THE HUMAN ORBITOFRONTAL CORTEX: LINKING REWARD TO HEDONIC EXPERIENCE

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Abstract | Hedonic experience is arguably at the heart of what makes us human. In recent neuroimaging studies of the cortical networks that mediate hedonic experience in the human brain, the orbitofrontal cortex has emerged as the strongest candidate for linking food and other types of reward to hedonic experience. The orbitofrontal cortex is among the least understood regions of the human brain, but has been proposed to be involved in sensory integration, in representing the affective value of reinforcers, and in decision making and expectation. Here, the functional neuroanatomy of the human orbitofrontal cortex is described and a new integrated model of its functions proposed, including a possible role in the mediation of hedonic experience.

REINFORCERS
Positive reinforcers (rewards) increase the frequency of behaviour that leads to their acquisition. Negative reinforcers (punishers) decrease the frequency of behaviour that leads to their encounter and increase the frequency of behaviour that leads to their avoidance.

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The human orbitofrontal cortex has received relatively little attention in studies of the prefrontal cortex, and many of its functions remain enigmatic. During primate evolution, the orbitofrontal cortex has developed considerably, and although some progress has been made through neurophysiological recordings in non-human primates, it is only during the past couple of years that evidence has converged from neuroimaging, neuropsychology and neurophysiology to allow a better understanding of the functions of the human orbitofrontal cortex. These studies indicate that the orbitofrontal cortex is a nexus for sensory integration, the modulation of autonomic reactions, and participation in learning, prediction and decision making for emotional and reward-related behaviours. The orbitofrontal cortex functions as part of various networks that include regions of the medial prefrontal cortex, hypothalamus, amygdala, insula/operculum and dopaminergic midbrain, and areas in the basal ganglia including the ventral and dorsal striatum. These additional areas have been investigated in detail in rodents and other animals, and have been described in other reviews[1,2]. Here, I focus on the functions of the human orbitofrontal cortex, as the phylogenetic expansion and heterogeneous nature of this brain region mean that a full understanding of its functions must be informed by evidence from human neuroimaging and neuropsychology studies.

Recently, neuroimaging studies have found that the reward value[3], the expected reward value[4] and even the subjective pleasantness of foods[5] and other REINFORCERS are represented in the orbitofrontal cortex. Such findings could provide a basis for further exploration of the brain systems involved in the conscious experience of pleasure and reward, and, as such, provide a unique method for studying the hedonic quality of human experience. In particular, the links of the orbitofrontal cortex and related areas with the sensory and rewarding properties of reinforcers might offer important insights into emotional disorders such as depression, and the current worldwide obesity epidemic.

Neuroanatomy of the orbitofrontal cortex

The orbitofrontal cortex occupies the ventral surface of the frontal part of the brain (FIGS 1,2). It is defined as the part of the prefrontal cortex that receives projections from the magnocellular medial nucleus of the

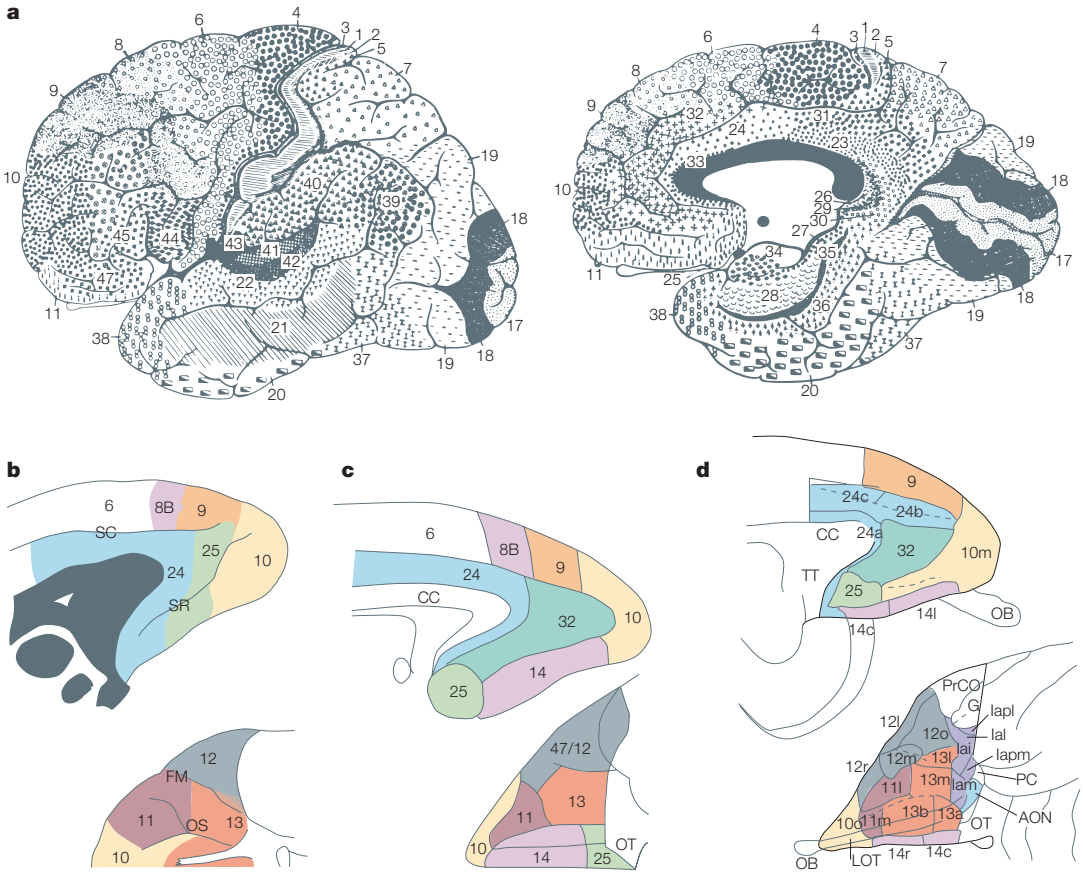

Figure 1 | **Cytoarchitectonic maps of human and monkey orbitofrontal cortices. a** | Brodmann's original cytoarchitectonic maps of the human brain with a ventral view of the brain on the left and a medial view of the cortical areas on the medial wall of the brain on the right[8,111]. The complex cytoarchitecture of the orbitofrontal cortex was reduced to three areas, 11, 47 and 10. **b** | Later investigations further subdivided the orbitofrontal cortex to reflect its heterogeneity, as first proposed in the maps of Walker. Views of the medial wall and ventral surface are shown for the monkey *Macaca fascicularis*. Walker proposed a further parcellation of the orbitofrontal cortex into five areas (areas 10, 11, 12, 13 and 14). FM, sulcus frontomarginalis; OS, sulcus orbitalis; SC, sulcus callosomarginalis; SR, sulcus rostralis. **c** | Walker's nomenclature was then reconciled with that used in Brodmann's primate and human brains by Petrides and Pandya[10], with lateral parts of the orbitofrontal cortex designated area 47/12. CC, corpus callosum; OT, olfactory tubercle. **d** | Even further subdivisions of the orbitofrontal cortex were subsequently proposed by Carmichael and Price[11]. AON, anterior olfactory nucleus; G, gustatory cortex; lai, intermediate agranular insula area; lal, lateral agranular insula area; lam, medial agranular insula area; lapl, posterolateral agranular insula area; lapm, posteromedial agranular insula area; LOT, lateral olfactory tract; OB, olfactory bulb; PC, piriform cortex; PrCO, precentral opercular cortex; TT, tenia tectum. Panel **a** modified from REF. 8. Panel **b** modified from REF. 9. Panel **c** modified, with permission, from REF. 10 © (1994) Elsevier Science. Panel **d** modified, with permission, from REF. 11 © (2000) John Wiley & Sons.

mediodorsal thalamus[6]. This is in contrast to areas of the prefrontal cortex that receive projections from other parts of the mediodorsal thalamus. For example, the dorsolateral prefrontal cortex (BRODMANN'S AREA (BA) 46/9) receives projections from the parvocellular lateral part of the mediodorsal thalamic nucleus, whereas the frontal eye fields in the anterior bank of the arcuate sulcus (BA 8) receive projections from the paralamellar part of the mediodorsal thalamic nucleus. This is a broad connectional topography, in which each specific portion of the mediodorsal thalamus is connected to more than one architectonic region of the prefrontal cortex[7], and a better definition therefore includes each cortical area's cortico-cortical connectivity and morphological features.

Brodmann[8] carried out one of the first comprehensive cytoarchitectural analyses of the human and the primate (*Cercopithecus*) brain, in which different cytoarchitectonic areas were assigned unique numbers (FIG. 1a). Unfortunately, he did not investigate the orbitofrontal cortex in detail, and his maps of the human brain include only three orbitofrontal cortical areas — 10, 11 and 47. Furthermore, his nomenclature was not consistent across species: area 11 in the primate map is extended laterally, and area 12 takes over the medial area that is occupied by area 11 in the human map, whereas area 47 is not included at all in the non-human primate map.

Some clarification of the cross-species inconsistencies that are present in Brodmann's maps was provided by Walker[9], who investigated the monkey species *Macaca fascicularis*. He found the orbitofrontal cortex to be much less homogeneous than Brodmann had specified, and he proposed parcellating the primate

BRODMANN'S AREAS (BA). Korbinian Brodmann (1868–1918) was an anatomist who divided the cerebral cortex into numbered subdivisions on the basis of cell arrangements, types and staining properties (for example, the dorsolateral prefrontal cortex contains several subdivisions, including BA 46 and BA 9). Modern derivatives of Brodmann's maps are commonly used as the reference system for the discussion of brain-imaging findings.

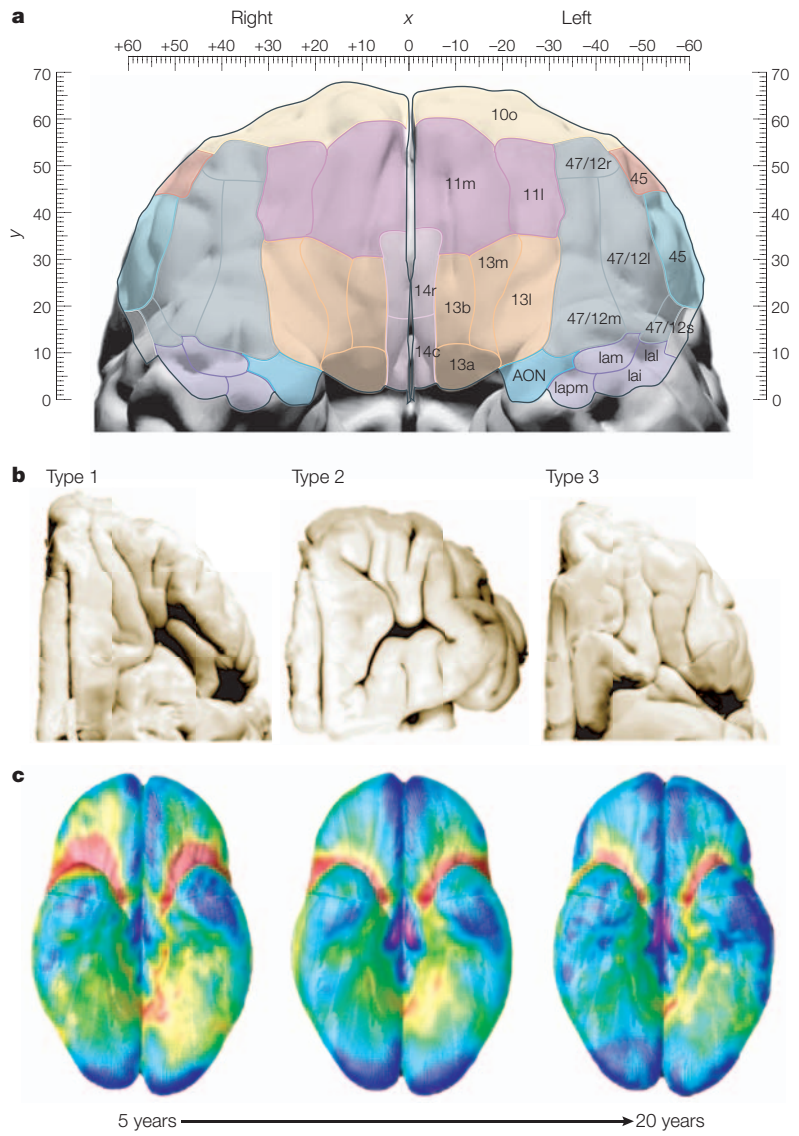

Figure 2 | **Anatomy, variability and development of the human orbitofrontal cortex.** **a** | A human cytoarchitectonic map of the orbitofrontal cortex rendered on the orbital surface in normalized space (based on the template provided by the Montreal Neurological Institute). AON, anterior olfactory nucleus. **b** | The sulcal variability of the human orbitofrontal cortex is shown with ventral views of the three main patterns of gyri and sulci, taken from the left hemisphere. It is clear that this variability poses substantial challenges for normalization across brains, but some possible strategies have recently been proposed[28]. **c** | A study investigated the dynamic anatomical sequence of human cortical grey matter development from the age of 4 to 21 years using quantitative models of the cortical surface and sulcal landmarks, and a statistical model for grey matter density[117]. The figure shows a ventral view of the averaged group maps, with three time points of grey matter maturation across the cortical surface. The colour indicates grey matter volume, from low (blue) to high (pink). The orbitofrontal cortex matures late compared with other ventral areas. Panel **a** modified, with permission, from REF. 28 © (2004) Elsevier Science. Panel **b** modified, with permission, from REF. 12 © (2000) John Wiley & Sons. Panel **c** modified, with permission, from REF. 117 © (2004) National Academy of Sciences, USA.

orbital surface into five distinct areas (areas 10, 11, 12, 13 and14; FIG. 1b). Walker's areas 12 and 13 occupy the lateral and medial orbital surfaces, respectively, whereas area 14 is on the ventromedial convexity near the gyrus rectus. More anteriorly, area 10 occupies the frontal pole, whereas area 11 occupies the remaining anterior orbital surface.

However, this left the problem of area 47 from the human map, which was still not included in Walker's map. Petrides and Pandya[10] subsequently tried to reconcile the remaining inconsistencies between the human and monkey cytoarchitectonic maps by labelling the lateral parts of the orbitofrontal gyri as 47/12 (FIG. 1c). Further subdivisions of the orbitofrontal cortex were later proposed on the basis of nine different histochemical and immunohistochemical stains[11] (FIG. 1d).

Two important cytoarchitectonic features of the orbitofrontal cortices are the phylogenetic differences (BOX 1) and the considerable variability between individuals[12,13] (FIG. 2). The former poses potential problems when trying to understand functional relationships across species, and the latter poses interesting methodological challenges for those who hope to normalize individual brains to a template brain to allow them to explore the functional anatomy of the human orbitofrontal cortex.

The orbitofrontal cortex receives inputs from the five classic sensory modalities: gustatory, olfactory, somatosensory, auditory and visual[14]. It also receives visceral sensory information, and all this input makes the orbitofrontal cortex perhaps the most polymodal region in the entire cortical mantle, with the possible exception of the rhinal regions of the temporal lobes[15].

The orbitofrontal cortex also has direct reciprocal connections with other brain structures, including the amygdala[16,17], cingulate cortex[18,19], insula/operculum[20], hypothalamus[21], hippocampus[22], striatum[23], periaqueductal grey[21] and dorsolateral prefrontal cortex[14,24].

Functional neuroanatomy in humans

In terms of its neuroanatomical connectivity, the orbitofrontal cortex is uniquely placed to integrate sensory and visceral motor information to modulate behaviour through both visceral and motor systems. This has led to the proposal that the orbitofrontal cortex is an important part of the networks that are involved in emotional processing[25,26] (BOX 2). The orbitofrontal cortex has direct connections to the basolateral amygdala, and these two brain areas probably have an important role in GOAL-DIRECTED BEHAVIOUR[26].

The orbitofrontal cortex is a comparatively large brain area in non-human primates and humans, and is heterogeneous in terms of its connectivity and morphological features, so its constituent parts probably have different functional roles. One proposal, based on neuroanatomical and neurophysiological evidence from non-human primates, is that the orbitofrontal cortex should be viewed as part of a functional network known as the orbital and medial prefrontal cortex (OMPFC)[19]. 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, which includes areas 11, 13 and 47/12 of the orbitofrontal cortex and receives input from all the sensory modalities, including visceral afferents, is proposed to be important for

GOAL-DIRECTED BEHAVIOUR
Behaviour directed towards the attainment of a future state (for example, obtaining the next meal).

Box 1 | **Phylogeny of the orbitofrontal cortex**

The prefrontal cortex shows considerable variation across mammalian species, especially in terms of the amount of granular versus agranular cortex, but there is mounting evidence that there are similarities in the position and connections of the orbitofrontal and medial prefrontal cortex across species[10,108,109]. It has been proposed that the relative cognitive sophistication of higher primates is linked to increases in the size of the prefrontal cortex with respect to the whole brain that have occurred through mammalian evolution[110,111], although it seems more likely that cognitive gains are linked to increases in overall brain size compared with body size[112].

Size is not everything, of course — the intrinsic and extrinsic neural connections within and between brain areas are just as important. Homologies between human and non-human primate orbitofrontal cortical areas can be surmised on the basis of connections and cytoarchitectonic data, but comparisons with rodents are difficult to make because the temporal visual cortical areas have developed considerably during primate evolution, although some progress has been made towards this goal[113].

Cytoarchitectonic analysis of the prefrontal cortex reveals differences in cortical organization. The dorsolateral prefrontal cortex consists of fully laminated six-layered granular cortex, and 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)[19]. These differences in cytoarchitecture and cortical organization probably correspond to functional differences.

the regulation of food intake. The medial network, which includes medial areas 11, 13, 14 and lateral area 47/12 of the orbitofrontal cortex, as well as areas 25, 32 and 10 on the medial wall, has extensive visceromotor outputs. The two networks might, therefore, serve as a crucial sensory–visceromotor link for consummatory behaviours. It should be noted that the definition of the medial network partly overlaps with that of the VENTROMEDIAL PREFRONTAL CORTEX, a term used by Bechara, Damasio and colleagues[27], but the latter does not include central and lateral regions of the orbitofrontal cortex.

Another proposal, based on evidence from human neuroimaging and neuropsychology studies, extends the OMPFC network, suggesting that there are medial–lateral and posterior–anterior distinctions within the human orbitofrontal cortex[28]. A large meta-analysis of the existing neuroimaging data was used to show that activity in the medial orbitofrontal cortex is related to the monitoring, learning and memory of the reward value of reinforcers, whereas lateral orbitofrontal cortex activity is related to the evaluation of punishers, which can lead to a change in ongoing behaviour. The analysis also showed a posterior–anterior distinction, with more complex or abstract reinforcers (such as monetary gain and loss) represented more anteriorly in the orbitofrontal cortex than less complex reinforcers (such as taste).

Other proposed functions of the orbitofrontal cortex include a role for the lateral parts in RESPONSE INHIBITION[29], based on the observation that humans and non-human primates will perseverate in choosing a previously but no longer rewarded stimulus in object REVERSAL-LEARNING tasks[30,31]. There is now strong evidence that this inhibition cannot be a simple form of response inhibition. Lesion studies in monkeys have 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[32]. Similarly, simple response inhibition cannot account for the severe impairment on the reversal part of an object reversal-learning task that is shown by patients with discrete bilateral surgical lesions to the lateral orbitofrontal cortex[33]. It is possible that the orbitofrontal cortex has a role in more complex behavioural changes that could be interpreted as being inhibitory to behaviour, and that this behaviour arises in conjunction with activity in other brain structures, such as the anterior cingulate cortex, as discussed below.

Other researchers have proposed that the orbitofrontal cortex is involved in the integration of bodily signals that help decision making processes and have been termed, for example, 'interoceptive'[25] or 'somatic' markers[34]. Such proposals, which are variations on the JAMES–LANGE THEORY of the embodiment of emotions[35,36], have been the subject of considerable debate over the years. Among the objections to these bodily theories of emotion are the claims that they are underspecified with regard to what constitute emotional stimuli; that signals from the body are noisy and it is not clear whether they can distinguish the different emotions; and that animals and humans with severe spinal cord damage seem to have normal emotions[26,37]. Some of these objections are addressed in the 'somatic marker' theory, which includes an 'as-if' loop for decision making situations with relatively low uncertainty that allows the brain to bypass the role of the body[34]. It has also been argued that emotions are constituted in large measure by visceral and endocrine responses rather than through the spinal cord. The orbitofrontal cortex certainly has the connectivity to receive and integrate visceral sensory signals to influence behaviour, and although it is not clear how this information is integrated, it remains possible that these signals have a significant role in decision making and emotion[38]. Note that most primary reinforcers are signalled through an interoceptive route, and this is likely to be essential for hedonic experience.

These influential proposals share some similarities and conclusions, but the exact functions and underlying mechanisms of the various parts of the orbitofrontal cortex have yet to be discovered. Here, I consider new evidence from neuroimaging and neuropsychology studies that can help to illuminate the functions of the orbitofrontal cortex in sensory integration, reward processing, decision making, reward prediction and subjective hedonic processing. It is important to remember that studies using functional MRI (fMRI) are prone to signal dropout, geometric distortion and susceptibility artefacts in the orbitofrontal cortex due to its close proximity to the air-filled sinuses[39,40], so negative findings should be treated with caution.

Sensory integration and reward value. Neurophysiological recordings have found that the non-human primate orbitofrontal cortex receives input from the five senses[26], and neuroimaging has confirmed that the

VENTROMEDIAL PREFRONTAL CORTEX
An anatomical term that refers to most of the medial orbitofrontal cortex and areas on the medial wall, but not to more central and lateral regions of the orbitofrontal cortex.

RESPONSE INHIBITION
Lack of control and general perseveration are symptoms that commonly follow damage to the frontal lobes, and have often been ascribed to a lack of inhibitory control over the appropriate responses.

REVERSAL LEARNING
Describes a task in which participants are trained to respond differentially to two stimuli under conditions of reward and punishment (or non-reward), and subsequently have to learn to change their behaviour when the reward values are reversed (that is, when the previously rewarded stimulus is no longer rewarded, and vice versa).

JAMES–LANGE THEORY
Two nineteenth-century scholars, William James and Carl Lange, independently proposed that emotions arise as a result of bodily physiological events, such as increases in heart rate, rather than being the cause of them

Box 2 | **Emotion**

For many years, emotion remained an elusive scientific topic and was generally defined in opposition to cognition as that which moves us in some way, as is implied by the Latin root (*movere*, to move). Owing to its perceived subjective nature, the scientific study of emotion was stunted despite ideas put forward by pioneering individuals such as Charles Darwin[114], who investigated the evolution of emotional responses and facial expressions, and suggested that emotions allow an organism to make adaptive responses to salient stimuli in the environment.

A highly successful scientific strategy has been to divide the concept of emotion into two parts: the emotional state, which can be measured through physiological changes such as autonomic and endocrine responses; and feelings, which are seen as the subjective experience of emotion[115]. This allows emotional states to be measured in animals using, for example, conditioning, and emotions are now typically regarded as states that are elicited by rewards and punishments (although this definition is, of course, rather circular)[116]. How emotional stimuli (primary and secondary reinforcers) are represented depends on the type of reinforcer. The subsequent emotional processing is a multistage process mediated by networks of brain structures. The results of this processing influence the behaviour that is selected, the autonomic responses that are elicited and the conscious feelings that are produced (at least in humans).

The orbitofrontal cortex, amygdala and cingulate cortex contribute to emotional processing in the human brain. Other important brain structures include the hypothalamus, insula/operculum, nucleus accumbens and various brainstem nuclei, including the periaqueductal grey. These brain regions provide some of the necessary input and output systems for multimodal association regions, such as the orbitofrontal cortex, that are involved in representing and learning about the reinforcers that elicit emotions and conscious feelings.

human orbitofrontal cortex is activated by auditory[41], gustatory[42], olfactory[43], somatosensory[44] and visual[45] inputs. This cortical region also receives information from the visceral sensory system[46], and even abstract reinforcers such as money can activate the human orbitofrontal cortex[47,48].

Most sensory inputs enter the orbitofrontal cortex through its posterior parts (see below). Here they are available for multisensory integration[5,49,50] and subsequent encoding of the reward value of the stimulus. One approach that can be used to demonstrate the encoding of the reward value of a stimulus is 'sensory-specific' or SELECTIVE SATIETY[51], which is a form of reinforcer devaluation. This approach was used in neuroimaging studies of hungry human participants who were scanned while being presented with two food-related stimuli. Participants were fed to satiety on one of the stimuli, which led to a selective decrease in the reward value of the food eaten, and scanned again in their satiated state using exactly the same procedure. Neuroimaging experiments using olfactory[3] and whole-food[5] stimuli showed that the activity in more anterior parts of the orbitofrontal cortex tracks the changes in reward value of the two stimuli such that activity selectively decreases for the food eaten but not for the other food.

This is compatible with studies in non-human primates in which monkeys with lesions of the orbitofrontal cortex responded normally to associations between food and conditioners but failed to modify their behaviour to the cues when the incentive value of the food was reduced[52], and in which lesions of the orbitofrontal cortex altered food preferences in monkeys[53]. Similarly, crossed unilateral lesions in monkeys — between the orbitofrontal cortex in one hemisphere and the amygdala in the other — disrupted devaluation effects in a procedure in which the incentive value of a food was reduced by satiation on that particular food[54].

A malfunction of these satiation mechanisms could explain the profound changes in eating habits (escalating desire for sweet food coupled with reduced satiety) that are often followed by enormous weight gain in patients with frontotemporal dementia. This progressive neurodegenerative disorder is associated with major and pervasive behavioural changes in personality and social conduct that resemble those produced by orbitofrontal lesions[55] (although it should be noted that more focal lesions of the orbitofrontal cortex have not been associated with obesity).

Further evidence for the representation of the reward value of more abstract reinforcers has been provided by neuroimaging studies of social judgements[56] and music[57], among others. A meta-analysis of neuroimaging studies (FIG. 3) found that abstract reinforcers such as money are represented more anteriorly in the orbitofrontal cortex than less complex reinforcers such as taste[28]. These studies show that the orbitofrontal cortex represents the affective value of both primary and abstract secondary reinforcers.

Decision making and prediction. During decision making, the brain must compare and evaluate the predicted reward values of various behaviours. This processing can be complex, as the estimations vary in quality depending on the sampling rate of the behaviour and the variance of reward distributions. It is difficult to provide a reliable estimate of the reward value of a food that appears to be highly desirable and is high in nutritional value but is only rarely available and varies significantly in quality. This raises the classic problem in animal learning of how to optimize behaviour such that the amount of exploration is balanced with the amount of exploitation, where exploration is the time spent sampling the outcome of different behaviours, and exploitation is the time spent using existing behaviours with known reward values. Food-related behaviours have to be precisely controlled because the decision to swallow toxins, microorganisms or non-food objects on the basis of erroneously judging the sensory properties of the food can be fatal. Humans and other animals have therefore developed elaborate food-related behaviours to balance conservative risk-minimizing and life-preserving strategies (exploitation) with occasional novelty seeking (exploration) in the hope of discovering new, valuable sources of nutrients[58].

The orbitofrontal and anterior cingulate cortices were implicated in decision making in 1848 by the classic case of Phineas Gage, whose frontal lobes were penetrated by a metal rod[59]. Gage survived but his personality and emotional processing were changed completely (although the case should be viewed with caution because the information available is limited[60]).

SELECTIVE SATIETY
A form of reinforcer devaluation in which participants that have been fed to satiety on one food still find other foods rewarding, and will eat some of these other foods. Selective satiety is particularly useful for studying affective representation in the brain, because it provides a means of altering the affective value of a stimulus without modifying its physical attributes, allowing a change in reward value to be detected.

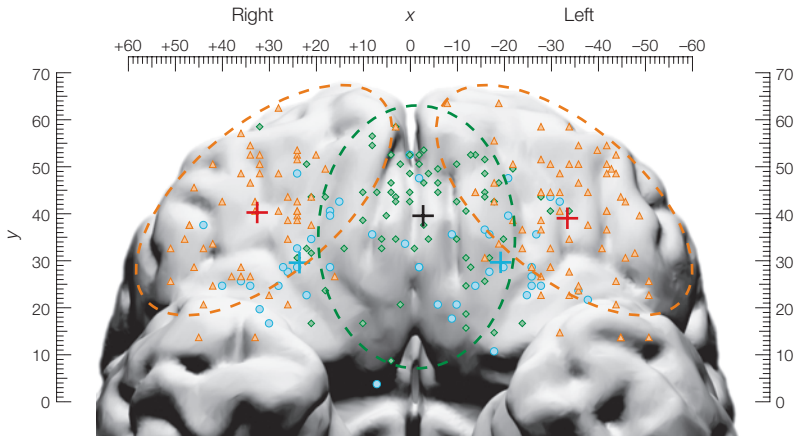

Figure 3 | **Meta-analysis of the functions of the orbitofrontal cortex.** The results of a recent meta-analysis, with all 267 areas of activation in stereotaxic space shown rendered on the orbital surface of the human brain[28]. The meta-analysis showed that there is a medial–lateral distinction in the human orbitofrontal cortex, such that activity in the medial orbitofrontal cortex is related to the monitoring, learning and memory of the reward value of reinforcers (activated areas indicated by one green oval), whereas lateral orbitofrontal cortex activity is related to the evaluation of punishers that can lead to a change in behaviour (activated areas indicated by dashed orange ovals). Similarly, a posterior–anterior distinction was shown, with more complex or abstract reinforcers (such as monetary gain and loss) being represented more anteriorly in the orbitofrontal cortex than less complex reinforcers such as taste. The two centres of mass of the clusters of activations that relate to motivation-independent reinforcer representation (blue circles) are marked with blue crosses; and the centre of mass of the cluster of activations that relate to the monitoring of reward value (green diamonds) is marked with a black cross. Similarly, the two centres of mass of the clusters that relate to punishers (orange triangles), which lead to changes in behaviour, are marked with red crosses. Statistical analysis confirmed that the clusters' centres of mass are significantly separated. Modified, with permission, from REF. 28 © (2004) Elsevier Science.

In more recent cases of orbitofrontal cortex damage, patients have often experienced problems with decision making, a lack of affect, and social inappropriateness and irresponsibility[31,61–63]. Such patients are impaired in identifying social signals that are important for decision making, including, for example, face and voice expressions[63,64].

Reliable prediction underlies decision making[65], and neuroimaging has been used to investigate the predicted reward value of rewarding and punishing stimuli. Often this is done using classical conditioning paradigms, in which an arbitrary neutral stimulus is paired with a reward or punishment. After learning, the arbitrary stimulus takes on the predictive value of the specific reward value of the unconditioned stimulus, but it can also code for various aspects of the sensory or general affective properties of the unconditioned stimulus. In an fMRI study using selective satiation, participants were presented with predictive cues associated with one of two food-related odours[4] (FIG. 5b). By comparing brain activity in response to the cues before and after devaluation (by feeding to satiety) of the associated food, it was found that neural responses in the orbitofrontal cortex, amygdala and ventral striatum tracked the relative changes in the specific predictive reward values of the odours.

When the specific predictive reward values of different behaviours are in place, comparison and evaluation mechanisms must choose between them to optimize behaviour. Bechara and colleagues developed a gambling task in which participants were asked to select cards from four decks and maximize their winnings[27]. 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 therefore be considered high risk), whereas the other two packs produce small payouts but smaller penalties (low risk). So, the most profitable strategy is to select cards from the two low-risk decks, which is the strategy adopted by healthy control subjects. During the task, electrodermal activity (skin conductance responses, SCRs) is used as an index of visceral sensory arousal. Patients with damage to the ventromedial prefrontal cortex (including parts of the medial orbitofrontal cortex), but not the dorsolateral prefrontal cortex, persistently draw cards from the high-risk packs, and lack anticipatory SCRs while they consider risky choices[66] (for a recent critique of this experiment, see REF. 67).

In another decision making task, a visual discrimination reversal task, participants had to associate an arbitrary stimulus with monetary wins or losses, and then rapidly reverse these associations when the reinforcement contingencies altered. Probabilistic reward and punishment schedules were used such that selecting either the currently rewarded stimulus or 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. An fMRI study of this task in healthy participants found a dissociation of activity in the medial and lateral parts of the orbitofrontal cortex: activity in the medial orbitofrontal cortex correlated with how much money was won on single trials, and activity of the lateral orbitofrontal cortex correlated with how much money was lost on single trials[48]. Another study, which used positron emission tomography (PET), also found that predominantly lateral parts of the orbitofrontal cortex were significantly activated during decision making[68].

Further studies have since confirmed the role of the medial orbitofrontal cortex in monitoring and learning about the reward value of stimuli that have no immediate behavioural consequences. Neuroimaging experiments have found activations in the medial orbitofrontal cortex that monitor the affective properties of olfaction[69,70], gustation[71], and somatosensory[44] and multimodal[50] stimuli. This monitoring process is consistent with intriguing findings in spontaneously confabulating patients with lesions of the medial orbitofrontal cortex[72,73]. A PET study has found that the medial orbitofrontal cortex monitors outcomes even when no reward is at stake[74].

By contrast, the lateral orbitofrontal cortex is often CO-ACTIVE with the anterior cingulate cortex when participants evaluate punishers, which, when detected, can lead to a change in ongoing behaviour (FIG. 4). A PET study investigating analgesia and placebo

CO-ACTIVATION
The presence, in a neuroimaging experiment, of significant activity in two brain structures in the same subtraction.

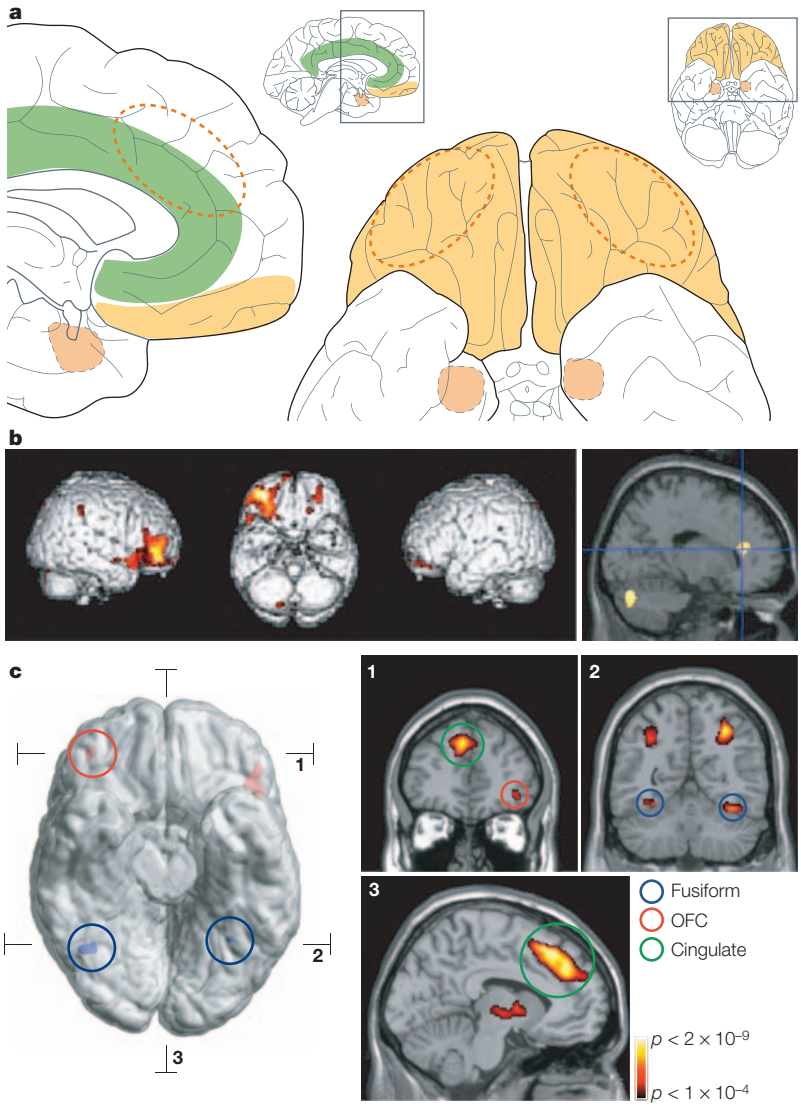

Figure 4 | **Co-activation of the lateral orbitofrontal and anterior cingulate cortices.** **a** | The lateral orbitofrontal cortex (yellow) and parts of the anterior cingulate cortices (green) in the rostral cingulate zone are often co-activated in neuroimaging studies (activated areas are marked by dashed orange ovals), often when evaluating punishers that, when detected, can lead to a change in ongoing behaviour. The amygdala is shaded orange. **b** | A positron emission tomography study investigating analgesia and placebo found that the lateral orbitofrontal and anterior cingulate cortices were co-active in participants that responded to the placebo, which suggests that the pain relief provided by placebos might relate to co-activation of these two brain areas. **c** | A recent functional MRI study found that, together, the lateral orbitofrontal and the anterior cingulate/paracingulate cortices are responsible for changing behaviour in an object reversal task. This task was set up to model aspects of human social interactions. Participants were required to keep track of the faces of two people and to select the 'happy' person. The mood of this person changed after a period of time, and participants had to learn to change (reverse) their behaviour and choose the other person. The most significant activity during the reversal phase was found in the lateral orbitofrontal and cingulate cortices (marked by red and green circles, respectively), whereas the main effects of faces were found in the fusiform gyrus and intraparietal sulcus (blue circles). OFC, orbitofrontal cortex. Panel **b** modified, with permission, from REF. 75 © (2002) American Association for the Advancement of Science. Panel **c** modified, with permission, from REF. 78 © (2003) Elsevier Science.

found that the lateral orbitofrontal and anterior cingulate cortices were co-active in participants who responded to the placebo, which suggests that the pain relief effect of the placebo might be related to the co-activation of these two brain areas[75,76] (FIG. 4b). Another neuroimaging study provided evidence that the lateral orbitofrontal cortex is related to changing behaviour, in this case when there were unexpected breaches in expectation in a visual attention task[77].

A direct investigation of the role of the lateral orbitofrontal cortex was carried out using a face reversal-learning task that solved the problem inherent in the monetary reversal-learning task (mentioned above)[48], in which the probabilistic nature of the task meant that the magnitude of negative reinforcers (money loss) was slightly confounded by the reversal event *per se*. This new reversal-learning study showed that the lateral orbitofrontal cortex and a region of the anterior cingulate cortex are together responsible for supporting general reversal learning in the human brain[78,79] (FIG. 4c). This is consistent with the finding that the passive presentation of angry facial expressions — a signal that social behaviour should be changed — activates the orbitofrontal and anterior cingulate cortices[80]. Further strong, causal evidence has been provided by a similar reversal-learning experiment in patients with discrete, surgical lesions to the orbitofrontal cortex, in which bilateral lesions to the lateral orbitofrontal cortex — but not unilateral lesions to medial parts of the orbitofrontal cortex — produce significant impairments in reversal learning[33].

A recent fMRI study investigated the interaction between decision making and performance monitoring[81]. The orbitofrontal cortex was more involved in outcome monitoring for the externally instructed condition than in the internally generated volition condition. By contrast, the anterior cingulate cortex was more active when the selected response was internally generated than when it was externally instructed by the experimenter.

In summary, decision making, performance and outcome monitoring require complex processing that relies strongly on frontal cortical areas, and in particular on interactions between the orbitofrontal and anterior cingulate cortices. Different parts of these cortical regions have been implicated in different aspects and timings of decision making and outcome monitoring[82]. In particular, there is now evidence from a large meta-analysis of the neuroimaging literature for differential roles of the medial and lateral parts of the orbitofrontal cortex[28] (FIG. 3). Activity in the medial orbitofrontal cortex is related to the monitoring, learning and memory of the reward value of reinforcers, whereas activity in the lateral orbitofrontal cortex is related to the evaluation of punishers, which can lead to a change in behaviour. As already mentioned, the meta-analysis also found evidence for a posterior–anterior distinction between more complex or abstract and less complex reinforcers.

Subjective pleasantness. All animals constantly make decisions in order to survive and procreate, but perhaps only humans can evaluate and directly report the subjective pleasantness associated with this process. This hedonic experience is related to subjective experience,

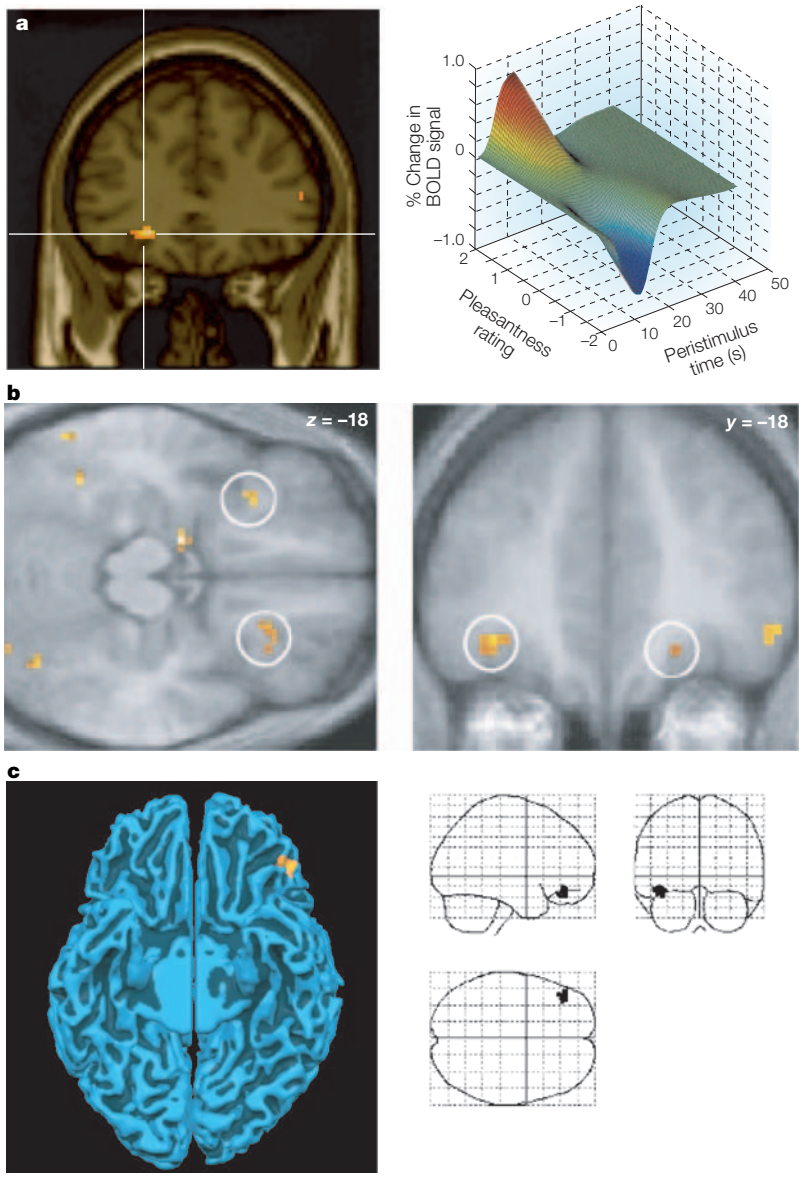

Figure 5 | **Hedonic processing. a** | A functional MRI (fMRI) study using selective satiation found that activation in the mid-anterior parts of the orbitofrontal cortex correlates with the participants' subjective pleasantness ratings of the foods throughout the experiment (left). The plot on the right shows the magnitude of the fitted haemodynamic response from a representative participant against the subjective pleasantness ratings (on a scale from –2 to +2) and peristimulus time in seconds. **b** | The activity in adjacent mid-anterior parts of the orbitofrontal cortex (circled) selectively decreased in response to an arbitrary visual cue that was linked to an odour that had been devalued in a selective satiation neuroimaging paradigm. Similar effects were found in other brain regions, including the amygdala and the ventral striatum, although activity in these other regions was not found to correlate with subjective pleasantness, which indicates that the orbitofrontal cortex represents this aspect of human experience. **c** | Further evidence for the role of the orbitofrontal cortex in subjective experience comes from an fMRI experiment that investigated the supra-additive effects of combining the umami tastants monosodium glutamate and inosine 5′-monophosphate. The region of mid-anterior orbitofrontal cortex that is showing activity related to taste synergism can be seen in the left panel (rendered on the ventral surface of human cortical areas with the cerebellum removed). On the right the unmasked results are shown in a glass brain. The perceived synergy is unlikely to be expressed in the taste receptors themselves, and activity in the orbitofrontal cortex might, therefore, reflect the subjective enhancement of umami taste, which must be closely linked to subjective experience. Panel **a** modified, with permission, from REF. 5 © (2003) Oxford University Press. Panel **b** modified, with permission, from REF. 4 © (2003) American Association for the Advancement of Science. Panel **c** modified, with permission, from REF. 93 © (2003) American Physiological Society.

qualia, which has been described as 'the hard problem of consciousness'[83] and which some philosophers believe will never be amenable to scientific analysis. But, as shown below, recent neuroimaging studies of the hedonic processes that are associated with food and other reinforcers suggest that this line of scientific inquiry might yield important insights into the core of subjective experience.

Historically, early theories of motivation proposed that hedonic behaviour is controlled by need states[84]. But such theories do not explain why, for example, people still continue to eat when sated. This led to theories of incentive motivation in which hedonic behaviour is determined mainly by the incentive value of a stimulus or its capacity to function as a reward[85]. Need states such as hunger are still important but only work indirectly on the incentive value of the stimulus. The principle of modulation of the hedonic value of a consummatory sensory stimulus by homeostatic factors has been termed 'alliesthesia' (from *allios*, changed, and *esthesia*, sensation)[86]. A useful distinction between two aspects of reward has been proposed, in which hedonic impact refers to the liking or pleasure related to the reward, and incentive salience refers to the wanting or desire for the reward[87,88].

Using food as stimuli in neuroimaging has proved to be an interesting approach to studying the hedonic quality of life, which is perhaps not surprising given that the essential energy to sustain life is obtained from food, as is much of the pleasure of life (especially on an empty stomach)[89]. Food intake in humans is not only regulated by homeostatic processes, as is illustrated by our easy overindulgence on sweet foods and rising obesity levels, but relies on the interactions between homeostatic regulation and hedonic experience[90]. This complex subcortical and cortical processing involves higher-order processes such as learning, memory, planning and prediction, and gives rise to conscious experience of not only the sensory properties of the food (such as its identity, intensity, temperature, fat content and viscosity) but also the valence elicited by the food (including, most importantly, the hedonic experience).

In humans and higher primates, the orbitofrontal cortex receives multimodal information about the sensory properties of food and is therefore a candidate region for representing incentive salience, hedonic impact and subjective hedonic experience. A recent neuroimaging study of activity in the mid-anterior region of the orbitofrontal cortex showed not only a sensory-specific decrease in the reward value of a whole food eaten to satiety (and not of a whole food not eaten), but also a correlation between brain activity and pleasantness ratings[91] (FIG. 5a). This indicates that the reward value of the taste, olfactory and somatosensory components of a whole food is represented in the orbitofrontal cortex, and that the subjective pleasantness of food might be represented here.

As mentioned above, a related fMRI study found that activity in adjacent mid-anterior parts of the orbitofrontal cortex was selectively decreased in response to

an arbitrary visual cue linked to an odour that had been devalued using a selective satiation paradigm in which subjects were fed on the associated food[4] (FIG. 5b). Another recent PET study found that the extrinsic incentive value of foods was located in a similar part of the orbitofrontal cortex[92].

Further evidence of neural correlates of subjective experience was found in an fMRI experiment that investigated TRUE TASTE SYNERGISM[93]. The results of the study showed that the strong subjective enhancement of umami taste was correlated with increased activity in a mid-anterior part of the orbitofrontal cortex (FIG. 5c). The perceived synergy is unlikely to be expressed in the taste receptors themselves, and the activity in the orbitofrontal cortex might, therefore, reflect the subjective enhancement of umami taste. Similarly, a neuroimaging study showed that the synergistic enhancement of a matched taste and retronasal smell (in which the multimodal combination was significantly more pleasant than the sum of the unimodal stimuli) correlated with activity in a mid-anterior region of the orbitofrontal cortex[50].

Other neuroimaging studies have directly correlated brain activity with the subjective ratings of the pleasantness and intensity of different positive and negative reinforcers, but, crucially, without devaluing or otherwise manipulating the reinforcers to change their valence during the course of the experiment. The results of these correlations are, therefore, perhaps better thought of in terms of monitoring processing in the orbitofrontal cortex, as described above. Consistent with this suggestion, correlations with pleasantness have been found almost exclusively in the medial orbitofrontal cortex. Pleasantness but not intensity ratings were correlated with activity in the medial orbitofrontal and anterior cingulate cortices for taste[94], odour[69,70], chocolate[95] and stimulus fat content (independent of viscosity)[96]. In addition, a study of thermal stimulation showed that the perceived thermal intensity was correlated with activity in the insula and orbitofrontal cortices[97]. A correlation was also recently found between a reliable index of the rush of intravenous methamphetamine in drug-naive subjects and activity in the medial orbitofrontal cortex[98]. Moreover, activation of the orbitofrontal cortex correlates with the negative dissonance (unpleasantness) of certain musical chords[57], and intensely pleasurable responses, or 'chills', elicited by music are correlated with activity in the orbitofrontal cortex, ventral striatum, cingulate and insula cortex[99].

Further evidence that the medial orbitofrontal cortex implements monitoring processing of the incentive salience of a stimulus is provided by the study of patients with damage to the ventromedial prefrontal cortex who are reported to have relatively intact SCRs when receiving monetary rewards and punishments[27]. By contrast, activity in the mid-anterior parts of the orbitofrontal cortex correlates directly with subjective hedonic impact. It seems, therefore, that dissociable regions of the human orbitofrontal cortex represent the wanting and the liking aspects of reward.

These exciting findings from neuroimaging extend previous findings in non-human primates of reinforcer representations to representations of the subjective affective value of these reinforcers. We must be careful not to overinterpret mere correlations with the elusive qualities of subjective experience, and it is unlikely that hedonic experience depends on only one cortical region. Even so, it would be interesting to determine whether the subjective affective experiences of patients with selective lesions of these areas are changed. Some evidence has already been obtained to suggest that this is the case[100].

Linking reward to hedonic experience

The recent convergence of findings from neuroimaging, neuropsychology and neurophysiology indicates that the human orbitofrontal cortex is an important nexus for sensory integration, emotional processing and hedonic experience. It has become clear that the orbitofrontal cortex has an important role in emotional disorders such as depression[101] and addiction[102], and it is now possible to offer a tentative model of the functional neuroanatomy of the human orbitofrontal cortex (FIG. 6). The posterior parts of the orbitofrontal cortex process the sensory information for further MULTIMODAL INTEGRATION. The reward value of the reinforcer is assigned in more anterior parts of the orbitofrontal cortex, where it can be modulated by hunger and other internal states, and can be used to influence subsequent behaviour, stored for monitoring, learning and memory, and made available for subjective hedonic experience. At all times, important reciprocal information flows between the various regions of the orbitofrontal cortex and other brain regions, including the anterior cingulate cortex and the amygdala. Significant differences in terms of laterality have not been demonstrated in the orbitofrontal cortex[28]. However, this is a highly heterogeneous brain region, and future neuroimaging and neuropsychology studies are likely to find many more functional distinctions between its constituent parts.

The proposed link to subjective hedonic processing makes the orbitofrontal cortex an important gateway to subjective conscious experience. The orbitofrontal and anterior cingulate cortices could be viewed as part of a global workspace for access to consciousness with the specific role of evaluating the affective valence of stimuli[103]. In this context, it is interesting that the medial parts of the orbitofrontal cortex are part of a proposed network for the baseline activity of the human brain at rest[104].

Future perspectives

Many questions remain about the functions of the orbitofrontal cortex. Central to these are the exact temporal neural mechanisms that underlie its functions, and structural and functional changes of the orbitofrontal cortex during development.

On a timescale of milliseconds, neuroimaging techniques such as MAGNETOENCEPHALOGRAPHY (MEG) could be used to elucidate the precise role of the human

TRUE TASTE SYNERGISM
The combined effect of two taste stimuli, when greater than the sum of the effects of each one present alone.

MULTIMODAL INTEGRATION
The process of combining information from different sensory modalities.

MAGNETOENCEPHALOGRAPHY
(MEG). A non-invasive technique that allows the detection of the changing magnetic fields that are associated with brain activity on the timescale of milliseconds.

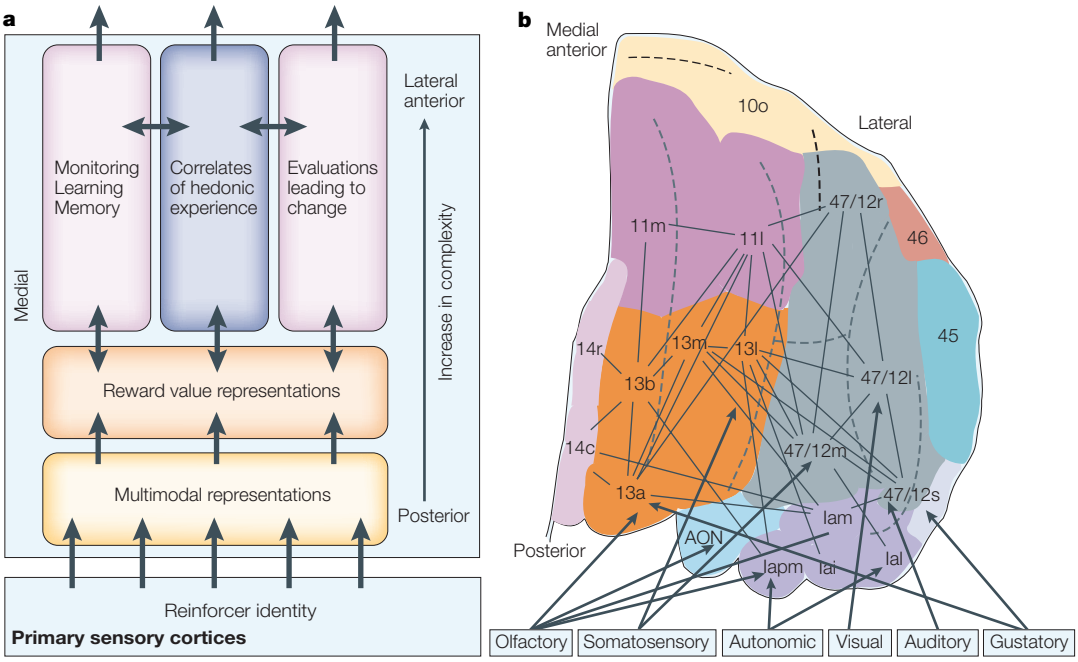

Figure 6 | **A model of orbitofrontal cortex function.** A model of the interactions between sensory and hedonic systems in the human brain. **a** | The proposed model. **b** | A schematic of the functional connectivity of one hemisphere of the orbitofrontal cortex[28,109]. Information in the figure flows from bottom to top. Sensory information arrives from the periphery in the primary sensory cortices, where the stimulus identity is decoded into stable cortical representations. This information is then conveyed to brain structures in the posterior parts of the orbitofrontal cortex for further multimodal integration. The reward value of the reinforcer is assigned in more anterior parts of the orbitofrontal cortex, and from here it can be used to influence subsequent behaviour (in lateral parts of the anterior orbitofrontal cortex with connections to the anterior cingulate cortex), stored for learning and memory (in medial parts of the anterior orbitofrontal cortex) and made available for subjective hedonic experience (in the mid-anterior orbitofrontal cortex). The reward value and subjective hedonic experience can be modulated by hunger and other internal states. Important reciprocal information flows between the various regions of the orbitofrontal cortex and other brain regions. Panel **a** modified, with permission, from REF. 89 © (2004) Elsevier Science. Panel **b** modified, with permission, from REF. 28 © (2004) Elsevier Science.

orbitofrontal cortex, especially in reversal learning. The directionality and timing of neural activity between the orbitofrontal cortex and other key regions, including the anterior cingulate cortex, is not clear but could potentially be addressed with MEG by using sensitive measures such as GRANGER CAUSALITY[105].

On a longer, developmental timescale, it would be interesting to investigate the role of the orbitofrontal cortex in learning and, in particular, in the consolidation of learning. One novel hypothesis is that the rate of improvement in learning (that is, the derivative of the functional changes) in other structures involved in, for example, perceptual learning, depends crucially on reward, emotional and motivational influences, and, therefore, on changes in functional activity in structures known to be involved in emotion, such as the orbitofrontal cortex. This might have important implications for cases of learning, such as literacy, in which the development of reading depends on the connectivity and changes in the functional activity of brain regions in the occipital temporal cortices and in the visual word form area[106], which could initially be set up through top-down interactions with prefrontal areas such as the orbitofrontal cortex.

As the functional neuroanatomy of the orbitofrontal cortex is further elucidated, we should try to obtain a better understanding of maturation processes in this region in children and adolescents. Little is known of these processes[62,107], but one hypothesis is that the extensive individual sulcal variability of the orbitofrontal cortex and the maturation of its functional neuroanatomy relate to individual differences in personality and emotional processing. This might be important if the new field of social neuroscience is to unravel the neural basis of social interaction. In any case, a better understanding of the functions of the orbitofrontal cortex might allow the development of effective treatments for common emotional disorders. Obesity and eating disorders have been linked to disturbances of satiety mechanisms, and given the evidence presented here, it seems highly likely that the orbitofrontal cortex has a pivotal role in these disorders. Depression is often present in individuals with obesity and eating disorders, often with pronounced ANHEDONIA. A better understanding of hedonic processing in general might help us to understand the human condition and to develop new strategies to deal with a range of problems, including depression, eating disorders and obesity.

GRANGER CAUSALITY
A technique for determining whether one time series is useful in predicting another.

ANHEDONIA
Loss of interest or pleasure in almost all activities.

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The author declares no competing financial interests.

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