual variability is still likely to obscure important finer details about the functional neuroanatomy of the orbitofrontal cortex.

New strategies taking these problems into account clearly need to be developed to provide better analyses of orbitofrontal cortex functions. A key issue is how to standardise the individual variability. One possible route would be to use methods for inflating and unfolding the cortex (see Fig. 13). Such methods have been used to map the primary visual areas (Dale et al., 1999; Fischl et al., 1999; Van Essen et al., 2001), and it is likely that similar methods could be successfully used on the orbitofrontal cortex (see Fig. 14).
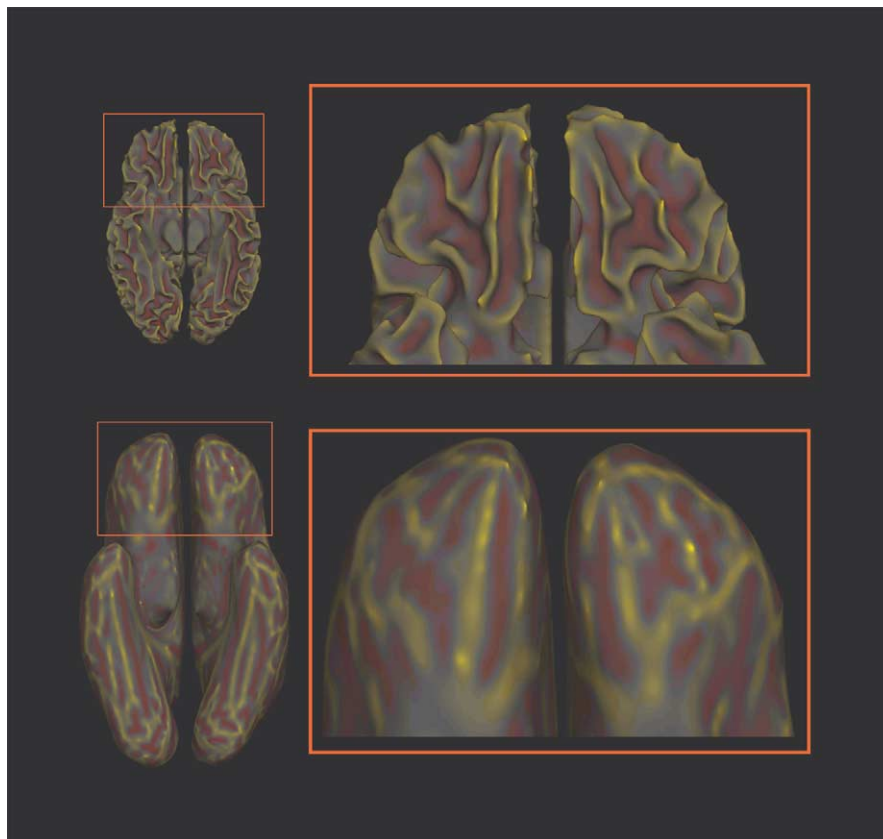

Fig. 14. Inflation of orbitofrontal cortex. At the top of the figure is shown the white matter rendering of the two hemispheres of an individual's brain. On the left is shown the full ventral view (without the cerebellum) of the brain, and on the right there is an expanded view of the orbitofrontal cortex. At the bottom of the figure is shown a ventral view of the full inflated brain (left), and an expanded view of the orbitofrontal cortex (right).
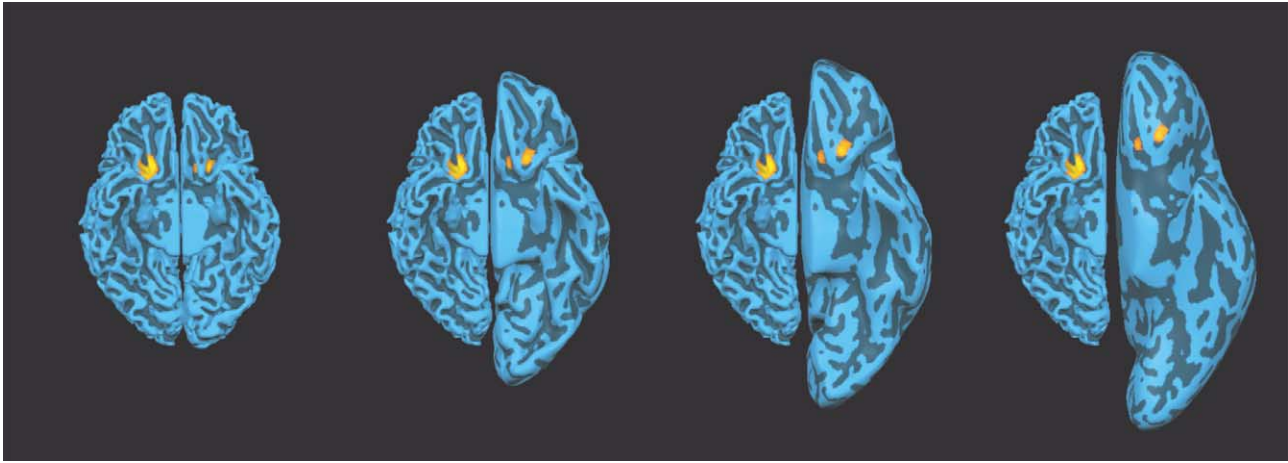
Fig. 15. Inflation of functional data in a single subject. The figure demonstrates how the data from a single subject can be inflated on the subject's own brain. The figure shows the steps in inflation of the left hemisphere, which then can mapped to an inflated spherical standardised space. From this standardised space individual differences are substantially reduced when compared to standard normalisation methods and appropriate statistical modelling can then be carried out on functional data in this standardised space (Fischl et al., 1999). This will yield more accurate activation patterns in the orbitofrontal cortex and thus give more detailed information about the functional neuroanatomy of the orbitofrontal cortex.

The main idea behind these methods is that the sulci and gyri of the cortex are obscuring otherwise fairly constant patterns of cortical processing. It is, of course, still an open question whether the apparent variability of higher order cortical areas such as the orbitofrontal cortex is merely superficial, or reflects functional cortical variability acquired through development whether this is related to learning or the nature of the genetic specification.

We have nevertheless started to develop and use a number of methods to investigate these questions. The results of mapping functional data from a taste experiment in a single individual onto a high resolution structural image, and subsequently inflating the two hemispheres, are shown in Fig. 15. The next step is then to map this inflated brain to an inflated spherical standardised space. From this standardised space individual differences are substantially reduced when compared to standard normalisation methods (Fischl et al., 2001). Statistical modelling can then be carried out on data in this standardised space. Normally the data to be modelled would come from different individuals, but there is also the possibility of using multiple datasets from a single subject to test the reliability of activations. This work demonstrates great potential to unravel even more information about the functional neuroanatomy of the orbitofrontal cortex.

5. Conclusions

Based on evidence from neuroimaging experiments and complemented by evidence from primate neuroanatomy and neurophysiology, and human neuropsychology, this review has tried to synthesise the functions of the human orbitofrontal cortex in terms of the spatial distribution of the observed activations in the neuroimaging literature.

Two general trends of neural activity have emerged, with a mediolateral distinction between activity related to monitoring the reward value of reinforcers versus their punishment value which can lead to behavioural change, and a posterior–anterior distinction which appears to be related to hierarchical processing and towards brain systems closer to conscious subjective report.

Overall the results from the neuroimaging experiments in humans reviewed here are consistent with the results from neurophysiological recordings in non-human primates indicating an important role of the primate orbitofrontal cortex in representing the reward and punishment value of primary reinforcers, and in learning associations between previously neutral stimuli and primary reinforcers. Neuroimaging of the human brain allows these findings to be extended to representations in the human orbitofrontal cortex of uniquely human rewards, such as abstract monetary reward and punishment. In the following we will summarise the main conclusions about the role of the orbitofrontal cortex that can be drawn from neuroimaging experiments.

5.1. The representation of reinforcers in the orbitofrontal cortex

Some of the neuroimaging experiments reviewed here investigate the affective responses to primary and secondary reinforcers such as auditory (Frey et al., 2000), taste (Small et al., 1999), whole-food (Kringelbach et al., 2003), olfactory (Rolls et al., 2003a; Royet et al., 2001), pain (Petrovic et al., 2000; Rolls et al., 2003b), monetary reward and punishment (O'Doherty et al., 2001), social judgments (Farrow et al., 2001) and music (Blood et al., 1999). The results from the primary reinforcers are consistent with data from neurophysiological recordings in non-human primates, and

further demonstrate that the orbitofrontal cortex represents the affective value of both primary and abstract secondary reinforcers.

5.2. The representation of the reward value of reinforcers

Neurophysiological studies using sensory-specific satiety have clearly shown that neurons in the orbitofrontal cortex encode the reward value of the reinforcers (Critchley and Rolls, 1996a; Rolls et al., 1989). Experiments from our laboratory have shown that a region of the left lateral orbitofrontal cortex (area 11) showed a sensory-specific decrease in the reward value to the food eaten to satiety but not to the food not eaten (Kringelbach et al., 2003). This result indicates that the reward value of the taste, olfactory, and somatosensory components of a whole food are represented in the orbitofrontal cortex. Consistently, satiety-related responses in a very similar part of the anterior lateral orbitofrontal cortex have been found in a further sensory-specific satiety study (Gottfried et al., 2003).

Another study from our laboratory on abstract reward found a correlation between BOLD signal in dissociable regions of the orbitofrontal cortex and abstract monetary gains and losses (O'Doherty et al., 2001). Similarly another study found a correlation between subjective ratings of dissonance and consonance of musical chords in the orbitofrontal cortex (Blood et al., 1999). These correlations are further indication that the reward values of even abstract reinforcers are represented in the orbitofrontal cortex.

5.3. The specificity of reward and punishment representations

Our study on abstract reward found that monetary reward and punishment are correlated with activations in different regions of the orbitofrontal cortex. These results suggest that reward and punishment representations are spatially distinct in the human brain. Even this evidence cannot, however, does not show that reward and punishment have totally separate representations in the human brain. In particular, the medial regions of the orbitofrontal cortex that had activations correlating with the magnitude of monetary reward (area 11) also reflected monetary punishment in the sense that the activations in these medial regions correlated positively with the magnitude of monetary wins and negatively with losses. Similarly, the more lateral regions (area 10) had activations that correlated negatively with the magnitudes of monetary wins and gains, and positively with monetary loss/punishment. This means that in this experiment the medial and lateral regions were apparently coding for both monetary reward and punishment (albeit in opposite ways). The evidence from this experiment would therefore suggest that the segregation between reward and punishment is not spatial but rather encoded in the neuronal responses (as expressed by the BOLD signal).

We have however obtained evidence from an experiment using pleasant, painful and neutral somatosensory stimulation that there is some spatial segregation of the representation of reward and punishment, where the effects of pleasant somatosensory stimulation are spatially dissociable from the effects of painful stimulation in the human orbitofrontal cortex (Rolls et al., 2003b). Further, pleasant odours activate medial, and unpleasant odours lateral regions of the human orbitofrontal cortex (Rolls et al., 2003a). Moreover, a very recent study found that only the valence and not the intensity of gustatory stimuli are represented in the orbitofrontal cortex (Small et al., 2003). Interestingly, this study did not find a medial–lateral distinction between pleasant and unpleasant gustatory stimuli but this is perhaps not surprising given that the published BOLD detectability map for the orbitofrontal cortex indicates significant signal dropout in medial parts.

Overall, the evidence in the literature for spatial segregation of reward and punishment representations in the orbitofrontal cortex is not very consistent. Some experiments do seem to support the notion that there are spatially separable regions of the orbitofrontal cortex with graded neuronal responses to reward and punishment. It would be of considerable interest to run an experiment with pleasant (glucose) and unpleasant (saline) pure taste and to measure the BOLD signal of the main effects in individual subjects. Using the more sensitive inflation techniques proposed, it should then be possible to resolve the problem of possible spatial segregation or overlap of reward and punishment representations in the orbitofrontal cortex at both the individual level and the possible generalisation to a larger population. It may be noted that even if the locations of the orbitofrontal areas cannot be segregated according to reward versus punishment (i.e. what can be measured in neuroimaging studies), there is nevertheless an exquisite representation of the reward and punishment value of a very wide range of different primary and secondary reinforcers by different neurons in the primate orbitofrontal cortex, as shown by neurophysiological studies (Rolls, 1999a, 2002, 2003a, 2004).

5.4. Separation of representations of reward value

In order to make a behavioural decision between two rewards with different reward value, it is clearly necessary for the brain to represent the reward values. At least two different types of neural mechanism could represent these reward values. The reward values of each reinforcers could either be coded separately for each individual reinforcer, or there could be a single output activated by all reinforcers. It is therefore of considerable interest to note that the meta-analysis showed that representations for different types of reinforcers tend to form separate clusters in different locations (see Fig. 12). This could indicate that different regions of the orbitofrontal cortex represent the reward value of different types of reinforcers. In other words, it would appear that reward value is assigned for each type of

reinforcer separately, as is needed if a choice is to be made between different rewards that are available (Rolls, 1999a). As noted above, this evidence is exquisitely available at the single neuron level.

5.5. Subjective correlates of the affective valence of reinforcers

Some of the results from the experiments reviewed and those carried out in our laboratory can be interpreted as revealing the brain correlates of the subjective experience of the affective valence or reward value of reinforcers. In a whole-food experiment (Kringelbach et al., 2003), the subjective pleasantness ratings reflected the effects of sensory-specific satiety on the food eaten, and it was found that these ratings correlated with the activation of a region of the left mediolateral orbitofrontal cortex (area 11). Another study found a correlation between subjective ratings of dissonance and consonance of musical chords in the orbitofrontal cortex (Blood et al., 1999), which could also be interpreted as a correlation with subjective experience.

These are exciting findings, extending previous findings in non-human primates of representations of reinforcers, to representations of the 'subjective affective value' of these reinforcers. The findings indicate that the subjective experience of affective valence is represented in general more anteriorly in the orbitofrontal cortex, which would fit well with a model where the implicit reward value is assigned early on in the hierarchy for each type of reinforcer, with a further progression up the hierarchy of processing (reflecting we suggest the effects of combinations of stimuli) towards areas connected to brain regions necessary for conscious processing (see Rolls, 1999a).

One clearly has to be careful not to overinterpret mere correlations with the elusive qualities of subjective experience, and so it would be extremely interesting to obtain more evidence on this issue by investigating patients with selective lesions to these areas to investigate whether their subjective affective experiences have indeed changed. Evidence is already being obtained that this is the case (Hornak et al., 2003).

5.6. Mediolateral trend: monitoring versus evaluating

As demonstrated by the statistical analysis, two distinct trends have emerged from a meta-analysis of the neuroimaging literature. The medial versus lateral trend was first seen in the reversal-learning experiment (O'Doherty et al., 2001), where the correlations with the magnitudes of monetary reward and punishment were clearly dissociable. The medial areas of orbitofrontal cortex appear to be involved in ongoing monitoring of the reward value of reinforcers, while the lateral areas of the orbitofrontal cortex are involved in evaluating the punishment value of reinforcers which may lead to a change in current behaviour.

5.7. Posterior-to-anterior trend: increasing complexity

The other significant trend shown in the meta-analysis of the neuroimaging literature is the statistically significant increase in the complexity of the representation and processing of reinforcers from posterior to anterior parts of the orbitofrontal cortex. As an example, abstract reinforcers such as the loss of money appear to be represented much further anterior towards the frontal pole (O'Doherty et al., 2001) than posterior areas representing the main effects of reinforcers such as taste (De Araujo et al., 2003a,b,c; Kringelbach et al., 2003; Rolls et al., 2003a,b; Small et al., 1997). Similarly, supralinear responses to combinations of reinforcers are found in more anterior parts of the orbitofrontal cortex (De Araujo et al., 2003a,c) than the main (i.e. separate) effects of the same reinforcers. Furthermore, several studies have found that subjective ratings of, e.g. pleasantness correlate with brain activity in more anterior parts of the orbitofrontal cortex (De Araujo et al., 2003c; Kringelbach et al., 2003; O'Doherty et al., 2001; Rolls et al., 2003a; Völlm et al., 2004).

5.8. The functional neuroanatomy of emotion

Earlier in this review a number of different theories of emotion were briefly described. It is clear that the most practical and parsimonious definition of emotion is "states elicited by rewards and punishers" (Rolls, 1999a). This definition fits the experimental data for both the primate and the human orbitofrontal cortex, where the results have implicated the orbitofrontal cortex strongly in the representation, alteration and evaluation of reinforcers, and in emotion (Hornak et al., 2003; Hornak et al., 2004; Kringelbach, 2002; Petrovic and Ingvar, 2002; Rolls, 1999a,b, 2004). Using the proposed definition, the orbitofrontal cortex is thus directly implicated in the functional neuroanatomy of emotion. Overall, this review has demonstrated that the human orbitofrontal cortex has some specialisation of its different parts, and that when taken as a whole, the orbitofrontal cortex is a key region in the network of brain structures implementing the functional neuroanatomy of emotion in humans.

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