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The orbitofrontal cortex and emotion in health and disease, including depression☆

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ABSTRACT

The orbitofrontal cortex represents the reward or affective value of primary reinforcers including taste, touch, texture, and face expression. It learns to associate other stimuli with these to produce representations of the expected reward value for visual, auditory, and abstract stimuli including monetary reward value. The orbitofrontal cortex thus plays a key role in emotion, by representing the reward value of the goals for action. The learning process is stimulus-reinforcer association learning. Negative reward prediction error neurons are related to this affective learning. Activations in the orbitofrontal cortex correlate with the subjective emotional experience of affective stimuli, and damage to the orbitofrontal cortex impairs emotion-related learning, emotional behaviour, and subjective affective state. Top-down attention to affect modulates orbitofrontal cortex representations, and attention to intensity modulates representations in earlier cortical areas that represent the physical properties of stimuli. Top-down word-level cognitive inputs can bias affective representations in the orbitofrontal cortex, providing a mechanism for cognition to influence emotion. Whereas the orbitofrontal cortex provides a representation of reward or affective value on a continuous scale, areas beyond the orbitofrontal cortex such as the medial prefrontal cortex area 10 are involved in binary decision-making when a choice must be made. For this decision-making, the orbitofrontal cortex provides a representation of the value of each specific reward on the same scale, with no conversion to a common currency. Increased activity in a lateral orbitofrontal cortex non-reward area provides a new attractor-related approach to understanding and treating depression. Consistent with the theory, the lateral orbitofrontal cortex has increased functional connectivity in depression, and the medial orbitofrontal cortex, involved in reward, has decreased functional connectivity in depression.

1. Introduction

The functions of the orbitofrontal cortex are considered here, based on its connections, neurophysiology, activation in functional neuroimaging studies, and the effects of damage to and dysfunction of the orbitofrontal cortex. This evidence, and differences in its functional connectivity in depression, has led to a new non-reward attractor theory of depression. Activity in the orbitofrontal cortex is compared to that in the areas that project to it, and to the activity in the areas to which it projects. This enables development of a theory of how sensory representations in the input regions are transformed into reward-related value representations used to make decisions (choices) based on reward value in areas beyond the orbitofrontal cortex to which it projects. I also describe evidence for how top-down cognitive and attentional inputs coming from beyond the orbitofrontal cortex can influence the affective representations in the orbitofrontal cortex, showing how cognition and top-down attention descend down into this emotional system in the brain to influence what we feel. The paper is dedicated to Larry Weiskrantz, whose pioneering discoveries include that the amygdala is a part of the temporal lobe involved in emotion (Weiskrantz, 1956), and with colleagues that some aspects of emotion-related processing are present in patients with damage to the primary visual cortex, V1 (de Gelder et al., 1999; Tamietto et al., 2009, 2012). Larry Weiskrantz was an inspiring mentor when I was an undergraduate medical student at Cambridge, and a wonderful colleague at Oxford since then.

Given that emotions can be considered as states elicited by rewards and punishers, or of not receiving an expected reward (non-reward) or not receiving a punisher (relief) (Rolls, 2013b, 2014a, 2014b) (see Section 11), a key contribution of the orbitofrontal cortex to emotion is part of the context of the discoveries and advances described here, which are relevant to our understanding of emotion and its disorders,

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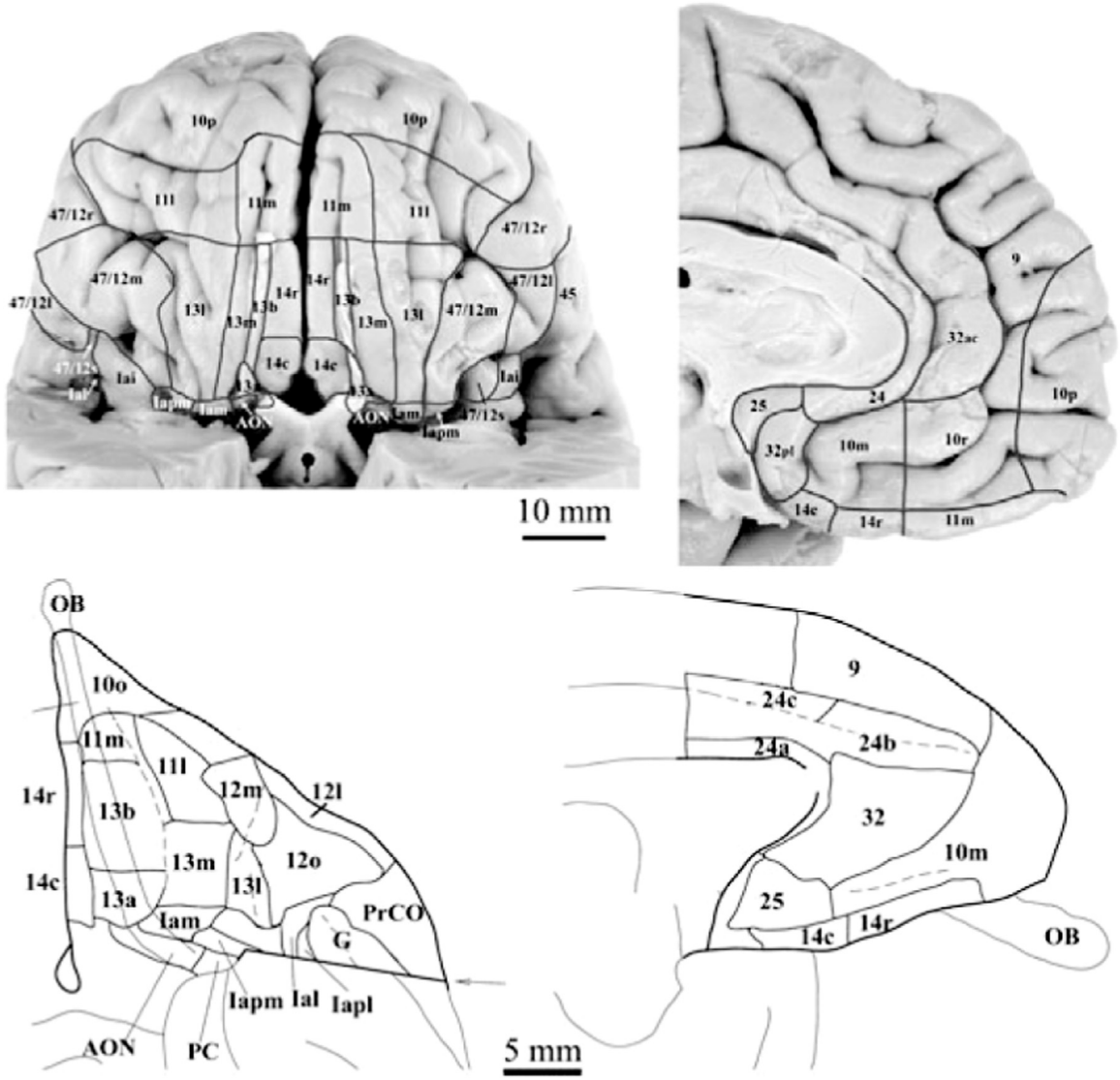

Fig. 1. Maps of architectonic areas in the orbitofrontal cortex and medial prefrontal cortex of humans (above) and monkeys (below). AON – anterior olfactory nucleus; G – primary gustatory cortex; Iai, Ial, Iam, Iapm – subdivisions of the agranular insular cortex; OB – olfactory bulb; PC – pyriform cortex; PrCO – precentral opercular area. (After Öngür et al. (2003), and Carmichael and Price (1994), reprinted from the Journal of Comparative Neurology with permission of John Wiley & Sons, Inc.)

including those produced by damage to the orbitofrontal cortex, and depression.

The focus is on humans and macaques, because there are many topological, cytoarchitectural, and probably connectional similarities between macaques and humans with respect to the orbitofrontal cortex (see Fig. 1 and Carmichael and Price, 1994; Henssen et al., 2016; Kringelbach and Rolls, 2004; Öngür and Price, 2000; Passingham and Wise, 2012; Petrides and Pandya, 1995; Price, 2006, 2007; Rolls, 2014a). The orbitofrontal cortex is much less well developed in rodents, which has only an agranular orbitofrontal cortex which corresponds to a small posterior part of the primate orbitofrontal cortex (Passingham and Wise, 2012; Rolls, 2014a; Wise, 2008), and that is why the rodent orbitofrontal cortex is not considered here. Indeed, the orbitofrontal cortex has increased in proportion more than any other part of the frontal lobes in humans (Semendeferi et al., 1998).

Moreover, the primate orbitofrontal cortex receives visual information from the inferior temporal visual cortex, which is a highly developed area for primate vision enabling invariant visual object and face recognition (Rolls, 2000a, 2007c, 2011b, 2012b, 2016a; Rolls and Deco, 2002), and which provides visual inputs used in the primate orbitofrontal cortex for one-trial object-reward association reversal learning, and for representing face expression and identity. Moreover, the specialization of the primate visual system for processing what is at the fovea makes the information that it passes on to receiving structures quite different from that in rodents (Rolls et al., 2003a; Rolls and Wirth, 2017). Further, even the taste system of primates and rodents may be different, with obligatory processing from the nucleus of the solitary tract via the thalamus to the cortex in primates, but a subcortical pathway in rodents via a pontine taste area to the amygdala, and differences in where satiety influences taste responsive neurons in primates and rodents (Norgren, 1984; Rolls, 2014a, 2015c, 2016b, 2016d, 2017b; Rolls and Scott, 2003).

2. Connections

Part of the background for understanding neuronal responses in the orbitofrontal cortex is the anatomical connections of the orbitofrontal cortex, linked across primates by cytoarchitectural comparisons (Barbas, 1995, 2007; Carmichael and Price, 1994, 1995; Henssen et al., 2016; Mackey and Petrides, 2010; Öngür and Price, 2000; Pandya and Yeterian, 1996; Petrides and Pandya, 1995; Petrides et al., 2012; Price, 2006, 2007; Rolls, 2017c; Saleem et al., 2008, 2014) (Figs. 2 and 1). It

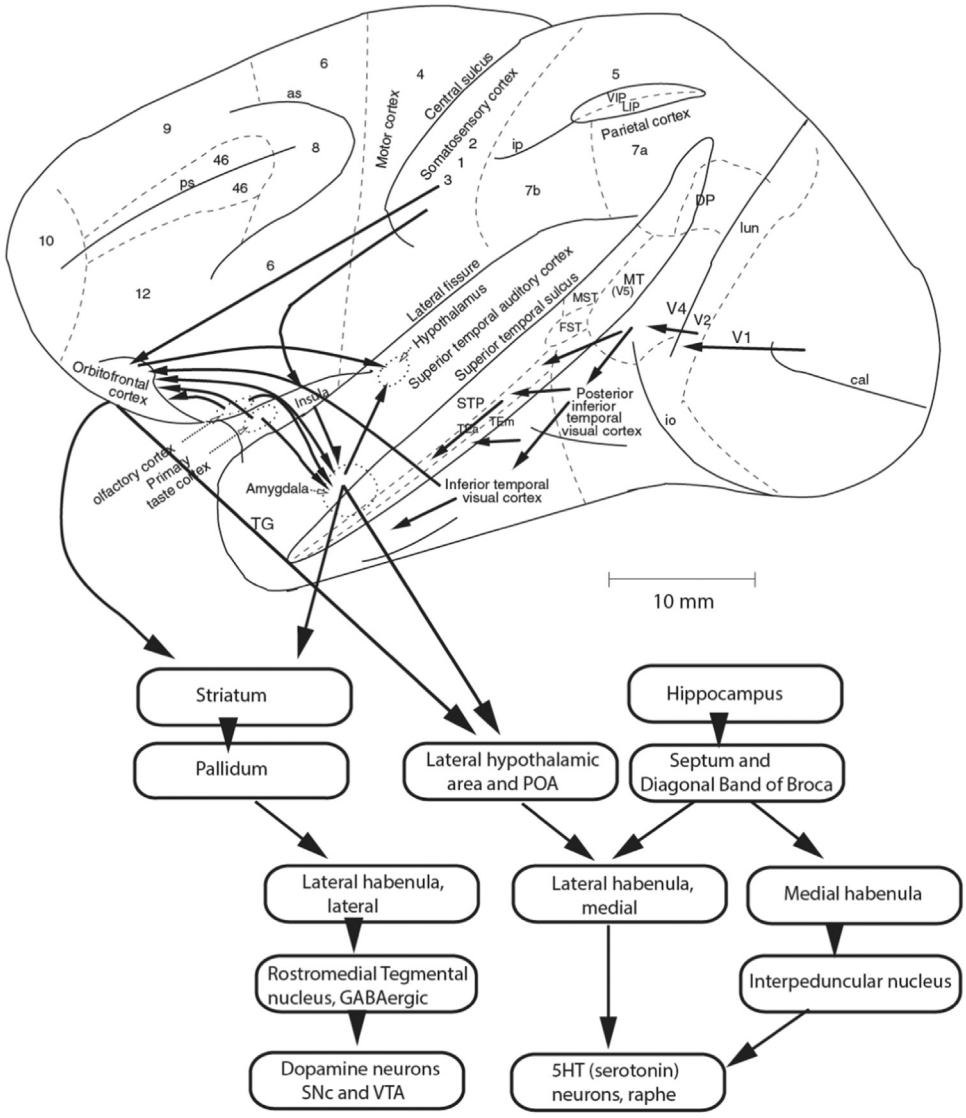

Fig. 2. The orbitofrontal cortex and amygdala systems involved in reward and non-reward can operate via a lateral hypothalamic area/lateral preoptic area (POA) to influence the Lateral Habenula, medial part, which in turn can influence the 5-HT (serotonin) neurons in the raphe nuclei. Many antidepressant drugs may influence this cortical to brainstem pathway by influencing the effects of the 5-HT neurons, which terminate in many brain areas. The hippocampus influence via the septal nuclei and diagonal band of Broca may enable reward context to access the same Lateral Habenula, medial part, to 5-HT-neuron system (Luo et al., 2011; Rolls, 2015b). The medial habenula also receives septal inputs, and projects to the interpeduncular nucleus, and thereby to 5-HT neurons (and probably dopamine neurons) (Loonen and Ivanova, 2016; Proulx et al., 2014). The orbitofrontal cortex, amygdala (and probably anterior cingulate cortex and subgenual cingulate cortex) systems involved in reward and non-reward can operate via a basal ganglia route (striatum, ventral pallidum, and globus pallidus/bed nucleus of the stria terminalis) to influence the Lateral Habenula, lateral part, which in turn via the GABAergic Rostromedial Tegmental nucleus can influence dopamine neurons in the Substantia Nigra pars compacta and ventral Tegmental Area (SNc and VTA). This provides a route for reward, non-reward, and reward prediction error signals of largely cortical origin to influence the dopamine neurons. Details of some of these anatomical connections are provided elsewhere (Loonen and Ivanova, 2016; Proulx et al., 2014). These connections are shown in the context of some of the pathways involved in reward-related processes and emotion shown on the lateral view of the brain of the macaque monkey in the upper part of the Figure (Rolls, 2014a). Connections from the primary taste and olfactory cortices to the orbitofrontal cortex and amygdala are shown. Connections are also shown in the 'ventral visual system' from the visual cortical areas V1 to V2, V4, the inferior temporal visual cortex, etc., with some connections reaching the amygdala and orbitofrontal cortex. In addition, connections from the somatosensory cortical areas BA 1, 2, and 3 that reach the orbitofrontal cortex directly and via the insular cortex, and that reach the amygdala via the insular cortex, are shown. as, arcuate sulcus; cal, calcarine sulcus; cs, central sulcus; lf, lateral (or Sylvian) fissure; lun, lunate sulcus; ps, principal sulcus; io, inferior occipital sulcus; ip, intraparietal sulcus (which has been opened to reveal some of the areas it contains); sts, superior temporal sulcus (which has been opened to reveal some of the areas it contains). AIT, anterior inferior temporal cortex; FST, visual motion processing area; LIP, lateral intraparietal area; MST, visual motion processing area; MT, visual motion processing area (also called V5); PIT, posterior inferior temporal cortex; STP, superior temporal plane; TA, architectonic area including auditory association cortex; TE, architectonic area including high order visual association cortex, and some of its subareas TEa and TEm; TG, architectonic area in the temporal pole; V1–V4, visual areas V1–V4; VIP, ventral intraparietal area; TEO, architectonic area including posterior visual association cortex. The numerals refer to architectonic areas, and have the following approximate functional equivalence: 1,2,3, somatosensory cortex (posterior to the central sulcus); 4, motor cortex; 5, superior parietal lobule; 7a, inferior parietal lobule, visual part; 7b, inferior parietal lobule, somatosensory part; 6, lateral premotor cortex; 8, frontal eye field; 12, part of orbitofrontal cortex; 46, dorsolateral prefrontal cortex.

should be noted from Fig. 1 that the lateral orbitofrontal cortex, area 47/12 in humans and 12 in macaques, extends round the inferior prefrontal convexity, where is adjoins area 45 in the inferior frontal gyrus (Saleem et al., 2014). A schematic diagram that helps to show the stage of processing in different sensory streams of the orbitofrontal cortex is provided in Fig. 3. This shows that the orbitofrontal cortex can be thought of as receiving from the ends of each modality-specific "what" cortical pathway.

Rolls et al. (1990) discovered a taste area with taste-responsive neurons in the lateral part of the macaque orbitofrontal cortex, and showed anatomically that this was the secondary taste cortex in that it receives a major projection from the primary taste cortex (Baylis et al., 1995). This region projects on to more anterior areas of the orbitofrontal cortex (Baylis et al., 1995). Taste neurons are also found more medially (Critchley and Rolls, 1996c; Pritchard et al., 2005; Rolls, 2008c; Rolls and Baylis, 1994; Rolls et al., 1996a).

In the mid orbitofrontal cortex, there is an area with olfactory neurons (Rolls and Baylis, 1994) and anatomically, there are direct connections from the primary olfactory cortex, pyriform cortex, to area 13a of the posterior orbitofrontal cortex, which in turn has onward projections to a middle part of the orbitofrontal cortex (area 13) (Barbas, 1993; Carmichael et al., 1994; Morecraft et al., 1992; Price, 2007; Price et al., 1991) (see Fig. 1).

Thorpe et al. (1983) found neurons with visual responses in the orbitofrontal cortex, and anatomically, visual inputs reach the orbitofrontal cortex directly from the inferior temporal cortex (Saleem et al., 2008) (where object and face identity are represented (Rolls, 2007c, 2016a)), from the cortex in the superior temporal sulcus (Saleem et al., 2008) (where face expression and gesture are represented (Hasselmo et al., 1989)), and from the temporal pole (see Barbas, 1988, 1993, 1995; Barbas and Pandya, 1989; Carmichael and Price, 1995; Morecraft et al., 1992; Seltzer and Pandya, 1989). There are corresponding

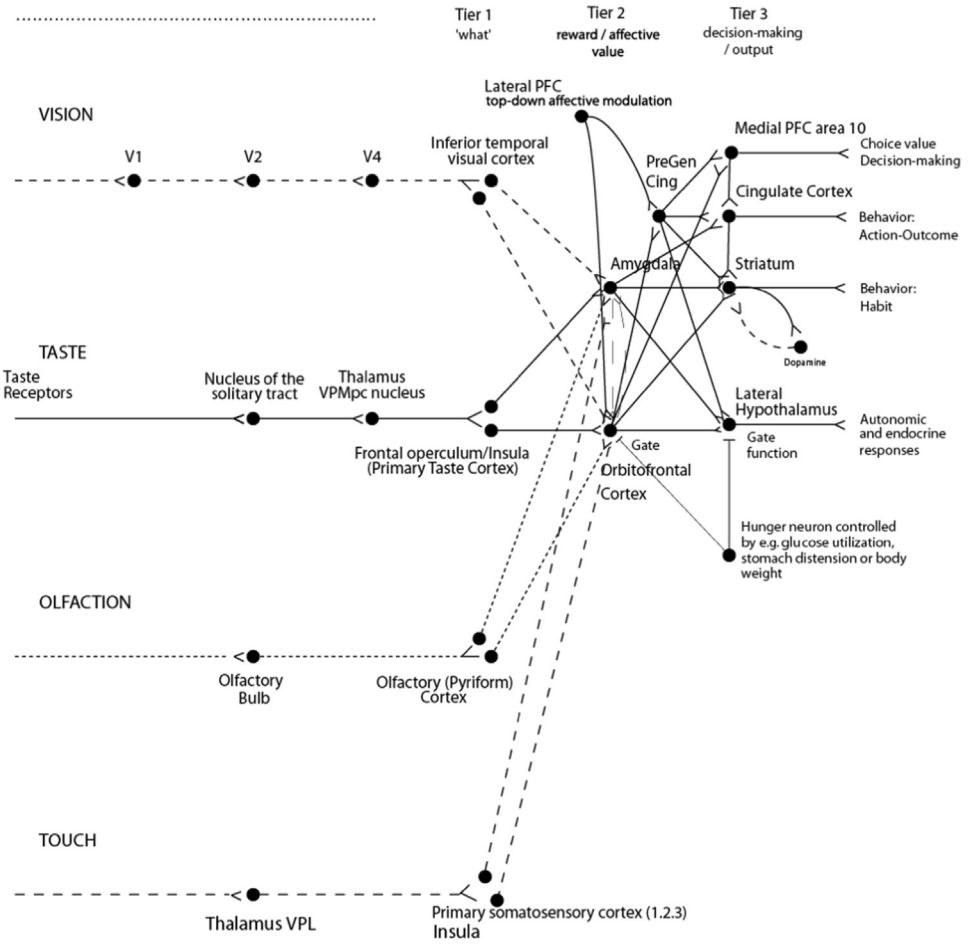

Fig. 3. Schematic diagram showing some of the gustatory, olfactory, visual and somatosensory pathways to the orbitofrontal cortex, and some of the outputs of the orbitofrontal cortex, in primates. The secondary taste cortex, and the secondary olfactory cortex, are within the orbitofrontal cortex. V1 – primary visual cortex. V4 – visual cortical area V4. PreGen Cing – pregenual cingulate cortex. "Gate" refers to the finding that inputs such as the taste, smell, and sight of food in some brain regions only produce effects when hunger is present (Rolls, 2014a). Tier 1: the column of brain regions including and below the inferior temporal visual cortex represents brain regions in which 'what' stimulus is present is made explicit in the neuronal representation, but not its reward or affective value which are represented in the next tier of brain regions (Tier 2), the orbitofrontal cortex and amygdala, and in the anterior cingulate cortex. In Tier 3 areas beyond these such as medial prefrontal cortex area 10, choices or decisions about reward value are taken (Rolls, 2014a, 2016a; Rolls and Deco, 2010). Top-down control of affective response systems by cognition and by selective attention from the dorsolateral prefrontal cortex is also indicated. Medial PFC area 10 – medial prefrontal cortex area 10; VPMpc – ventralposteromedial thalamic nucleus, the thalamic nucleus for taste.

auditory inputs (Barbas, 1988, 1993; Rolls et al., 2006b; Romanski and Goldman-Rakic, 2001; Romanski et al., 1999).

Some neurons in the orbitofrontal cortex respond to oral somatosensory stimuli such as the texture of food (Rolls et al., 1999a, 2003c), and anatomically there are inputs to the orbitofrontal cortex from somatosensory cortical areas 1, 2 and SII in the frontal and pericentral operculum, and from the insula (Barbas, 1988; Carmichael and Price, 1995). The caudal orbitofrontal cortex receives inputs from the amygdala (Price, 2006; Price et al., 1991). The orbitofrontal cortex also receives inputs via the mediodorsal nucleus of the thalamus, pars magnocellularis, which itself receives afferents from temporal lobe structures such as the prepyriform (olfactory) cortex, amygdala, and inferior temporal cortex (see Öngür and Price, 2000). These connections provide some routes via which the responses of orbitofrontal cortex neurons can be produced. Within the orbitofrontal cortex, there are many intrinsic connections (Öngür and Price, 2000), and these may be part of what enables many orbitofrontal cortex neurons to have multimodal responses, as described below and elsewhere (Rolls, 2006, 2014a, 2016a).

The orbitofrontal cortex projects back to temporal lobe areas such as the amygdala (Barbas, 2007) and temporal cortex (Saleem et al., 2008, 2014). The orbitofrontal cortex also has projections to the anterior cingulate cortex (Carmichael and Price, 1996; Morecraft and Tanji, 2009; Palomero-Gallagher et al., 2015; Price, 2006; Vogt, 2009), medial prefrontal cortex area 10 (Price, 2007), entorhinal and perirhinal cortex (Barbas, 2007; Insausti et al., 1987; Saleem et al., 2008, 2014) providing a route for reward information to reach the hippocampus (Rolls, 2015b; Rolls and Xiang, 2005), preoptic region and lateral hypothalamus (where neurons respond to the sight and taste of food, and show sensory-specific satiety (Burton et al., 1976; Rolls et al., 1976)), and these connections provide some routes via which the orbitofrontal cortex can influence behaviour (Rolls, 2014a) and memory (Rolls, 2015b; Rolls and Xiang, 2005). The orbitofrontal cortex also projects to the ventral striatum (Ferry et al., 2000) and head of the caudate nucleus (Haber et al., 2006; Kemp and Powell, 1970), and these pathways in part via the habenula provide a route for the orbitofrontal cortex and related structures to introduce reward and non-reward-related information partly via the habenula into the dopamine and serotonin systems in the brainstem, as shown in Fig. 2 (Rolls, 2017c). Indeed, the computation of expected value, outcome value, and their difference which is an error signal is computed in the orbitofrontal cortex and its connected structures, and provides a source of this information for the dopamine neurons implicated in positive reward error processing (Schultz, 2016) and the serotonin neurons via which many antidepressants act (Rolls, 2017c) (see below).

3. Effects of damage to the macaque orbitofrontal cortex

Part of the evidence on the functions of the orbitofrontal cortex comes from the effect of lesions of the orbitofrontal cortex. Macaques with lesions of the orbitofrontal cortex are impaired at tasks that involve learning about which stimuli are rewarding and which are not, and are especially impaired at altering behaviour when reinforcement contingencies change. The monkeys may respond when responses are inappropriate, e.g., no longer rewarded, or may respond to a non-rewarded stimulus. For example, monkeys with lateral orbitofrontal/inferior prefrontal convexity damage are impaired on Go/NoGo task performance in that they Go on the NoGo trials (Iversen and Mishkin, 1970); and in an object reversal task in that they respond to the object which was formerly rewarded with food (Iversen and Mishkin, 1970).

Similar effects were found in another study when the lesions included the lateral orbitofrontal cortex (Jones and Mishkin, 1972). Below, I interpret this as a failure to respond to non-reward, given the activations found in humans in this region in a reward reversal task (Kringelbach and Rolls, 2003) (confirmed in monkeys (Chau et al., 2015)) and when losing money (O'Doherty et al., 2001a).

Medial orbitofrontal cortex (areas 13 and 11) lesions do not impair non-reward tasks, but, consistent with our evidence that neurons in the medial orbitofrontal cortex represent reward value in that they no longer respond to the reward when it is devalued by feeding it to satiety (Critchley and Rolls, 1996a; Rolls et al., 1989), do impair the effects on behaviour of reward devaluation (Izquierdo et al., 2004; Murray and Izquierdo, 2007).

Damage to the caudal orbitofrontal cortex in the monkey also produces emotional changes (e.g., decreased aggression to humans and to stimuli such as a snake and a doll), and a reduced tendency to reject foods such as meat (Butter et al., 1969, 1970; Butter and Snyder, 1972; Murray and Izquierdo, 2007) or to display the normal preference ranking for different foods (Baylis and Gaffan, 1991).

In the next sections, the representations of reward value found in the orbitofrontal cortex but not in the preceding cortical areas from which the orbitofrontal cortex receives it inputs (Fig. 3) (Rolls, 2014a, 2014b, 2016a) are described.

4. Taste, olfaction, flavor, oral texture, temperature: reward value

4.1. Taste: a primary reinforcer

One of the discoveries that have helped us to understand the functions of the orbitofrontal cortex in behaviour is that it contains a major cortical representation of taste (see Kadohisa et al., 2005; Rolls, 2008c, 2014a, 2016d; Rolls and Scott, 2003; Rolls et al., 1990) (cf. Figs. 2 and 3). Given that taste can act as a primary reinforcer, that is without learning as a reward or punisher, we now have the start for a fundamental understanding of the function of the orbitofrontal cortex in stimulus-reinforcer association learning (Rolls, 1999a, 2004a, 2014a, 2016a). We know how one class of primary reinforcers reaches and is represented in the orbitofrontal cortex. A representation of primary reinforcers is essential for a system that is involved in learning associations between previously neutral stimuli and primary reinforcers, e.g. between the sight of an object, and its taste (Rolls, 2014a).

The representation (shown by analysing the responses of single neurons in macaques) of taste in the primate orbitofrontal cortex includes robust representations of the prototypical tastes sweet, salt, bitter and sour (Rolls et al., 1990), but also separate representations of the "taste" of water (Rolls et al., 1990), and of protein or umami as exemplified by monosodium glutamate (Baylis and Rolls, 1991; Rolls, 2000c) and inosine monophosphate (Rolls et al., 1996a, 1998). Examples of two orbitofrontal cortex neurons with different responses to different taste stimuli are shown in Fig. 4. A very important discovery is that each neuron responds to different combinations of the stimuli. This provides the basis for the brain to encode very many different stimuli, because the responses of the neurons are relatively independent (Rolls, 2017a; Rolls and Treves, 2011). It also provides the basis for sensory-specific satiety, that is, for devaluation of the reward value of a particular food eaten to satiety by habituation of one type of combination-sensitive neuron (Rolls, 2014a, 2016d). As will be described below, some neurons have taste-only responses, and others respond to a variety of oral somatosensory stimuli, including for some neurons viscosity (Rolls et al., 2003d), fat texture (Rolls et al., 1999a; Verhagen et al., 2003), and for other neurons astringency as exemplified by tannic acid (Critchley and Rolls, 1996c).

The nature of the representation of taste in the orbitofrontal cortex is that for the majority of neurons the reward value of the taste is represented. The evidence for this is that the responses of orbitofrontal taste neurons are modulated by hunger (as is the reward value or

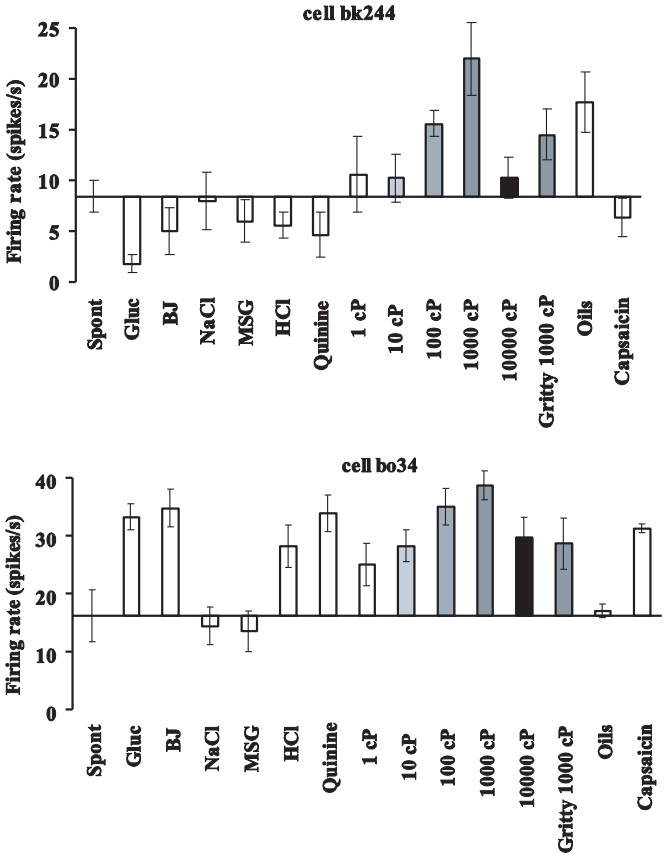

Fig. 4. Oral somatosensory and taste inputs to orbitofrontal cortex neurons. Above. Firing rates (mean ± sem) of viscosity-sensitive neuron bk244 which did not have taste responses, in that it did not respond differentially to the different taste stimuli. The firing rates are shown to the viscosity series, to the gritty stimulus (carboxymethylcellulose with Fillite microspheres), to the taste stimuli 1 M glucose (Gluc), 0.1 M NaCl, 0.1 M MSG, 0.01 M HCl and 0.001 M QuinineHCl, and to fruit juice (BJ). Spont = spontaneous firing rate. Below. Firing rates (mean ± sem) of viscosity-sensitive neuron bo34 which had no response to the oils (mineral oil, vegetable oil, safflower oil and coconut oil, which have viscosities which are all close to 50 cP). The neuron did not respond to the gritty stimulus in a way that was unexpected given the viscosity of the stimulus, was taste tuned, and did respond to capsaicin. (After Rolls et al., 2003a, 2003b, 2003c, 2003d.)

palatability of a taste). In particular, it has been shown that orbitofrontal cortex taste neurons gradually stop responding to the taste of a food as the monkey is fed to satiety (Rolls et al., 1996a, 1989). The example shown in Fig. 5 is of a single neuron with taste, olfactory, and visual responses to food, and the neuronal responses elicited through all these sensory modalities showed a decrease. The decrease is relatively specific to the food eaten to satiety, and the responses of these neurons are thus very closely related to sensory-specific satiety. The responses of these orbitofrontal cortex neurons thus reflect the preferences of the macaque for different sensory stimuli (Critchley and Rolls, 1996a; Rolls et al., 1989), and some neurons encode relative preferences (Tremblay and Schultz, 1999).

In contrast, the representation of taste in the primary taste cortex (Scott et al., 1986; Yaxley et al., 1990) is not modulated by hunger (Rolls et al., 1988; Yaxley et al., 1988). Thus in the primate primary taste cortex, the reward value of taste is not represented, and instead the identity and intensity of the taste are represented (Rolls, 2016b).

Additional evidence that the reward value of food is represented in the orbitofrontal cortex is that monkeys work for electrical stimulation of the orbitofrontal cortex if they are hungry, but not if they are satiated (Mora et al., 1979; Rolls, 2014a). Further, neurons in the orbitofrontal cortex are activated from many brain-stimulation reward sites (Mora et al., 1980; Rolls et al., 1980). Thus there is clear evidence that it is the reward value of taste that is represented in the orbitofrontal cortex (see

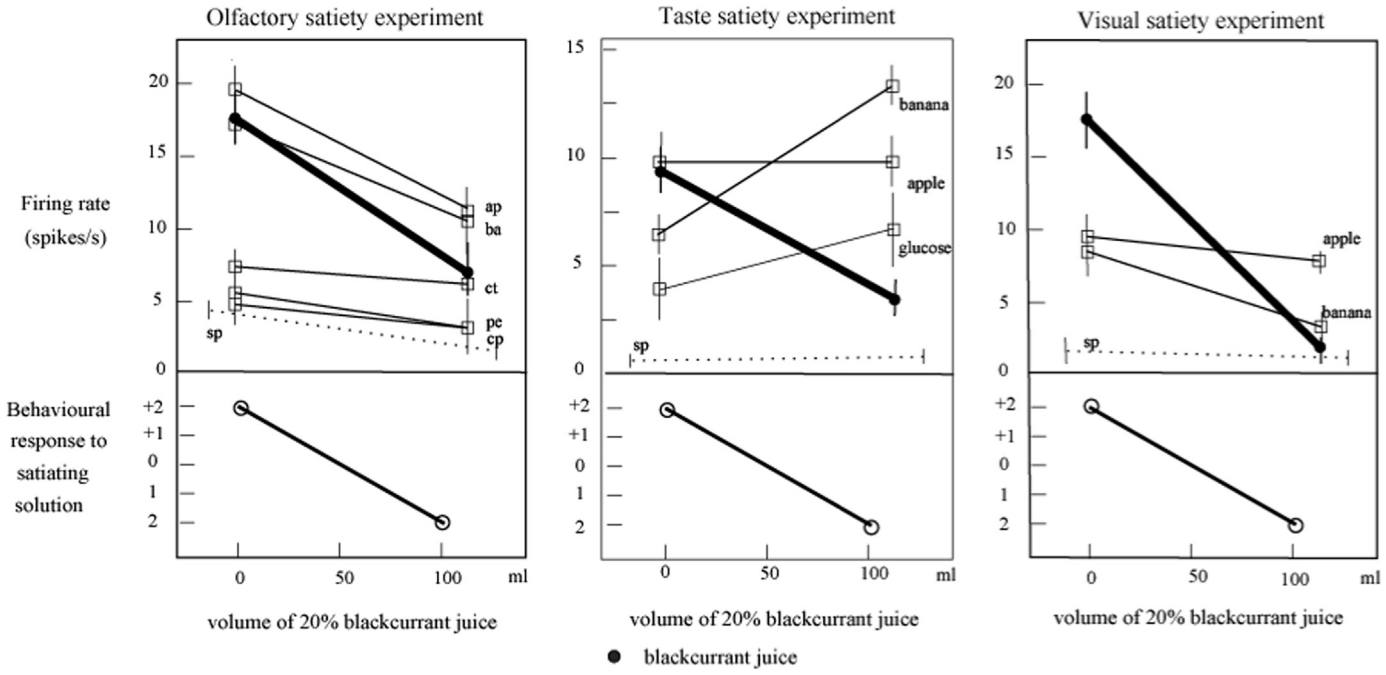

Fig. 5. Multimodal orbitofrontal cortex neuron with sensory-specific satiety-related responses to visual, taste and olfactory sensory inputs. The responses are shown before and after feeding to satiety with blackcurrant juice. The solid circles show the responses to blackcurrant juice. The olfactory stimuli included apple (ap), banana (ba), citral (ct), phenylethanol (pe), and caprylic acid (cp). The spontaneous firing rate of the neuron is shown (sp). (After Critchley and Rolls, 1996).

further Rolls, 1999a, 2000d, 2014a), and this is further supported by the finding that feeding to satiety decreases the activation of the human orbitofrontal cortex to the food eaten to satiety in a sensory-specific way (Kringelbach et al., 2003). Sensory-specific satiety is part of a mechanism to facilitate behavioural switching between different positive reinforcers, and in the case of food, may facilitate eating a varied diet with the consequent beneficial nutritional implications, but may contribute to overeating and obesity if too much variety is available (Rolls, 2014a, 2016d).

Although some taste neurons are found laterally in the orbitofrontal cortex (area 12o) (Rolls and Baylis, 1994; Rolls et al., 1996b, 1990), others are found through the middle and even towards the medial part of the orbitofrontal cortex in areas 13 m and 13 l (see Fig. 1) (Critchley and Rolls, 1996a, 1996c; Pritchard et al., 2005, 2007; Rolls and Baylis, 1994; Rolls et al., 1996a).

Functional neuroimaging studies have shown that the most medial part of the human orbitofrontal cortex is activated by taste, oral texture, and olfactory stimuli (de Araujo et al., 2003a, 2003c, 2005; de Araujo and Rolls, 2004; Francis et al., 1999; Gottfried et al., 2006; McCabe and Rolls, 2007; O'Doherty et al., 2000; Rolls et al., 2003b; Rolls and McCabe, 2007; Small et al., 2005, 2001), and that the activations correlate with ratings of subjective pleasantness (Kringelbach and Rolls, 2004; Rolls, 2014a). A study by Rolls, Verhagen and Kadohisa (see Rolls, 2008c) showed that there are taste neurons in the medial orbitofrontal cortex in regions more lateral than 7 mm from the midline, including areas 13 m and 13 l.

Corresponding to the findings in non-human primate single neuron neurophysiology, in human functional neuroimaging experiments (e.g., with functional magnetic resonance image, fMRI), it has been shown that there is an orbitofrontal cortex area activated by sweet taste (Francis et al., 1999; Small et al., 2007, 1999), and that there are at least partly separate areas activated by the aversive taste of saline (NaCl, 0.1 M) (O'Doherty et al., 2001b), by pleasant touch (Francis et al., 1999; Rolls et al., 2003c), and by pleasant vs. aversive olfactory stimuli (Francis et al., 1999; O'Doherty et al., 2000; Rolls, 2000d; Rolls et al., 2003b). Umami (protein) taste is not only represented by neurons in the primate orbitofrontal cortex (Baylis and Rolls, 1991; Rolls et al., 1996a), but also human fMRI studies show that umami taste is represented in the orbitofrontal cortex, with an anterior part responding supralinearly to a combination of monosodium glutamate and inosine monophosphate (de Araujo et al., 2003a). Some orbitofrontal cortex neurons respond to the 'taste' of water in the mouth (Rolls et al., 1990), and their responses occur only when thirsty and not when satiated (Rolls et al., 1989); and correspondingly in humans the pleasantness of the taste of water in the mouth is represented in the orbitofrontal cortex (de Araujo et al., 2003b).

4.2. An olfactory representation in the orbitofrontal cortex

A ventral frontal region has been implicated in olfactory processing in humans (Jones-Gotman and Zatorre, 1988; Zatorre et al., 1992). Rolls and colleagues have analysed the rules by which orbitofrontal olfactory representations are formed and operate in primates. For 65% of neurons in the orbitofrontal olfactory areas, Critchley and Rolls (1996b) showed that the representation of the olfactory stimulus was independent of its association with taste reward (analysed in an olfactory discrimination task with taste reward). For the remaining 35% of the neurons, the odors to which a neuron responded were influenced by the taste (glucose or saline) with which the odor was associated. Thus the odor representation for 35% of orbitofrontal neurons appeared to be built by olfactory-to-taste association learning. This possibility was confirmed by reversing the taste with which an odor was associated in the reversal of an olfactory discrimination task. It was found that 68% of the sample of neurons analysed altered the way in which they responded to odor when the taste reinforcement association of the odor was reversed (Rolls et al., 1996b). The olfactory-to-taste reversal was quite slow, both neurophysiologically and behaviourally, often requiring 20–80 trials, consistent with the need for some stability of flavor representations. Thus the rule according to which the orbitofrontal olfactory representation was formed was for some neurons by association learning with taste.

To analyse the nature of the olfactory representation in the orbitofrontal cortex, Critchley and Rolls (1996a) measured the responses of olfactory neurons that responded to food while they fed the monkey to

satiety. They found that the majority of orbitofrontal olfactory neurons decreased their responses to the odor of the food with which the monkey was fed to satiety (see example in Fig. 5). Thus for these neurons, the reward value of the odor is what is represented in the orbitofrontal cortex (cf. Rolls and Rolls, 1997). In that the neuronal responses decreased to the food with which the monkey is fed to satiety, and may even increase to a food with which the monkey has not been fed, it is the relative reward value of stimuli that is represented by these orbitofrontal cortex neurons (cf. Schultz et al., 2000), and this parallels the changes in the relative pleasantness of different foods after a food is eaten to satiety (Rolls et al., 1981a, 1981b; Rolls, 1997; see Rolls, 1999a, 2000d, 2014a). Although individual neurons do not encode large amounts of information about which of 7–9 odors has been presented (Rolls et al., 1996c), we have shown that the information does increase linearly with the number of neurons in the sample (Rolls et al., 2010b). This ensemble encoding does result in useful amounts of information about which odor has been presented being provided by orbitofrontal cortex olfactory neurons.

Corresponding to the findings in non-human primate single neuron neurophysiology, in human neuroimaging experiments it has been shown that there is an orbitofrontal cortex area activated by olfactory stimuli (Francis et al., 1999; Jones-Gotman and Zatorre, 1988; Zatorre et al., 1992). Moreover, the pleasantness or reward value of odor is represented in the orbitofrontal cortex, in that feeding the humans to satiety decreases the activation found to the odor of that food, and this effect is relatively specific to the food eaten in the meal (Howard et al., 2015; O'Doherty et al., 2000).

Importantly, the human medial orbitofrontal cortex has activation that is linearly related to the subjective pleasantness of a set of odors, and a more lateral area has activation that is related to the degree of subjective unpleasantness of odors (Rolls et al., 2003b). In contrast, in primary olfactory cortical areas the activations reflected the intensity of the odors (Rolls et al., 2003b).

In humans, the separate representations of pleasant and unpleasant odors appear to respond differently to hedonically complex odor mixtures that contain pleasant and unpleasant components. In brain areas such as the medial orbitofrontal cortex that represent pleasant odors, unpleasant components in the mixture were minimized and pleasant components were emphasized. In brain areas such as the mid orbitofrontal cortex that represent unpleasant odors, unpleasant components were emphasized more (Grabenhorst et al., 2007). An implication is that the system may be able to represent simultaneously the pleasantness and unpleasantness of odor mixtures. Part of the interest of this is that interesting affective phenomena can arise with odor mixtures. For example, though musk and indole are unpleasant on their own, their presence in a complex mixture may not be unpleasant, and indeed may enhance the pleasantness (Grabenhorst et al., 2007). Moreover, the separate and simultaneous representations of the positive and negative hedonic value of a complex affective stimulus may be important for affective decision-making in the brain, in that separate representations of different affective components of the same sensory stimulus may provide the inputs for making a decision about whether to choose the stimulus or not.

4.3. Convergence of taste and olfactory inputs in the orbitofrontal cortex: the representation of flavor

In the orbitofrontal cortex, not only unimodal taste neurons, but also unimodal olfactory neurons are found. In addition some single neurons respond to both gustatory and olfactory stimuli, often with correspondence between the two modalities (Rolls and Baylis, 1994). It is probably here in the orbitofrontal cortex of primates including humans that these two modalities converge to produce the representation of flavor (de Araujo et al., 2003c; Rolls and Baylis, 1994), for neurons in the primary taste cortex in the insular/frontal opercular cortex do not respond to olfactory (or visual) stimuli (Verhagen et al., 2004). Evidence will soon be described that indicates that these representations are built by olfactory-gustatory association learning, an example of stimulus-reinforcer association learning.

The importance of the combination of taste and smell for producing affectively pleasant and rewarding representations of sensory stimuli is exemplified by findings with umami, the delicious taste or flavor that is associated with combinations of components that include meat, fish, milk, tomatoes, and mushrooms, all of which are rich in umami-related substances such as glutamate or inosine 5′monophosphate. Umami taste is produced by glutamate acting on a fifth taste system (Chaudhari, 2013; Chaudhari et al., 2000, 2009; Maruyama et al., 2006; Rolls, 2009b; Zhao et al., 2003). However, glutamate presented alone as a taste stimulus is not highly pleasant, and does not act synergistically with other tastes (sweet, salt, bitter and sour). However, when glutamate is given in combination with a consonant, savory, odor (vegetable), the resulting flavor can be much more pleasant (McCabe and Rolls, 2007). We showed using functional brain imaging with fMRI that this glutamate taste and savory odor combination produced much greater activation of the medial orbitofrontal cortex and pregenual cingulate cortex than the sum of the activations by the taste and olfactory components presented separately (McCabe and Rolls, 2007). Supra-linear effects were much less (and significantly less) evident for sodium chloride and vegetable odor. Further, activations in these brain regions were correlated with the pleasantness and fullness of the flavor, and with the consonance of the taste and olfactory components. Supra-linear effects of glutamate taste and savory odor were not found in the insular primary taste cortex. We thus proposed that glutamate acts by the non-linear effects it can produce when combined with a consonant odor in multimodal cortical taste-olfactory convergence regions. We suggested that umami can be thought of as a rich and delicious flavor that is produced by a combination of glutamate taste and a consonant savory odor. Glutamate is thus a flavor enhancer because of the way that it can combine supra-linearly with consonant odors in cortical areas where the taste and olfactory pathways converge far beyond the receptors (McCabe and Rolls, 2007).

4.4. Oral texture and temperature

Some neurons in the macaque orbitofrontal cortex respond to the texture of food in the mouth. Some neurons alter their responses when the texture of a food is modified by adding gelatine or methyl cellulose, or by partially liquefying a solid food such as apple (Critchley et al., 1993).

Another population of orbitofrontal neurons responds when a fatty food such as cream is in the mouth. These neurons can also be activated by pure fat such as glyceryl trioleate, and by non-fat substances with a fat-like texture such as paraffin oil (hydrocarbon) and silicone oil ($Si(CH_3)_2O)_n$). These neurons thus provide information by somatosensory pathways that a fatty food is in the mouth (Rolls et al., 1999a). These inputs are perceived as pleasant when hungry, because of the utility of ingestion of foods that are likely to contain essential fatty acids and to have a high calorific value (Rolls, 2000d, 2014a, 2016d). Satiety produced by eating a fatty food, cream, can decrease the responses of orbitofrontal cortex neurons to the texture of fat in the mouth (Rolls et al., 1999a).

We have shown that the orbitofrontal cortex receives inputs from a number of different oral texture channels, which together provide a rich sensory representation of what is in the mouth. Using a set of stimuli in which viscosity was systematically altered (carboxymethylcellulose with viscosity in the range 10–10,000 centiPoise), we have shown that some orbitofrontal cortex neurons encode fat texture independently of viscosity (by a physical parameter that varies with the slickness of fat) (Verhagen et al., 2003); that other orbitofrontal cortex neurons encode the viscosity of the texture in the mouth (with some neurons tuned to viscosity, and others showing increasing or decrease firing rates as viscosity increases) (Rolls et al., 2003d); and that other neurons have

responses that indicate the presence of texture stimuli (such as grittiness and capsaicin) in the mouth independently of viscosity and slickness (Rolls et al., 2003d). The ensemble (i.e. population, distributed) encoding of all these variables is illustrated by the different tuning to the set of stimuli of the two neurons shown in Fig. 4.

An overlapping population of orbitofrontal cortex neurons represents the temperature of what is in the mouth (Kadohisa et al., 2004).

These single neuron recording studies thus provide clear evidence on the rich sensory representation of oral stimuli, and of their reward value, that is provided in the primate orbitofrontal cortex, and how this differs from what is represented in the primary taste cortex and in the amygdala (Kadohisa et al., 2005). In a complementary human functional neuroimaging study, it has been shown that activation of parts of the orbitofrontal cortex, primary taste cortex, and mid-insular somatosensory region posterior to the insular taste cortex have activations that are related to the viscosity of what is in the mouth, and that there is in addition a medial prefrontal/cingulate area where the mouth feel of fat is represented (de Araujo and Rolls, 2004). Also, in humans, there is a representation of the temperature of what is in the mouth (Guest et al., 2007). The oral temperature stimuli (cooled and warmed, 5, 20 and 50 °C) activated the insular taste cortex (identified by glucose taste stimuli), a part of the somatosensory cortex, the orbitofrontal cortex, the anterior cingulate cortex, and the ventral striatum. Brain regions where activations correlated with the pleasantness ratings of the oral temperature stimuli included the orbitofrontal cortex and pregenual cingulate cortex. Part of the advantage of having a representation of oral temperature in these regions is that neurons can then encode combinations of taste, texture and oral temperature (Kadohisa et al., 2004; Verhagen et al., 2004). These combination-responsive neurons may provide the basis for particular combinations of temperature, taste, texture and odor to be especially pleasant (E.T. Rolls et al., 1980; B.J. Rolls et al., 1980; Rolls, 2014a); for sensory-specific satiety to apply to that combination but not necessarily to the components; and more generally for learning and perception to apply to that combination and not necessarily to the components (Rolls, 2014a, 2016a).

5. Somatosensory and temperature inputs to the orbitofrontal cortex, and affective value

In addition to these oral somatosensory inputs to the orbitofrontal cortex, there are also somatosensory inputs from other parts of the body, and indeed an fMRI investigation we have performed in humans indicates that pleasant and painful touch stimuli to the hand produce greater activation of the orbitofrontal cortex relative to the somatosensory cortex than do affectively neutral stimuli (Francis et al., 1999; Rolls et al., 2003c).

Non-glabrous skin such as that on the forearm contains C fibre tactile afferents that respond to light moving touch (Olausson et al., 2002). The orbitofrontal cortex is implicated in some of the affectively pleasant aspects of touch that may be mediated through C fibre tactile afferents, in that it is activated more by light touch to the forearm than by light touch to the glabrous skin (palm) of the hand (McCabe et al., 2008; Rolls, 2010a, 2015a).

Warm and cold stimuli have affective components such as feeling pleasant or unpleasant, and these components may have survival value, for approach to warmth and avoidance of cold may be reinforcers or goals for action built into us during evolution to direct our behaviour to stimuli that are appropriate for survival. Understanding the brain processing that underlies these prototypical reinforcers provides a direct approach to understanding the brain mechanisms of emotion. In an fMRI investigation in humans, it was found that the mid-orbitofrontal and pregenual cingulate cortex and the ventral striatum have activations that are correlated with the subjective pleasantness ratings made to warm (41 °C) and cold (12 °C) stimuli, and combinations of warm and cold stimuli, applied to the hand (Rolls et al., 2008b) (see Fig. 6a–c). Activations in the lateral and some more anterior parts of the orbitofrontal cortex were correlated with the unpleasantness of the stimuli. In contrast, activations in the somatosensory cortex and ventral posterior insula were correlated with the intensity but not the pleasantness of the thermal stimuli (see Fig. 6d–f).

A principle thus is that processing related to the affective value and associated subjective emotional experience of thermal stimuli that are important for survival is performed in different brain areas to those where activations are related to sensory properties of the stimuli such as their intensity. This conclusion appears to be the case for processing in a number of sensory modalities, including taste (Grabenhorst and Rolls, 2008; Grabenhorst et al., 2008a) and olfaction (Anderson et al., 2003; Grabenhorst et al., 2007; Rolls et al., 2003b), and the finding with such prototypical stimuli as warm and cold (Rolls et al., 2008b) provides strong support for this principle (Rolls, 2014a, 2016a).

6. Visual inputs to the orbitofrontal cortex; and visual stimulus-reinforcement association learning and reversal

We have been able to show that there is a major visual input to many neurons in the orbitofrontal cortex, and that what is represented by these neurons is in many cases the reinforcement association of visual stimuli. The visual input is from the ventral, temporal lobe, visual stream concerned with “what” object is being seen (see Rolls, 2000a; Rolls, 2016a; Rolls and Deco, 2002). Many neurons in these temporal cortex visual areas have responses to objects or faces that are invariant with respect to size, position on the retina, and even view (Rolls, 2000a, 2007c, 2008b, 2012b, 2016a; Rolls and Deco, 2002), making these neurons ideal as an input to a system that may learn about the reinforcement association properties of objects and faces, for after a single learning trial, the learning then generalizes correctly to other views etc. (see Rolls, 2000a; Rolls, 2014a, 2016a; Rolls and Deco, 2002). Using this object-related information, orbitofrontal cortex visual neurons frequently respond differentially to objects or images depending on their reward association (Rolls et al., 1996b; Thorpe et al., 1983). The primary reinforcer that has been used is taste, and correlates of visual to taste association learning have been demonstrated in the human orbitofrontal cortex with fMRI (O'Doherty et al., 2002). Many of these neurons show visual-taste reversal in one or a very few trials (see example in Fig. 7). (In a visual discrimination task, they will reverse the stimulus to which they respond, from e.g., a triangle to a square, in one trial when the taste delivered for a behavioural response to that stimulus is reversed (Thorpe et al., 1983).) In principle, this could be implemented by associative modification of synapses conveying visual input onto taste-responsive neurons, implementing a pattern association network (Rolls, 2014a, 2016a). However, in primates, visual-to-taste reversal is so rapid that after a punishment has been received to the negative discriminative stimulus (S-), the next time that the previous S- is shown, the neurons respond to it as an S+, and the monkey chooses that stimulus (Rolls et al., 1996b; Thorpe et al., 1983). This is a non-associative process that involves a rule change, and this is a special contribution that the primate orbitofrontal cortex makes to reversal learning, and for which a computational theory that utilizes the conditional reward and error neurons has been produced (Deco and Rolls, 2005c). This theory provides an account of the utility of conditional reward neurons. The current rule must be held in short term memory, and this is one reason why a cortical structure, which can implement short-term memory, is involved in this rapid emotional learning used to rapidly update reward representations used for social and related behaviour based on inputs being received from the environment (Rolls, 2016a). A computational theory of how not receiving an expected reward reverses the rule neurons has been developed (Rolls and Deco, 2016). This reversal learning probably does occur in the orbitofrontal cortex, for it does not occur one synapse earlier in the visual inferior temporal cortex (Rolls et al., 1977), and it is in the orbitofrontal cortex that there is convergence of visual and taste pathways onto the same

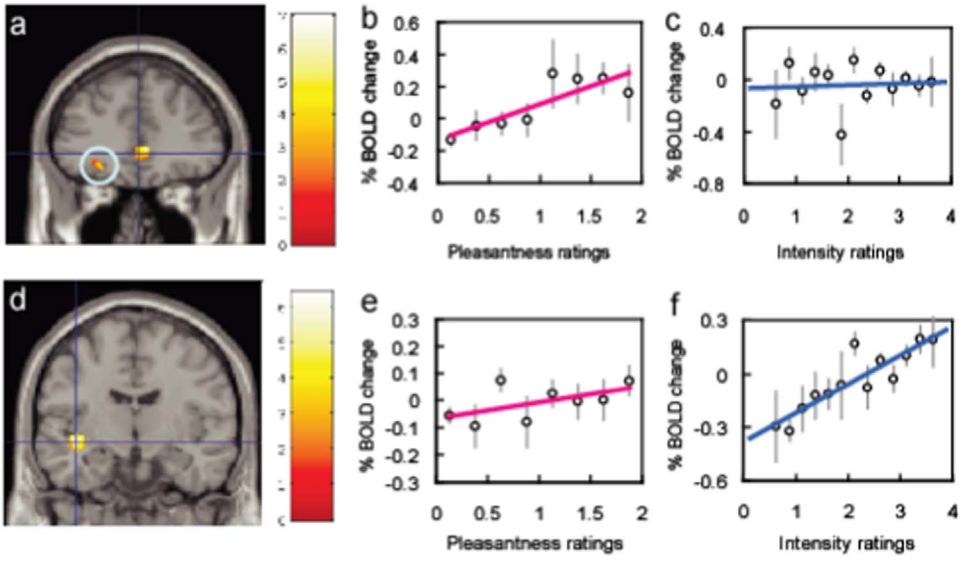

Fig. 6. Representation of the pleasantness but not intensity of thermal stimuli in the orbitofrontal cortex (top), and of the intensity but not the pleasantness in the mid ventral (somatosensory) insular cortex (bottom). a. SPM analysis showing a correlation in the mid orbitofrontal cortex (blue circle) at [− 26 38 − 10] between the BOLD signal and the pleasantness ratings of four thermal stimuli. Correlations are also shown in the pregenual cingulate cortex. For this mid orbitofrontal cortex region, (b) shows the positive correlation between the subjective pleasantness ratings and the BOLD signal ($r = 0.84$, $df = 7$, p d. SPM analysis showing a correlation with intensity in the posterior ventral insula with peak at [-40 -10 -8] between the BOLD signal and the intensity ratings for the four thermal stimuli. For this ventral insula cortex region, (e) shows no correlation between the subjective pleasantness ratings and the BOLD signal ($r = 0.56$, $df = 7$, $p = 0.15$), and (f) shows a positive correlation between the subjective intensity ratings and the BOLD signal ($r = 0.89$, $df = 12$, $p < 0.001$). (After Rolls et al., 2008c). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

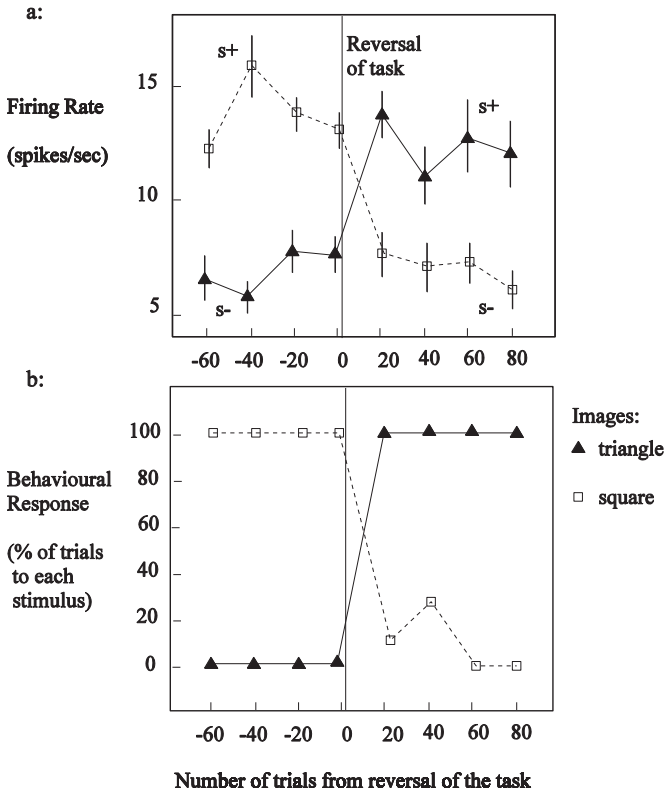

Fig. 7. Visual discrimination reversal of the responses of a single neuron in the macaque orbitofrontal cortex when the taste with which the two visual stimuli (a triangle and a square) were associated was reversed. Each point is the mean poststimulus firing rate measured in a 0.5 s period over approximately 10 trials to each of the stimuli. Before reversal, the neuron fired most to the square when it indicated (S+) that the monkey could lick to obtain a taste of glucose. After reversal, the neuron responded most to the triangle when it indicated that the monkey could lick to obtain glucose. The response was low to the stimuli when they indicated (S−) that if the monkey licked then aversive saline would be obtained. B shows the behavioural response to the triangle and the square, and indicates that the monkey reversed rapidly. (After Rolls et al., 1996b).

single neurons (Rolls and Baylis, 1994; Rolls et al., 1996b; Thorpe et al., 1983).

To analyse the nature of the visual representation of food-related stimuli in the orbitofrontal cortex, Critchley and Rolls (1996a) measured the responses of neurons that responded to the sight of food while they fed the monkey to satiety. They found that the majority of orbitofrontal visual food-related neurons decreased their responses to the sight of the food with which the monkey was fed to satiety (see example in Fig. 5). Thus for these neurons, the reward value of the sight of food is what is represented in the orbitofrontal cortex. In that the neuronal responses decreased to the food with which the monkey is fed to satiety, and may even increase to a food with which the monkey has not been fed, it is the relative reward value of stimuli that is represented by these orbitofrontal cortex neurons. At a stage of visual processing one synapse earlier, in the inferior temporal visual cortex, neurons do not show visual discrimination reversal learning, nor are their responses modulated by feeding to satiety (Rolls et al., 1977). Thus both these functions involved in representing expected reward value are implemented for visual processing in the orbitofrontal cortex.

7. Rewards are represented medially, and punishers and non-reward laterally, in the orbitofrontal cortex

Many types of reward and punisher are represented in the human orbitofrontal cortex. For example, monetary reward is represented in the medial orbitofrontal cortex, and losing money in the lateral orbitofrontal cortex (O'Doherty et al., 2001a). Beauty in a face is also represented in the medial orbitofrontal cortex (O'Doherty et al., 2003). In addition, it has been shown that amphetamine, a potent instrumental reinforcer, is self-administered to the orbitofrontal cortex by macaques (Phillips et al., 1981), and that in drug naïve human participants amphetamine activates the medial orbitofrontal cortex (Völlm et al., 2004). Many rewards are represented medially in the orbitofrontal cortex, in areas 13 and 11, and many punishers and non-rewards are represented laterally in area 47/12, as shown in Fig. 8 (Grabenhorst and Rolls, 2011; Rolls, 2014a).

8. Orbitofrontal cortex negative reward prediction error neurons

In addition to the neurons that encode the expected reward value of visual stimuli, other, 'error', neurons in the orbitofrontal cortex detect non-reward, in that they respond for example when an expected reward is not obtained when a visual discrimination task is reversed (Thorpe et al., 1983) (see Fig. 9), or when reward is no longer made available in a visual discrimination task. These neurons respond to a mismatch between the expected reward value (in this case signalled by the visual stimulus) and the reward outcome (in this case the taste). These

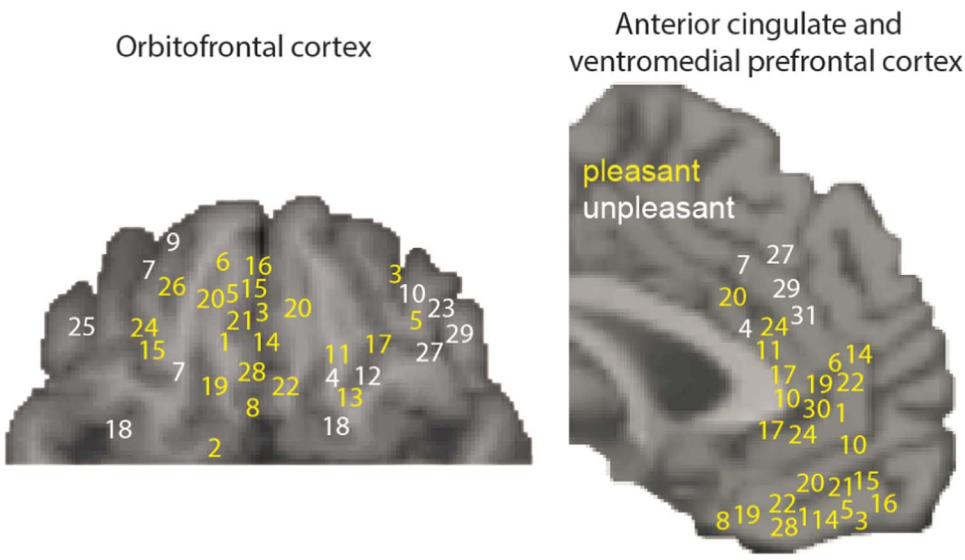

Fig. 8. Rewards tend to be represented medially in the human orbitofrontal cortex and in the pregenual cingulate cortex, and non-reward and punishment laterally in the orbitofrontal cortex and in the supracallosal anterior cingulate cortex. Maps of subjective pleasure in the human orbitofrontal cortex (ventral view) and anterior cingulate and ventromedial prefrontal cortex (sagittal view). Yellow: sites where activations correlate with subjective pleasantness. White: sites where activations correlate with subjective unpleasantness. The numbers refer to effects found in specific studies. Taste: 1, 2; odor: 3–10; flavor: 11–16; oral texture: 17, 18; chocolate: 19; water: 20; wine: 21; oral temperature: 22, 23; somatosensory temperature: 24, 25; the sight of touch: 26, 27; facial attractiveness: 28, 29; erotic pictures: 30; laser-induced pain: 31. Consistent laterality effects are not generally observed in these investigations. (Reprinted from Trends in Cognitive Sciences, 15 (2), Fabian Grabenhorst and Edmund T. Rolls, Value, pleasure and choice in the ventral prefrontal cortex, pp. 56–67, Copyright, 2011, with permission from Elsevier.) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

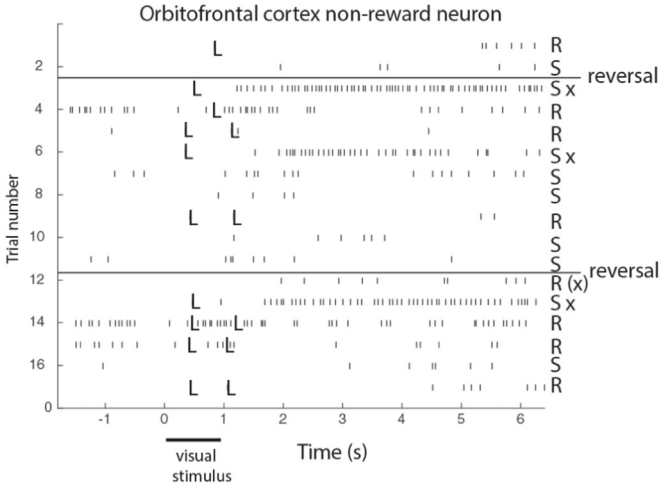

Fig. 9. Evidence that there are non-reward error-related neurons that maintain their firing after non-reward is obtained. Error neuron: Responses of an orbitofrontal cortex neuron that responded only when the macaque licked to a visual stimulus during reversal, expecting to obtain fruit juice reward, but actually obtained the taste of aversive saline because it was the first trial of reversal (trials 3, 6, and 13). Each vertical line represents an action potential; each L indicates a lick response in the Go-NoGo visual discrimination task. The visual stimulus was shown at time 0 for 1 s. The neuron did not respond on most reward (R) or saline (S) trials, but did respond on the trials marked S x, which were the first or second trials after a reversal of the visual discrimination on which the monkey licked to obtain reward, but actually obtained saline because the task had been reversed. The two times at which the reward contingencies were reversed are indicated. After responding to non-reward, when the expected reward was not obtained, the neuron fired for many seconds, and was sometimes still firing at the start of the next trial. It is notable that after an expected reward was not obtained due to a reversal contingency being applied, on the very next trial the macaque selected the previously non-rewarded stimulus. This shows that rapid reversal can be performed by a non-associative process, and must be rule-based. (After Thorpe et al., 1983.)

neurons are thus termed “negative reward prediction error neurons” (Rolls, 2014a, 2016a; Rolls and Grabenhorst, 2008). Both signals needed for the computation are represented in the orbitofrontal cortex, in the form of for example neurons that respond to the sight of a learned reinforcer such as the sight of a stimulus paired with taste, and neurons that respond to the primary reinforcer (or outcome), the taste (or texture or temperature). The orbitofrontal cortex is the probable brain region for this computation, because both of the signals required to compute negative reward prediction error are present in the orbitofrontal cortex, so are the negative reward prediction error neurons, and lesions of the orbitofrontal cortex impair tasks such as visual discrimination reversal in which this type of negative reward prediction error is needed (see above). Different populations of such neurons respond to other types of non-reward, including the removal of a formerly approaching taste reward, and the termination of a taste reward in the extinction of ad lib licking for juice, or the substitution of juice reward by aversive tasting saline during ad lib licking (Rolls and Grabenhorst, 2008; Thorpe et al., 1983). The presence of these neurons is fully consistent with the hypothesis that they are part of the mechanism by which the orbitofrontal cortex enables very rapid reversal of behaviour by stimulus-reinforcement association relearning when the association of stimuli with reinforcers is altered or reversed (Deco and Rolls, 2005c; Rolls and Deco, 2016). The finding that different orbitofrontal cortex neurons respond to different types of non-reward (or negative reward prediction error) (Thorpe et al., 1983) may provide part of the brain’s mechanism that enables task or context-specific reversal to occur.

Evidence that there may be similar error neurons in the human orbitofrontal cortex is that in a model of social learning, orbitofrontal cortex activation occurred in a visual discrimination reversal task at the time when the face of one person no longer was associated with a smile, but became associated with an angry expression, indicating on such error trials that reversal of choice to the other individual’s face should occur (Kringelbach and Rolls, 2003) (Fig. 10a). Consistent with this evidence for humans, functional neuroimaging in macaques reveals that the macaque lateral orbitofrontal cortex is activated by non-reward during a reversal task (Chau et al., 2015) (Fig. 10c).

It may be noted that the dopamine neurons in the midbrain may not be able to provide a good representation of negative reward prediction error, because their spontaneous firing rates are so low (Schultz, 2004) that much further reduction would provide only a small signal. In any case, the dopamine neurons would not appear to be in a position to *compute* a reward prediction error, as they are not known to receive inputs that signal expected reward, and the actual reward (outcome) that is obtained, and indeed do not represent the reward obtained (or ‘outcome’), in that they stop responding to a taste reward outcome if it is predictable. Although dopamine neurons do appear to represent a positive reward prediction error signal (responding if a greater than expected reward is obtained as the outcome) (Schultz, 2004, 2006, 2013, 2016), they do not appear to have the signals required to compute this, the expected reward, and the reward outcome obtained, so even this must be computed elsewhere. The orbitofrontal cortex does contain representations of these two signals, the expected reward and

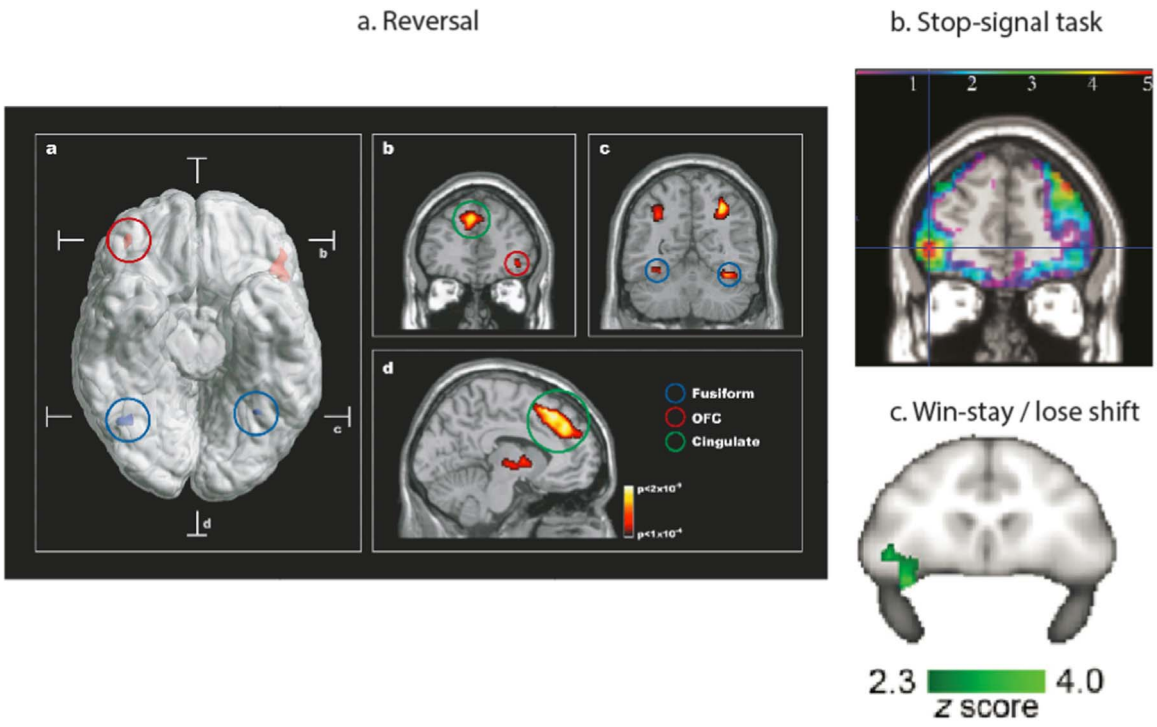

Fig. 10. a. Evidence that the human lateral orbitofrontal cortex is activated by non-reward. Activation of the lateral orbitofrontal cortex in a visual discrimination reversal task on reversal trials, when a face was selected but the expected reward was not obtained, indicating that the subject should select the other face in future to obtain the reward. a) A ventral view of the human brain with indication of the location of the two coronal slices (b, c) and the transverse slice (d). The activations with the red circle in the lateral orbitofrontal cortex (OFC, peaks at [42 42 − 8] and [− 46 30 − 8]) show the activation on reversal trials compared to the non-reversal trials. For comparison, the activations with the blue circle show the fusiform face area produced just by face expressions, not by reversal, which are also indicated in the coronal slice in (c). b) A coronal slice showing the activation in the right orbitofrontal cortex on reversal trials. Activation is also shown in the supracallosal anterior cingulate region (Cingulate, green circle) that is also known to be activated by many punishing, unpleasant, stimuli (see Grabenhorst and Rolls (2011)). (From NeuroImage 20 (2), Morten L. Kringelbach and Edmund T. Rolls, Neural correlates of rapid reversal learning in a simple model of human social interaction, pp. 1371–83, Copyright, 2003, with permission from Elsevier.) Fig. 10b. Activations in the human lateral orbitofrontal cortex are related to a signal to change behaviour in the stop-signal task. In the task, a left or right arrow on a screen indicates which button to touch. However on some trials, an up-arrow then appears, and the participant must change the behaviour, and stop the response. There is a larger response on trials on which the participant successfully changes the behaviour and stops the response, as shown by the contrast stop-success – stop-failure, in the ventrolateral prefrontal cortex in a region including the lateral orbitofrontal cortex, with peak at [− 42 50 − 2] indicated by the cross-hairs, measured in 1709 participants. There were corresponding effects in the right lateral orbitofrontal cortex [42 52 − 4]. Some activation in the dorsolateral prefrontal cortex in an area implicated in attention is also shown. (After Deng et al., 2017). Fig. 10c. Bold signal in the macaque lateral orbitofrontal related to win-stay/lose-shift performance, that is, to reward reversal performance. (After Chau et al., 2015). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the reward outcome, and has projections to the ventral striatum, which in turn projects in part via the habenula to the region of the midbrain dopamine neurons, and so this is one possible pathway along which the firing of positive reward prediction error might be computed (see Fig. 2) (Rolls, 2017c). Consistent with this, activations in parts of the human ventral striatum are related to positive reward prediction error (Hare et al., 2008; Rolls et al., 2008e). Thus the dopamine projections to the prefrontal cortex and other areas are not likely to convey information about reward to the prefrontal cortex, which instead is likely to be decoded by the neurons in the orbitofrontal cortex that represent primary reinforcers, and the orbitofrontal cortex neurons that learn associations of other stimuli to the primary reinforcers to represent expected value (Rolls, 2014a, 2016a; Rolls et al., 1996b, 2008e; Thorpe et al., 1983).

In responding when the reward obtained is less than that expected, the orbitofrontal cortex negative reward prediction error neurons are working in a domain that is related to the sensory inputs being received (expected reward and reward obtained). There are also error neurons in the anterior cingulate cortex that respond when errors are made (Niki and Watanabe, 1979), or when rewards are reduced (Shima and Tanji, 1998) (and in similar imaging studies, Bush et al., 2002). Some of these neurons may be influenced by the projections from the orbitofrontal cortex, and reflect a mismatch between the reward expected and the reward that is obtained. However, some error neurons in the anterior cingulate cortex may reflect errors that arise when particular actions are in error, and this type of error may be important in helping an action system to correct itself, rather than, as in the orbitofrontal cortex, a reward prediction system needs to be corrected. Consistent with this, many studies provide evidence that errors made in many tasks activate the anterior/midcingulate cortex, whereas tasks with response conflict activate the superior frontal gyrus (Matsumoto et al., 2007; Rushworth and Behrens, 2008; Rushworth et al., 2004; Vogt, 2009).

9. Face-selective processing in the orbitofrontal cortex

Another type of visual information represented in the orbitofrontal cortex is information about faces. There is a population of orbitofrontal cortex neurons that respond in many ways similar to those in the temporal cortical visual areas (Rolls, 1984, 1992, 1996, 2000a, 2007c, 2008b, 2012b, 2014a, 2016a; Rolls and Deco, 2002). The orbitofrontal face-responsive neurons, first observed by Thorpe et al. (1983), then by Rolls et al. (2006), tend to respond with longer latencies than temporal lobe neurons (140–200 ms typically, compared to 80–100 ms); also convey information about which face is being seen, by having different responses to different faces; and are typically rather harder to activate strongly than temporal cortical face-selective neurons, in that many of them respond much better to real faces than to two-dimensional images of faces on a video monitor (cf. Rolls and Baylis, 1986). Some of the orbitofrontal cortex face-selective neurons are responsive to face expression, gesture or movement (Rolls, 2007c, 2008b, 2011b; Rolls et al., 2006b). The findings are consistent with the likelihood that these

neurons are activated via the inputs from the temporal cortical visual areas in which face-selective neurons are found (see Figs. 2 and 3). The significance of the neurons is likely to be related to the fact that faces convey information that is important in social reinforcement in at least two ways that could be implemented by these neurons. The first is that some may encode face expression (Rolls et al., 2006b) (cf. Hasselmo et al., 1989), which can indicate reinforcement. The second way is that they encode information about which individual is present (Rolls et al., 2006b), which by stimulus-reinforcement association learning is important in evaluating and utilising learned reinforcing inputs in social situations, e.g., about the current reinforcement value as decoded by stimulus-reinforcement association, to a particular individual. When reversal learning was tested by altering the food reward with which each of two faces was associated, two neurons stopped responding differently to the two faces, and three neurons were not affected by the reversal learning (Critchley, 1994; Rolls et al., 2006b). The two neurons that changed their response during the reversal learning are termed 'conditional reward neurons', and are important to reversal learning (Deco and Rolls, 2005c; Rolls, 2014a).

This system has also been shown to be present in humans. For example, Kringelbach and Rolls (2003) showed that activation of a part of the human orbitofrontal cortex occurs during a face discrimination reversal task. In the task, the faces of two different individuals are shown, and when the correct face is selected, the expression turns into a smile. (The expression turns to angry if the wrong face is selected.) After a period of correct performance, the contingencies reverse, and the other face must be selected to obtain a smile expression as a reinforcer. It was found that activation of a part of the orbitofrontal cortex occurred specifically in relation to the reversal, that is when a formerly correct face was chosen, but an angry face expression was obtained (Fig. 10c). In a control task, it was shown that the activations were not related just to showing an angry face expression. Thus in humans, there is a part of the orbitofrontal cortex that responds selectively in relation to face expression specifically when it indicates that behaviour should change, and this activation is error-related (Kringelbach and Rolls, 2003) and occurs when the error neurons in the orbitofrontal cortex become active (Thorpe et al., 1983).

Also prompted by the neuronal recording evidence of face and auditory neurons in the orbitofrontal cortex (Rolls et al., 2006), it has further been shown that there are impairments in the identification of facial and vocal emotional expression in a group of patients with ventral frontal lobe damage who had socially inappropriate behaviour (Hornak et al., 1996). The expression identification impairments could occur independently of perceptual impairments in facial recognition, voice discrimination, or environmental sound recognition. Poor performance on both expression tests was correlated with the degree of alteration of emotional experience reported by the patients. There was also a strong positive correlation between the degree of altered emotional experience and the severity of the behavioural problems (e.g., disinhibition) found in these patients (Hornak et al., 1996). A comparison group of patients with brain damage outside the ventral frontal lobe region, without these behavioural problems, was unimpaired on the face expression identification test, was significantly less impaired at vocal expression identification, and reported little subjective emotional change (Hornak et al., 1996). It has further been shown that patients with discrete surgical lesions of restricted parts of the orbitofrontal cortex may have face and/or voice expression identification impairments, and these are likely to contribute to their difficulties in social situations (Hornak et al., 2003).

10. Top-down effects of cognition and attention on taste, olfactory, flavor, somatosensory, and visual processing: cognitive enhancement of the value of affective stimuli

How does cognition influence affective value? How does cognition influence the way that we feel emotionally? Do cognition and emotion interact in regions that are high in the brain's hierarchy of processing, or do cognitive influences descend down to influence the first regions that represent the affective value of stimuli?

An fMRI study to address these fundamental issues in brain design has shown that cognitive effects can reach down into the human orbitofrontal cortex and influence activations produced by odors (de Araujo et al., 2005). In this study, a standard test odor, isovaleric acid with a small amount of cheese flavor, was delivered through an olfactometer. (The odor alone, like the odor of brie, might have been interpreted as pleasant, or perhaps as unpleasant.) On some trials the test odor was accompanied with the visually presented word label "cheddar cheese", and on other trials with the word label "body odor". It was found that the activation in the medial orbitofrontal cortex to the standard test odor was much greater when the word label was cheddar cheese than when it was body odor. (Controls with clean air were run to show that the effect could not be accounted for by the word label alone.) Moreover, the word labels influenced the subjective pleasantness ratings to the test odor, and the changing pleasantness ratings were correlated with the activations in the human medial orbitofrontal cortex. Part of the interest and importance of this finding is that it shows that cognitive influences, originating here purely at the word level, can reach down and modulate activations in the first stage of cortical processing that represents the affective value of sensory stimuli (de Araujo et al., 2005; Rolls, 2014a).

Also important is how cognition influences the affective brain representations of the taste and flavor of a food. This is important not only for understanding top-down influences in the brain, but also in relation to the topical issues of appetite control and obesity (Rolls, 2007d, 2007e, 2016d). In an fMRI study it was shown that activations related to the affective value of umami taste and flavor (as shown by correlations with pleasantness ratings) in the orbitofrontal cortex were modulated by word-level descriptors (e.g. "rich and delicious flavor") (Grabenhorst et al., 2008a) (see Fig. 11). Affect-related activations to taste were modulated in a region that receives from the orbitofrontal cortex, the pregenual cingulate cortex, and to taste and flavor in another region that receives from the orbitofrontal cortex, the ventral striatum. Affect-related cognitive modulations were not found in the insular taste cortex, where the intensity but not the pleasantness of the taste was represented. Thus the top-down language-level cognitive effects reach far down into the earliest cortical areas that represent the appetitive value of taste and flavor. This is an important way in which cognition influences the neural mechanisms that control appetite.

When we see a person being touched, we may empathize the feelings being produced by the touch. Interestingly, cognitive modulation of this effect can be produced. When subjects were informed by word labels that a cream seen being rubbed onto the forearm was a "Rich moisturising cream" vs "Basic cream", these cognitive labels influenced activations in the orbitofrontal/pregenual cingulate cortex and ventral striatum to the sight of touch and their correlations with the pleasantness ratings (McCabe et al., 2008). Some evidence for top-down cognitive modulation of the effects produced by the subject being rubbed with the cream was found in brain regions such as the orbitofrontal and pregenual cingulate cortex and ventral striatum, but some effects were found in other brain regions, perhaps reflecting back-projections from the orbitofrontal cortex (McCabe et al., 2008).

What may be a fundamental principle of how top-down attention can influence affective vs non-affective processing has been discovered. For an identical taste stimulus, paying attention to pleasantness activated some brain systems, and paying attention to intensity, which reflected the physical and not the affective properties of the stimulus, activated other brain systems (Grabenhorst and Rolls, 2008). In an fMRI investigation, when subjects were instructed to remember and rate the pleasantness of a taste stimulus, 0.1 M monosodium glutamate, activations were greater in the medial orbitofrontal and pregenual cingulate cortex than when subjects were instructed to remember and rate the intensity of the taste (Fig. 12a–c). When the subjects were instructed

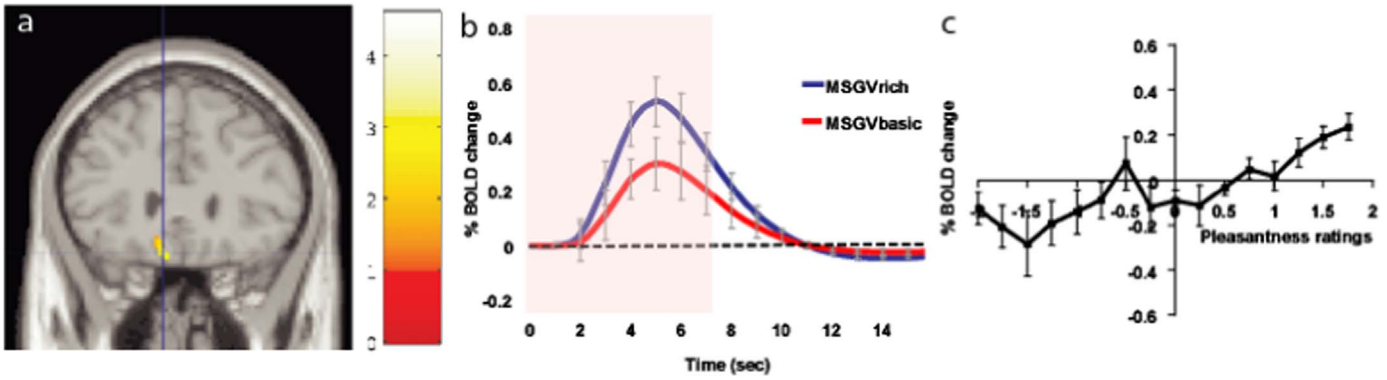

Fig. 11. Cognitive modulation of affective representations in the medial orbitofrontal cortex. a. The medial orbitofrontal cortex was more strongly activated when the flavor stimulus was labelled 'rich and delicious flavor' (MSGVrich) than when it was labelled 'boiled vegetable water' (MSGVbasic) ([− 8 28 − 20]). b. The timecourse of the BOLD signals for the two conditions. The means across subjects ± sem are shown. c. The BOLD signal in the medial orbitofrontal cortex was correlated with the subjective pleasantness ratings of taste and flavor (mean across subjects ± sem, r = 0.86, p < 0.001). (After Grabenhorst et al., 2008a)

to remember and rate the intensity, activations were greater in the insular taste cortex (Fig. 12d–f). (Consistent with this role in representing what taste may be present independently of its affective value, trying to detect the presence of taste in a tasteless solution resulted in enhanced activity in the taste insula and overlying operculum but not the orbitofrontal cortex (Veldhuizen et al., 2007). For comparison, the orbitofrontal cortex responded preferentially during receipt of an unpredicted taste stimulus (Veldhuizen et al., 2007), and this could be related to emotional effects, or to novelty which is represented in the orbitofrontal cortex.) Thus, depending on the context in which tastes are presented and whether affect is relevant, the brain responds to a taste differently. These findings show that when attention is paid to affective value, the brain systems engaged to represent the sensory stimulus of taste are different from those engaged when attention is directed to the physical properties of a stimulus such as its intensity. This differential biasing of brain regions engaged in processing a sensory stimulus depending on whether the attentional demand is for affect-related vs more sensory-related processing may be an important aspect of cognition and attention. This has many implications for understanding attentional effects to affective value not only on taste, but also on other sensory stimuli.

Indeed, the concept has been validated in the olfactory system too.

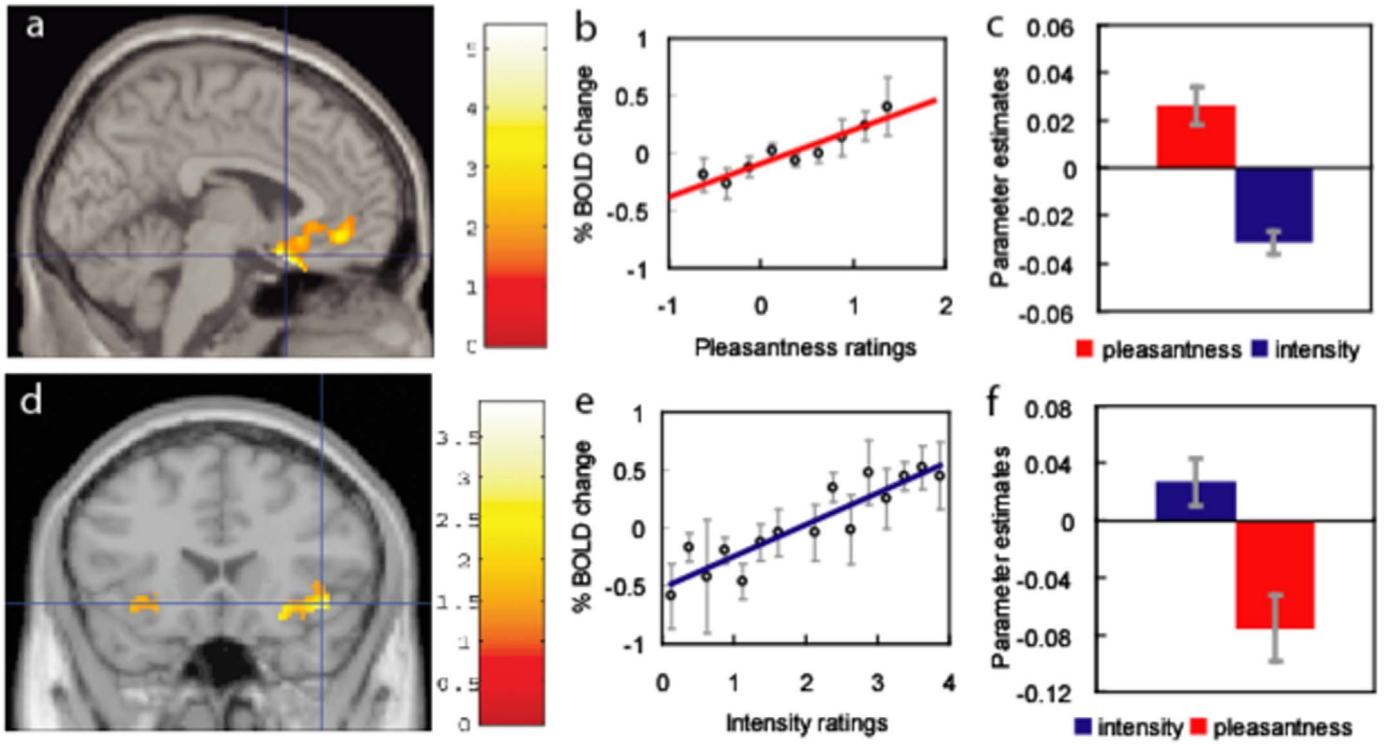

Fig. 12. Effects of attention to the pleasantness vs the intensity of a taste stimulus (0.1 M monosodium glutamate, which was identical on all trials). Top: The contrast paying attention to pleasantness – paying attention to intensity. a: A significant difference was found in the medial orbitofrontal cortex at [− 6 14 − 20] (at the cursor) which extended forward into the pregenual cingulate cortex (at [− 4 46 − 8]). b: The activations (% BOLD change) were correlated with the subjective pleasantness ratings in the medial orbitofrontal cortex. (r = 0.94, df = 8, p < < 0.001). c.: The parameter estimates (mean ± sem across subjects) for the medial orbitofrontal cortex activations for the conditions of paying attention to pleasantness or to intensity. The parameter estimates were significantly different ($p < 10^{-4}$). Bottom : The contrast paying attention to intensity – paying attention to pleasantness. d: A significant difference was found in the taste insula at [42 18 − 14] (indicated by the cursor). e: The activations (% BOLD change) were correlated with the subjective intensity ratings in the taste insula medial orbitofrontal cortex. (r = 0.89, df = 15, p < < 0.001). f.: The parameter estimates (mean ± sem across subjects) for the taste insula for the conditions of paying attention to intensity or to pleasantness. The parameter estimates were significantly different (p < 0.001). (After Grabenhorst and Rolls, 2008)

In an fMRI investigation, when subjects were instructed to remember and rate the pleasantness of a jasmin odor, activations were greater in the medial orbitofrontal and pregenual cingulate cortex than when subjects were instructed to remember and rate the intensity of the odor (Rolls et al., 2008a). When the subjects were instructed to remember and rate the intensity, activations were greater in the inferior frontal gyrus. These top-down effects occurred not only during odor delivery, but started in a preparation period after the instruction before odor delivery, and continued after termination of the odor in a short term memory period. Thus, depending on the context in which odors are presented and whether affect is relevant, the brain prepares itself, responds to, and remembers an odor differently. These findings show that when attention is paid to affective value, the brain systems engaged to prepare for, represent, and remember a sensory stimulus are different from those engaged when attention is directed to the physical properties of a stimulus such as its intensity. This differential biasing of brain regions engaged in processing a sensory stimulus depending on whether the cognitive demand is for affect-related vs more sensory-related processing may be important for understanding how the context can influence how we process stimuli that may have affective properties, how different people may respond differently to stimuli if they process the stimuli in different ways, and more generally, how attentional set can influence the processing of affective stimuli by influencing processing in for example the orbitofrontal cortex and related areas.

The principle thus appears to be that top-down attentional and cognitive effects on affective value influence representations selectively in cortical areas that process the affective value and associated subjective emotional experience of taste (Grabenhorst and Rolls, 2008; Grabenhorst et al., 2008a) and olfactory (Anderson et al., 2003; Grabenhorst et al., 2007; Rolls et al., 2003b) stimuli in brain regions such as the orbitofrontal cortex; whereas top-down attentional and cognitive effects on intensity influence representations in brain areas that process the intensity and identity of the stimulus such as the primary taste and olfactory cortical areas (Anderson et al., 2003; Grabenhorst and Rolls, 2008; Grabenhorst et al., 2008a, 2007; Rolls et al., 2003b). This is computationally appropriate in top-down biased competition models of attention (Deco and Rolls, 2005a; Rolls, 2016a; Rolls and Deco, 2002). However, we note that in one study a cognitive label that increased the pleasantness of an odor did have some effect in primary olfactory areas such as the olfactory tubercle, though in that study the general principle was still evident, that odors independently of their pleasantness have strong effects on the primary olfactory areas, whereas pleasantness vs unpleasantness are selectively (and separately) represented in areas such as the orbitofrontal cortex (de Araujo et al., 2005).

The mechanisms that underlie these top-down attentional and cognitive effects include top-down biased competition and biased activation of the bottom-up (sensory) effects, and are now starting to be elucidated computationally (Deco and Rolls, 2005b; Desimone and Duncan, 1995; Rolls, 2008d, 2013a, 2014a, 2016a; Rolls and Deco, 2002).

11. A representation of novel visual stimuli in the orbitofrontal cortex

A population of neurons has been discovered in the primate orbitofrontal cortex that responds to novel but not familiar visual stimuli, and takes typically a few trials to habituate (Rolls et al., 2005). The memories of these neurons last for at least 24 h. Exactly what role these neurons have in memory is not yet known, but there are connections from the area in which these neurons are recorded to the temporal lobe, and activations in a corresponding orbitofrontal cortex area in humans are found when new visual stimuli must be encoded in memory (Frey and Petrides, 2002, 2003; Petrides, 2007).

12. Emotion and the orbitofrontal cortex

From earlier approaches (Gray, 1975; Millenson, 1967; Weiskrantz, 1968), Rolls has developed the theory over a series of stages that emotions are states elicited by instrumental reinforcers[2] (Rolls, 1986a, 1986b, 1990, 1999a, 1999b, 2000b, 2014a). Given that the evidence described above indicates that primary (unlearned) reinforcers, such as taste, touch, oral texture, are made explicit in the representations in the orbitofrontal cortex, there is a basis for understanding part of the role of the orbitofrontal cortex in emotion. (By made explicit, I mean that the firing rate of the neurons is related to what is being represented (Rolls, 2016a), for example the reward value of taste by a neuron that responds to sweet taste only when hunger is present and there is an appetite for the taste.)

Further, the evidence described above indicates that associations between previously neutral stimuli such as a visual stimulus with primary reinforcers are formed and rapidly reversed in the orbitofrontal cortex, and thus the orbitofrontal cortex is likely because of this to have important functions in emotions that are produced by these secondary (learned) reinforcers. For example, the ability to perform this learning very rapidly is probably very important in social situations in primates, in which reinforcing stimuli are continually being exchanged, and the reinforcement value of stimuli must be continually updated (relearned), based on the actual reinforcers received and given. This type of learning also allows the stimuli or events that give rise to emotions and are represented in the orbitofrontal cortex to be quite abstract and general, including for example working for 'points' or for monetary reward, as shown by visual discrimination reversal deficits in patients with orbitofrontal cortex lesions working for these rewards (Berlin et al., 2004; Fellows, 2007; Fellows and Farah, 2003, 2005; Hornak et al., 2004; Rolls et al., 1994a), and activation of different parts of the human orbitofrontal cortex by monetary gain vs. loss (O'Doherty et al., 2001a), and other reinforcers (Kringelbach and Rolls, 2004).

To help clarify some of the fundamental ways in which emotion is linked to instrumental reinforcers, but not to all properties of stimuli that happen to be rewards or punishers, and as a guide to further research, it is useful to specify some important points about Rolls' theory of emotion (Rolls, 2014a).

First, the theory specifies that it is instrumental reinforcers, which specify the goals for action, that produce emotions. The theory is set in an evolutionary, Darwinian context, for it holds that the specification by genes of a set of primary reinforcers (such as sweet taste when hungry, affiliative touch, pain, attachment, altruism) is an efficient way for genes to direct adaptive behaviour, and is much more efficient than specifying actions (such as climbing a tree when an apple is seen, reaching for the apple, and putting it in the mouth). By specifying the goals for action, the process allows the actual behaviour required to obtain the goal to be learned, providing great flexibility in the actions. The actual emotion that is produced by the reinforcer depends on the contingency (delivery of a reward or punisher; omission or termination of a reward or punisher); on the primary reinforcer; and on the particular secondary reinforcer (Rolls, 2014a). The point made here is that it is by virtue of being a goal for action that instrumental reinforcers produce emotions. A stimulus that happens to be an instrumental reinforcer may be able to produce many other effects, and disrupting these other effects might not alter emotions. This is important when interpreting the effects of brain damage on emotion and reinforcers: it is only the goal-related aspect of the reinforcing stimulus that the theory holds is closely related to emotion (Rolls, 2014a). An example comes from considering autonomic responses. An instrumental reinforcer such

[2] For the purposes of this paper, a positive reinforcer or reward can be defined as a stimulus that the animal will work to obtain, and a punisher as a stimulus that will reduce the probability of an action on which it is contingent or that an animal will work to avoid or escape (see further Rolls, 2014a).

as sweet taste when hungry will produce autonomic responses such as salivation (and these can be classically conditioned). But the mechanisms and brain's circuitry for producing salivation, and more generally for classical (Pavlovian) conditioning (see Section 3.2 of Rolls, 2016a), may be quite different from the circuitry involved in specifying a stimulus as a goal for action, and performing action-outcome instrumental learning (where outcome refers to whether the reinforcer, the goal for action, is received). (This highlights how different Rolls' theory of emotion (Rolls, 2014a) is to that of Damasio, 1994, who argues that emotions are related to autonomic feedback, and his theory is not based on the concept of emotions as being states elicited by instrumental reinforcers.) Evidence that autonomic effects are not required for emotions (Rolls, 2014a) includes findings that patients with peripheral autonomic failure do not suffer from disrupted emotions (Heims et al., 2004).

Reinforcing stimuli may produce many other effects (Rolls, 2014a, 2016a), including informational in which they may not be acting as a goal for an action (Murray and Izquierdo, 2007), Pavlovian Instrumental Transfer in which a classically conditioned stimulus may enhance instrumental behaviour (Cardinal et al., 2002), incentive effects in which reward devaluation outside the instrumental task may not immediately influence the goal value with respect to instrumental actions (Balleine and Dickinson, 1998), etc (Cardinal et al., 2002), and these will only be related to emotion in so far as they influence the goal-related aspects of the stimulus for instrumental behaviour. In summary, we would expect a close link between the goal-related aspects of the reinforcing stimulus and emotion, but not necessarily between other effects produced by stimuli that happen to be instrumental reinforcers, or produce classically conditioned effects (see Section 3.2 of Rolls, 2014a; Rolls, 2016a). It is important to appreciate this when assessing whether there are in fact any dissociations between brain mechanisms involved in emotion and brain mechanisms that are involved in instrumental learning where the stimulus acts as a goal for action as in action-outcome learning (cf. Murray and Izquierdo, 2007). In so far as classical (Pavlovian) conditioning can influence instrumental actions, for example in some of the ways described above, then this type of learning can play a role in emotion, and indeed the amygdala has been implicated in some of these classically conditioned effects on emotion (Cardinal et al., 2002; Rolls, 2014a; Seymour and Dolan, 2008). Further, in so far as stimulus-reinforcer association learning (also known as stimulus-outcome learning, where the outcome is the reinforcer) is essential for defining the goals for action when the stimulus is associated by learning with a reinforcer, then this is very important in emotion, and neurons in the orbitofrontal cortex learn this type of association, and can reverse it rapidly, and this is a fundamental role that the orbitofrontal cortex plays in emotion. The use of these goals identified by associative learning for association with action to implement action-outcome learning is a process that we identify in this review as taking place beyond the orbitofrontal cortex, in structures to which it projects such as the anterior cingulate cortex.

To make the point in everyday language, Rolls' (2014a) theory holds that emotions are states elicited by goals (which are reinforcers). Does not this resonate with common understanding of emotions? Do we not have emotions when we attain our goals; and if we do not?

We may note that it is not an improvement to the theory to hold that the goal for which the animal or human works is the emotional state, for this does not provide an answer, but immediately leads to the questions: What is it that accounts for these emotional states? Why and how are emotions related to goals for action? How are emotional states selected for in evolution so that they are produced by something in the environment? That approach would not provide an explanation, but would just raise questions. It is much clearer to hold that instrumental reinforcers are selected in evolution to be the goals for action because they are a way for genes to specify useful goals in terms of survival value; and then to note that the states elicited by these instrumental reinforcers are emotional states (Rolls, 2014a). Unless exceptions are found to this rule (that instrumental reinforcers in their goal-related effects produce emotional states, and that emotional states are produced by instrumental reinforcers in their goal-related effects), then this seems a powerful account of emotions (Rolls, 2014a).

Second, action-outcome learning, not habit learning, even though the latter is instrumental, is what the theory holds is related to emotion (Rolls, 2014a). If a rewarded behaviour is performed for a large number of trials, it becomes a habit and may be implemented by stimulus-response associations that are formed in brain regions such as the basal ganglia (Rolls, 2014a). After such overlearning, the behaviour may be performed rather automatically and calmly, without much emotion, as in a well-learned active avoidance task. It is therefore argued that instrumental behaviour when performed in this automated way by a 'habit' system does not require the type of processing that is related to emotion. On the other hand, while the instrumental behaviour is being learned, associations are being formed between actions and outcomes, and the outcomes are being tested to see whether they meet the goals. Thus in action-outcome learning the goals are being explicitly processed and are instrumental reinforcers, and are being met or not, and it is in these conditions of goal-related events that the theory holds that emotions arise (Rolls, 2014a).

Third, the instrumental reinforcer and the emotion correspond. If a food reward is not given, the emotional state will be different from when a social reinforcer is not given, or when a monetary reward is not given (Rolls, 2014a). As there is some dissociation between brain systems involved in processing different instrumental reinforcers, the prediction is that a particular emotion will only be impaired if the relevant brain system involved in representing the goals or instrumental reinforcers involved in that particular emotion are impaired. It would of course be necessary to test cases where this correspondence of instrumental reinforcer and the emotion being measured applies in order to test whether instrumental reinforcers are linked to emotional states. It would be important to consider this when assessing the effects of lesions on emotion (cf. Murray and Izquierdo, 2007).

13. Effects of damage to and dysfunction of the human orbitofrontal cortex

In humans, euphoria, irresponsibility, lack of affect, and impulsiveness can follow frontal lobe damage (Damasio, 1994; Kolb and Whishaw, 2003; Rolls, 1999a), particularly orbitofrontal damage (Berlin et al., 2005, 2004; Hornak et al., 2003, 1996; Rolls, 1999a, 2014a; Rolls et al., 1994a), and the human literature is considered further below. These emotional changes may be related at least in part to a failure to rapidly update the reinforcement associations of stimuli when the contingencies are changed as in a visual discrimination reversal task (Fellows and Farah, 2003; Hornak et al., 2004; Rolls, 1999b, 2014a; Rolls et al., 1994a). Similar mechanisms may contribute at least in part to the poor performance of humans with ventromedial prefrontal cortex damage on the Iowa Gambling Task (Bechara et al., 2000; Maia and McClelland, 2004).

The evidence from the effects of lesions to the orbitofrontal cortex indicates that there are close links between representing reinforcers, rapidly changing learned associations to reinforcers, and emotion including subjective emotional states. For example patients with damage to the orbitofrontal cortex may be impaired at decoding face and voice expression (which are social reinforcers) (Hornak et al., 2003, 1996; Rolls, 1999b), in reversing stimulus-reward associations (Berlin et al., 2004; Fellows, 2007; Fellows and Farah, 2003, 2005; Hornak et al., 2004; Rolls et al., 1994a), and in emotional behaviour and subjective emotional states (Hornak et al., 2003; Rolls et al., 1994a). To provide more detail, patients with discrete surgical lesions producing 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). Further evidence on these close links (Hornak et al., 1996; Rolls, 2016a; Rolls et al., 1994a) provides further support for the theory that because the orbitofrontal cortex decodes and represents reinforcers, and updates the representations by rapid learning, it is an important brain region for emotion.

The changes in emotion produced by damage to the orbitofrontal cortex are large, as the evidence described above shows. The importance of the orbitofrontal cortex in emotion in humans is emphasized by a comparison with the effects of bilateral amygdala damage in humans, which although producing demonstrable deficits in face processing (Adolphs et al., 2005; Spezio et al., 2007), decision-making with linked autonomic deficits (Bechara et al., 1999; Brand et al., 2007), and autonomic conditioning (Phelps and LeDoux, 2005), may not produce major changes in emotion that are readily apparent in everyday behaviour (Phelps and LeDoux, 2005; Rolls, 2016a; Seymour and Dolan, 2008). A comparison of the roles of the amygdala and orbitofrontal cortex in emotion is provided elsewhere (Rolls, 2014a).

It is also becoming possible to relate the functions of the orbitofrontal cortex to some psychiatric symptoms that may reflect changes in behavioural responses to reinforcers, which may be different in different individuals. We compared the symptoms of patients with a personality disorder syndrome, Borderline Personality Disorder (BPD), with those of patients with lesions of the orbitofrontal cortex (Berlin and Rolls, 2004; Berlin et al., 2005, 2004). The symptoms of the self-harming Borderline Personality Disorder patients include high impulsivity, affective instability, and emotionality; and low extroversion. It was found that orbitofrontal cortex and Borderline Personality Disorder patients performed similarly in that they were more impulsive, reported more inappropriate behaviours in the Frontal Behaviour Questionnaire, and had more Borderline Personality Disorder characteristics, and anger, and less happiness, than control groups (either normals, or patients with lesions outside the orbitofrontal cortex).

Both the orbitofrontal and BPD groups also had a faster perception of time (i.e. they underproduced time) than normal controls (Berlin and Rolls, 2004; Berlin et al., 2005, 2004). This may be one factor underlying their increased impulsiveness, in that they feel that sufficient time has elapsed to initiate action. This interesting hypothesis and finding deserve further exploration. It was of interest that the BPD group, as well as the orbitofrontal group, scored highly on a Frontal Behaviour Questionnaire which assessed inappropriate behaviours typical of orbitofrontal cortex patients including disinhibition, social inappropriateness, perseveration, and uncooperativeness. Both groups were also less open to experience (i.e. less open-minded), a personality characteristic. On the other hand, other aspects of Borderline Personality Disorder do not appear to be related to orbitofrontal cortex functions, including the more neurotic and more emotional personality characteristics of the BPD patients together with their lower extroversion and conscientious (Berlin and Rolls, 2004; Berlin et al., 2005, 2004).

Another case in which it is possible to relate psychiatric types of symptom to the functions of the orbitofrontal cortex in processing reinforcers 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 some of which resemble those produced by orbitofrontal lesions (Rahman et al., 1999; Viskontas et al., 2007). Patients appear either socially disinhibited with facetiousness and inappropriate jocularity, or apathetic and withdrawn. The dementia is accompanied by gradual withdrawal from all social interactions. These behaviours could reflect impaired processing of reinforcers. (In addition, 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. 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.

The negative symptoms of schizophrenia include flattening of affect. As part of a dynamical attractor systems theory of schizophrenia in which hypofunction of NMDA receptors (Coyle et al., 2003) contributes to the cognitive symptoms such as attentional, working memory, and dysexecutive impairments by reducing the depth of the basins of attraction of the prefrontal cortex networks involved in these functions, it has been proposed that the flattening of affect is produced by the same reduced NMDA receptor function, which decreases the neuronal firing rates, and in the orbitofrontal cortex and related areas would lead to decreased affect (Loh et al., 2007; Rolls, 2014a, 2016a; Rolls et al., 2008d).

Conversely, it has been proposed that hyperfunctionality of the glutamate system in obsessive compulsive disorder (Chakrabarty et al., 2005; Pittenger et al., 2006) would contribute to overstability in prefrontal and related networks that would contribute to the perseverative/obsessional symptoms, and that the concomitant increased firing rates of neurons in the orbitofrontal cortex and related areas contributes to the increased emotionality that may be present in obsessive-compulsive disorder (Rolls et al., 2008c).

14. Individual differences in emotion, and the orbitofrontal cortex

Given that there are individual differences in emotion, can these individual differences be related to the functioning of brain systems involved in affective behaviour such as the orbitofrontal and pregenual cingulate cortex?

Some individuals, chocolate cravers, report that they crave chocolate more than non-cravers, and this is associated with increased liking of chocolate, increased wanting of chocolate, and eating chocolate more frequently than non-cravers (Rodriguez et al., 2007). In a test of whether these individual differences are reflected in the affective systems in the orbitofrontal cortex and pregenual cingulate cortex that are the subject of this paper, Rolls and McCabe (2007) used fMRI to measure the response to the flavor of chocolate, to the sight of chocolate, and to their combination, in chocolate cravers vs non-cravers. SPM analyses showed that the sight of chocolate produced more activation in chocolate cravers than non-cravers in the medial orbitofrontal cortex and ventral striatum. For cravers vs non-cravers, a combination of a picture of chocolate with chocolate in the mouth produced a greater effect than the sum of the components (i.e. supralinearity) in the medial orbitofrontal cortex and pregenual cingulate cortex. Furthermore, the pleasantness ratings of the chocolate and chocolate-related stimuli had higher positive correlations with the fMRI BOLD signals in the pregenual cingulate cortex and medial orbitofrontal cortex in the cravers than in the non-cravers. Thus there were differences between cravers and non-cravers in their responses to the sensory components of a craved food in the orbitofrontal cortex, pregenual cingulate cortex, and ventral striatum, and in some of these regions the differences are related to the subjective pleasantness of the craved foods. An implication is that individual differences in brain responses to very pleasant foods

help to understand the mechanisms that drive the liking for specific foods by indicating that some brain systems (but not others such as the insular taste cortex) respond more to the rewarding aspects of some foods, and thus influence and indeed even predict the intake of those foods (which was much higher in chocolate cravers than non-cravers) (Rolls, 2016d; Rolls and McCabe, 2007).

Investigating another difference between individuals, Beaver et al. (2006) showed that reward sensitivity in different individuals (as measured by a behavioural activation scale) is correlated with activations in the orbitofrontal cortex and ventral striatum to pictures of appetizing vs disgusting food.

When cognitive labels (such as "Rich delicious flavor") modulate humans' ratings of the pleasantness of flavor, it is possible that some individuals are more affected by this suggestion than others. We investigated this in relation to the study by Grabenhorst et al. (2008a) on cognitive effects on flavor by measuring the suggestibility of the subjects using parts of the SHSS (Stanford Hypnotic) Suggestibility Scale (Weitzenhoffer and Hilgard, 1962). It was found that one of the most reliable measures in this scale, the moving hands apart test in which subjects are told that there is a force pushing the hands apart, was correlated with the magnitude of the effect of the cognitive label "Rich delicious flavor" on the pleasantness rating of a standard flavor ($r = 0.71$, $df = 9$, $p = 0.023$) in the subjects used in this study. An implication is that an underlying personality variable related to suggestibility is also related to cognitive effects on affective ratings (and thus emotion), with the brain region showing a large modulation of its BOLD response by the cognitive labels to these stimuli being the medial orbitofrontal cortex and pregenual cingulate cortex (Grabenhorst et al., 2008a).

15. Beyond the orbitofrontal cortex to choice decision-making

In the neurophysiological studies described above, we have found that neuronal activity is related to the reward value of sensory stimuli, and how these change when reward contingencies change, but is not related to the details of actions that are being performed, such as mouth or arm movements (Rolls, 2014a, 2016a). Wallis (2007) and Padoa-Schioppa and Assad (2006) have obtained evidence that supports this. An implication is that the orbitofrontal cortex represents the reward, affective (or, operationally, goal) value of a stimulus. Further, this value representation is on a continuous scale, as shown by the gradual decrease in orbitofrontal cortex neuronal responses to taste, olfactory and visual rewarding stimuli during feeding to satiety (Critchley and Rolls, 1996a; Rolls et al., 1996a, 1999a, 1989). Consistently, in humans the BOLD activations in different parts of the orbitofrontal cortex are continuously, indeed typically linearly, related to subjective pleasantness ratings of taste (de Araujo et al., 2003b; Grabenhorst and Rolls, 2008; Grabenhorst et al., 2008a), olfactory (Grabenhorst et al., 2007), flavor (Grabenhorst et al., 2008a; Kringelbach et al., 2003; McCabe and Rolls, 2007; Plassmann et al., 2008), oral temperature (Guest et al., 2007), hand temperature (Rolls et al., 2008b), and face beauty (O'Doherty et al., 2003) stimuli, and to monetary reward value (O'Doherty et al., 2001a), as shown by correlation analyses. An implication of these findings is that the orbitofrontal cortex may contribute to decision-making by representing on a continuous scale the value of each reward, with, as shown by the single neuron neurophysiology, different subsets of neurons for each different particular reward. It is of course essential to represent each reward separately, in order to make decisions about and between rewards, and separate representations (using distributed encoding (Rolls, 2016a; Rolls and Treves, 2011)) of different rewards are present in the orbitofrontal cortex.

Approaches used in neuroeconomics help to define further the nature of the representation of reinforcers in the orbitofrontal cortex. When monkeys choose between different numbers of drops of two juices, one more preferred than the other, some neurons in the orbitofrontal cortex encode the offer value, some the choice value, and some the taste, but not the details of the motor response that is chosen (Padoa-Schioppa, 2011; Padoa-Schioppa and Assad, 2006; Padoa-Schioppa and Cai, 2011). Further, these neurons encode economic value, not relative preference, as shown by a study in which a particular reward was paired with other rewards. The fact that the neuronal responses are menu invariant suggests that transitivity, a fundamental trait of economic choice, may be rooted in the activity of individual neurons (Padoa-Schioppa and Assad, 2008). There is also evidence that relative reward value may be represented in the orbitofrontal cortex (Tremblay and Schultz, 1999), and in a resolution of this, we have found that some parts of the orbitofrontal cortex represent the absolute pleasantness of stimuli and others the relative pleasantness of stimuli (Grabenhorst and Rolls, 2009).

When a choice is made between stimuli with different reward values, the choice made depends on the probability with which each reward will be obtained. In this probabilistic decision-making situation, we can define *expected value* as probability × reward magnitude) (Glimcher, 2004). In an investigation of such a probabilistic choice decision task in which humans chose between two rewards each available with different probabilities, it was found that the activation of the orbitofrontal cortex was related to expected value while the decision was being made, and also to the reward magnitude announced later on each trial (Rolls et al., 2008e). Further evidence in a variety of tasks implicates a related and partly overlapping region of the ventromedial prefrontal cortex with expected value (Daw et al., 2006; Hare et al., 2008; Kim et al., 2006; Tanaka et al., 2004). In contrast, the reward prediction errors or temporal difference errors as defined in reinforcement learning (Schultz, 2006; Sutton and Barto, 1998) are usually evident in the ventral striatum in imaging studies (Hare et al., 2008; Rolls et al., 2008e), though we should remember that negative reward prediction errors are represented by the error neurons in the primate orbitofrontal cortex (Thorpe et al., 1983), and that the lateral orbitofrontal cortex is activated when a negative reward prediction error is generated in the reversal of a visual discrimination task (Kringelbach and Rolls, 2003).

Although it might be anticipated that the actual utility or 'subjective utility' of an offer (a choice) to an individual approximately tracks the expected value, this is not exactly the case, with subjects typically undervaluing high rewards, and being over-sensitive to high punishments (Bernoulli, 1738/1954; Gintis, 2000; Kahneman and Tversky, 1979; Kahneman and Tversky, 1984; Rangel et al., 2008; Tversky and Kahneman, 1986; von Neumann and Morgenstern, 1944). Subjects also typically have a subjective utility function that discounts rewards the further in the future they are delayed. Some parts of the ventromedial prefrontal cortex have activations that may follow the subjective utility, of for example delayed rewards. In a study of this, it was found that activations in the ventromedial prefrontal cortex were correlated with the subjective utility of rewards delayed for different times, with the discount curve for each subject reconstructed from each subject's choices (Kable and Glimcher, 2007). Moreover, the activations in the ventromedial prefrontal cortex fitted the curves for each participant well, even though there were large individual differences in the reward discounting function, with some participants being impulsive and placing much more value on rewards available immediately, and other 'patient' participants showing very little discounting of rewards available a long time in the future. Thus activations in the ventromedial prefrontal cortex may continuously track even the subjective utility of available rewards. In further studies, it has been shown that counterfactual effects are manifested in the human orbitofrontal cortex during expectation of outcomes, such that the anticipated affective impact of outcomes is modulated by the nature of the various possible alternative outcomes (Ursu and Carter, 2005); and that activity in the orbitofrontal cortex correlated with the degree of regret, measured in a gambling task in which the outcome of the unchosen gamble would have been greater than the outcome that was obtained by the choice made (Coricelli et al.,

2005).

Clearly a representation of reward magnitude, expected reward, and even the subjective utility of a reward is an important input to a decision-making process, and the orbitofrontal cortex (with the ventromedial prefrontal area), appears to provide this information. When making a decision between two rewards, or whether to work for a reward that has an associated cost, it is important that the exact value of each reward is represented and enters the decision-making process. However, when a decision is reached, a system is needed that can make a binary choice, so that on one trial the decision might be reward 1, and on another trial reward 2, so that a particular action can be taken. For the evaluation, the neural activity needs to represent a stimulus in a way that continuously and faithfully represents the affective value of the stimulus, and this could be present independently of whether a binary choice decision is being made or not. On the other hand, when a binary (choice) decision must be reached, a neural system is needed that does not continuously represent the affective value of the stimulus, but which instead falls into a binary state, in which for example the high firing of some neurons represents one decision (i.e. choice), and the high firing of other neurons represents a different choice.

To investigate whether representing the affective value of a reward on a continuous scale may occur before and separately from making a binary, for example yes-no, decision about whether to choose the reward, Grabenhorst et al. (2008b) used functional magnetic resonance imaging (fMRI) to measure activations produced by pleasant warm, unpleasant cold, and affectively complex combinations of these stimuli applied to the hand. On some trials the affective value was rated on a continuous scale, and on different trials a Yes-No (binary choice) decision was made about whether the stimulus should be repeated in future. Activations that were continuously related to the pleasantness ratings and which were not influenced when a binary (choice) decision was made were found in the orbitofrontal and pregenual cingulate cortex, implicating these regions in the continuous representation of affective value. The orbitofrontal cortex projects to the pregenual cingulate cortex (Carmichael and Price, 1996; Price, 2006), and both these areas have reward and punishment value representations that correlate on a continuous scale with the subjective pleasantness/unpleasantness ratings of olfactory (Anderson et al., 2003; Grabenhorst et al., 2007; Rolls et al., 1996b, 2003b), taste (Grabenhorst et al., 2008a; Rolls et al., 1989; Small et al., 2003), somatosensory (Rolls et al., 2003c), temperature (Guest et al., 2007), visual (O'Doherty et al., 2003), monetary (Knutson et al., 2007; O'Doherty et al., 2001a), and social stimuli (Hornak et al., 2003; Kringelbach and Rolls, 2003; Moll et al., 2006; Spitzer et al., 2007) (see further Bush et al., 2000; Rolls, 2009a, 2014a). In the study with warm and cold stimuli, and mixtures of them, decision-making contrasted with just rating the affective stimuli revealed activations in the medial prefrontal cortex area 10, implicating this area in choice decision making (Grabenhorst et al., 2008b) (see Fig. 13).

Support for a contribution of medial prefrontal cortex area 10 to taking binary (choice) decisions comes from a fMRI study in which two odors were separated by a delay, with instructions on different trials to decide which odor was more pleasant, or more intense, or to rate the pleasantness and intensity of the second odor on a continuous scale without making a binary (choice) decision. Activations in the medial prefrontal cortex area 10, and in regions to which it projects including the anterior cingulate cortex and insula, were higher when binary choice decisions were being made compared to ratings on a continuous scale, further implicating these regions in binary decision-making (Rolls et al., 2010d).

Consistent with a role of medial prefrontal cortex area 10 in decision-making, patients with medial prefrontal cortex lesions are impaired in a decision-making shopping task, as reflected for example by visits to previously visited locations (Burgess, 2000; Burgess et al., 2007; Shallice and Burgess, 1991). In another imaging study, area 10 activation has been related to moral decision-making (Heekeren et al., 2005).

To further explore how choice decision-making is implemented in the brain, we have utilized an attractor network model of decision-making with spiking neurons in which the representations of each choice are by a subpopulation of neurons, and the attractor network settles into one of its two or more high firing rate attractor states each representing a choice (Deco and Rolls, 2006; Deco et al., 2013; Rolls, 2016a; Rolls and Deco, 2010; Wang, 2002). We showed that the model predicts that the BOLD signal become larger with the easiness of the decision (i.e. the difference between the two decision variables) on correct trials, and showed that this signature is found anterior to the orbitofrontal cortex, in medial prefrontal cortex area 10 (which may overlap with what some other investigators have termed the ventromedial prefrontal cortex) during choice of pleasantness for both olfactory and thermal stimuli (warmth to the hand) (Rolls et al., 2010b). The model also predicts that the BOLD signal become smaller with the easiness of the decision on error trials, and we showed that this signature is also found in medial prefrontal cortex area 10 in the same pleasantness choice tasks (Rolls et al., 2010c).

Thus there is considerable evidence that value representation on a continuous scale is provided by the orbitofrontal cortex, and that choices between these value representations are made just anterior to this by an attractor decision-making network (Rolls, 2014a). Consistent with the evidence and discoveries described here for humans, posterior orbitofrontal cortex (area 13) lesions in macaques impair the effects of satiation on reward value, whereas anterior orbitofrontal cortex (area 11) lesions impair choice decision-making (Murray et al., 2015).

16. The orbitofrontal cortex and depression

16.1. Foundations

Major depressive disorder is ranked by the World Health Organization as the leading cause of years-of-life lived with disability (Drevets, 2007; Gotlib and Hammen, 2009; Hamilton et al., 2013). Major depressive episodes, found in both major depressive disorder and bipolar disorder are pathological mood states characterized by persistently sad or depressed mood. Major depressive disorders are generally accompanied by: (a) altered incentive and reward processing, evidenced by amotivation, apathy, and anhedonia; (b) impaired modulation of anxiety and worry, manifested by generalized, social and panic anxiety, and oversensitivity to negative feedback; (c) inflexibility of thought and behaviour in association with changing reinforcement contingencies, apparent as ruminative thoughts of self-reproach, pessimism, and guilt, and inertia toward initiating goal-directed behaviour; (d) altered integration of sensory and social information, as evidenced by mood-congruent processing biases; (e) impaired attention and memory, shown as performance deficits on tests of attention set-shifting and maintenance, and autobiographical and short-term memory; and (f) visceral disturbances, including altered weight, appetite, sleep, and endocrine and autonomic function (Drevets, 2007; Gotlib and Hammen, 2009).

A new theory of how mechanisms in the orbitofrontal cortex are involved in depression has recently been developed (Rolls, 2016c). The theory is related to attractor network dynamics, which enable states to be maintained by continuing firing within a population of neurons with strong excitatory synaptic inter-connections (Rolls, 2016a; Rolls and Deco, 2010), and which are evident for non-reward in the lateral orbitofrontal cortex, as described next. The theory extends hypotheses of depression to the concept that over-active attractor networks (Deco et al., 2013; Rolls, 2016a; Rolls and Deco, 2010) in some brain regions related to emotion (Rolls, 2014a) are involved in depression.

The foundations for the theory include the following.

First, neurophysiological evidence indicates that neurons in the orbitofrontal cortex respond to non-reward. The orbitofrontal cortex contains a population of error neurons that respond to non-reward and maintain their firing for many seconds after the non-reward, providing

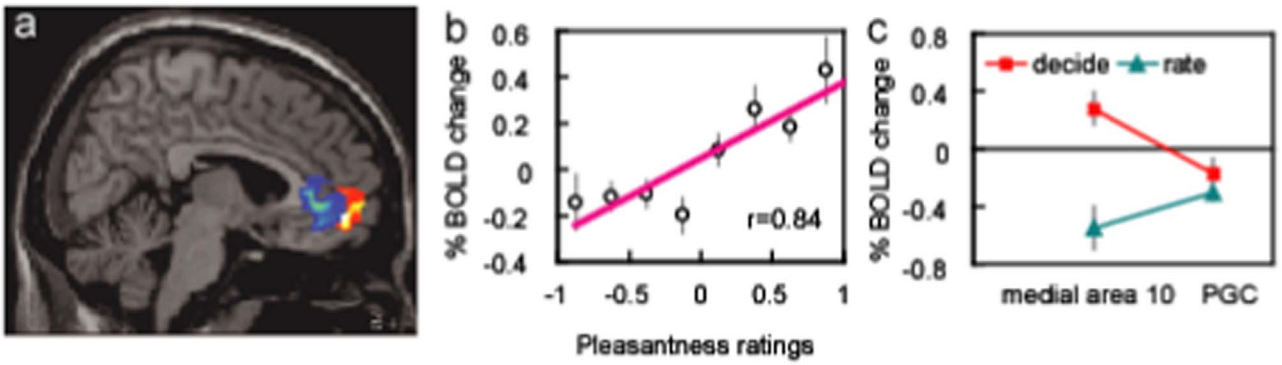

Fig. 13. Pregenual cingulate cortex vs medial area 10 in decision-making. (a) A contrast of all trials on which decisions were made vs all trials on which ratings were made between thermal stimuli showed a significant effect in the medial prefrontal cortex area 10, as indicated in red ([6 54 − 8]). This contrast showed no significant difference in the pregenual cingulate cortex, although here, as shown in blue, there was a strong and significant correlation with the pleasantness ratings ([4 38 − 2]). (b) Shows that the % BOLD signal in the pregenual cingulate cortex was correlated with the pleasantness ratings on the trials on which ratings were made ($r = 0.84$, $df = 7$, $p = 0.005$). (c) Compares the activations (mean ± sem) in medial area 10 with those in the pregenual cingulate cortex (PGC) for decision and rating trials. There was a significant interaction ($p = 0.015$). (After Grabenhorst et al., 2008b) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

evidence that they have entered an attractor state that maintains a memory of the non-reward (Fig. 9) (Rolls, 2014b; Thorpe et al., 1983). Attractor networks once triggered can maintain their high firing rate because of the strong recurrent excitatory synaptic connections between the neuronal sub-population (Rolls, 2016a) (with Appendix B describing attractor networks available at http://www.oxcns.org). This short-term memory of a recent negatively reinforcing event is an essential component of a system that must change its operation after non-reward in a rule-based way, and this has been modelled (Deco and Rolls, 2005c).

Second, human functional neuroimaging evidence indicates that the lateral orbitofrontal cortex is activated by non-reward, and also by punishers that affect emotion-related behaviour similarly (Rolls, 2014a). The activation of the human lateral orbitofrontal cortex during reward reversal is illustrated in Fig. 10a, which shows activations on reversal trials, that is when the human subject chose one person's face, and did not obtain the expected reward (Kringelbach and Rolls, 2003). Activations in the lateral orbitofrontal cortex are also produced by a signal to stop a response that is now incorrect, which is another situation in which behaviour must change in order to be correct (Fig. 10b) (Deng et al., 2017). Orbitofrontal cortex activations in the stop-signal task have further been related to how impulsive the behaviour is (Whelan et al., 2012). In this context, it has been suggested that impulsiveness may reflect how sensitive an individual is to non-reward or punishment (Rolls, 2014a), and indeed we have shown that people with orbitofrontal cortex damage become more impulsive (Berlin et al., 2005, 2004). The lateral orbitofrontal cortex also responds to many punishing, unpleasant, stimuli (Grabenhorst and Rolls, 2011; Rolls, 2014b) including bad odor (Rolls et al., 2003b) and losing money (O'Doherty et al., 2001a), as shown in Fig. 8. The computations involved in non-reward referred to below are more complicated than those involved in representing punishers, but both types of representation are present in the orbitofrontal cortex, are implemented by different neurons, and both are involved in changing behaviour to no longer choose the now non-rewarded stimulus, or the punisher (Rolls, 2014a, 2016a; Thorpe et al., 1983). The lateral orbitofrontal cortex projects to the supracallosal anterior cingulate cortex, in which non-rewards and punishers are also represented (Grabenhorst and Rolls, 2011; Rolls, 2014a; Rolls and Grabenhorst, 2008) (Figs. 3 and 8) in this region implicated in action-outcome learning (Grabenhorst and Rolls, 2011; Noonan et al., 2011; Rolls, 2014a). The effects of reward reversal on this supracallosal cingulate cortex system are illustrated in Fig. 10a (green circle).

Consistent with this evidence for humans, functional neuroimaging in macaques reveals that the macaque lateral orbitofrontal cortex is activated by non-reward during a reversal task (Chau et al., 2015) (Fig. 10c). Investigations into the effects of lesions in macaques have not yet fully investigated the differences between the medial orbitofrontal cortex areas (including 13 posteriorly and 11 anteriorly) and the lateral orbitofrontal cortex (area 12) (Rudebeck and Murray, 2014). The discoveries described in this paper indicate that in humans, there are at least three main divisions. The medial orbitofrontal cortex areas (13 and 11) are involved in reward value representations with subjective pleasantness linearly related to the activity and with devaluation by satiety reducing the response (Rolls, 2014b). The lateral orbitofrontal cortex areas (12/47 extending round the inferior convexity towards the ventral part of the inferior frontal gyrus to perhaps include a ventral part of right area 45) is involved in detecting and representing non-reward as a difference between the expected value and the outcome value (i.e. negative reward prediction error) and punishment, both of which can be used to change instrumental actions, and which relate to the older literature which used the less specific term behavioural inhibition (Rolls, 2014b). The more anterior parts of the orbitofrontal cortex, including part of what may be medial area 10 and parts of anterior 11), are involved in choice decision-making between stimuli with different value (Grabenhorst and Rolls, 2011; Grabenhorst et al., 2008b; Rolls, 2014b; Rolls and Grabenhorst, 2008; Rolls et al., 2010c, d, e).

Third, lesion evidence also shows that the orbitofrontal cortex is involved in changing rewarded behaviour when non-reward is detected, in that damage to the human orbitofrontal cortex impairs reward reversal learning, with the previously rewarded stimulus still being chosen during reversal even when no reward is being obtained (Fellows, 2011; Fellows and Farah, 2003; Hornak et al., 2004; Rolls et al., 1994a). There is consistent evidence in macaques (Rolls, 2016a) with orbitofrontal cortex damage impairing performance on Go/NoGo task performance, in that they Go on the NoGo trials (Iversen and Mishkin, 1970), and in an object-reversal task in that they respond to the object that was formerly rewarded with food, and in extinction in that they continue to respond to an object that is no longer rewarded (Butter, 1969; Jones and Mishkin, 1972; Meunier et al., 1997). The visual discrimination reversal learning deficit shown by monkeys with orbitofrontal cortex damage (Murray and Izquierdo, 2007) may be due at least in part to the tendency of these monkeys not to withhold choosing non-rewarded stimuli (Jones and Mishkin, 1972) including objects that were previously rewarded during reversal (Rudebeck and Murray, 2011), and including foods that are not normally accepted (Baylis and Gaffan, 1991; Butter et al., 1969). Consistently, orbitofrontal cortex (but not amygdala) lesions impaired instrumental extinction (Murray and Izquierdo, 2007).

In an evolutionary context, this very rapid, rule-based, reversal of stimulus-reward associations possible in primates including humans may be an important adaptation to allow rapid and flexible changes of behaviour when reinforcement contingencies change, and is likely to be very important in social interaction (Rolls, 2014a, 2016a). The detection of this non-reward may be computed in the orbitofrontal cortex using reciprocally inhibiting Reward and Non-Reward attractor neuronal populations in a single network (Rolls and Deco, 2016).

16.2. A non-reward attractor theory of depression

It is well established that not receiving expected reward, or receiving unpleasant stimuli or events, can produce depression (Beck, 2008; Drevets, 2007; Eshel and Roiser, 2010; Harmer and Cowen, 2013; Price and Drevets, 2012; Pryce et al., 2011). More formally, in terms of learning theory, the omission or termination of a reward can give rise to sadness or depression, depending on the magnitude of the reward that is lost, if there is no action that can be taken to restore the reward (Rolls, 2013b, 2014a). If an action can be taken, then frustration and anger may arise for the same reinforcement contingency (Rolls, 2014a). This relates the current approach to the learned helplessness approach to depression, in which depression arises because no actions are being taken to restore rewards (Forgeard et al., 2011; Pryce et al., 2011). The sadness or depression may be short lasting if it is a minor non-reward. The depression may be longer lasting if for example a member of the family dies, for every time that we remember the person we are aware of the loss of the reward of being with them, and this contributes to the longer-term depression that may arise.

On the basis of the evidence just described on the brain mechanisms involved in non-reward, and the non-reward triggers for depression, the theory has been proposed that in depression, the lateral orbitofrontal cortex non-reward/punishment attractor network system is more easily triggered and/or is very strongly triggered, and is therefore activated more often and maintains its attractor-related firing for longer (Rolls, 2016c). The greater attractor-related firing of the orbitofrontal cortex non-reward/punishment system then triggers negative cognitive states held on-line in other cortical systems, such as the dorsolateral prefrontal cortex which is implicated in attentional control, and language areas, which in turn have top-down effects on the orbitofrontal non-reward system that help to bias it in a negative direction and thus to increase its sensitivity to non-reward and maintain its overactivity (Rolls, 2013a, 2016a). It is proposed that the interaction of two different brain systems of this type contributes to the long-lasting ruminating and continuing depressive thoughts which occur as a result of a positive feedback attractor cycle between these types of brain system. This can be described as a long-loop attractor system, involving reciprocal interactions between cortical areas (Rolls, 2016c) (Fig. 14).

Indeed, we have shown that cognitive states can have top-down effects on affective representations in the orbitofrontal cortex (de Araujo et al., 2005; Grabenhorst et al., 2008a; McCabe et al., 2008; Rolls, 2013a). Further, top-down selective attention can also influence affective representations in the orbitofrontal cortex (Ge et al., 2012; Grabenhorst and Rolls, 2008, 2010; Luo et al., 2013; Rolls, 2013a; Rolls et al., 2008a), and paying attention to depressive symptoms when depressed may in this way exacerbate the problems in a positive feedback way. (Top-down attention refers to the process whereby an area such as the prefrontal cortex can hold in short-term memory what it is that attention should enhance, and can then bias 'lower' brain areas to respond more to some properties of what they respond to (Deco and Rolls, 2005b; Desimone and Duncan, 1995; Rolls, 2013a, 2016a; Rolls and Deco, 2002)).

More generally, the presence of the cognitive ability to think ahead and see the implications of recent events that is afforded by language may be a computational and evolutionary development in the brain that exacerbates the vulnerability of the human brain to depression (Rolls, 2014a). The circuitry that may implement this is illustrated in Fig. 14. Further, whenever a memory is retrieved from the hippocampal and related systems the emotional component reactivates the orbitofrontal cortex emotional system (Rolls, 2015b), contributing to the long-lasting nature of depression.

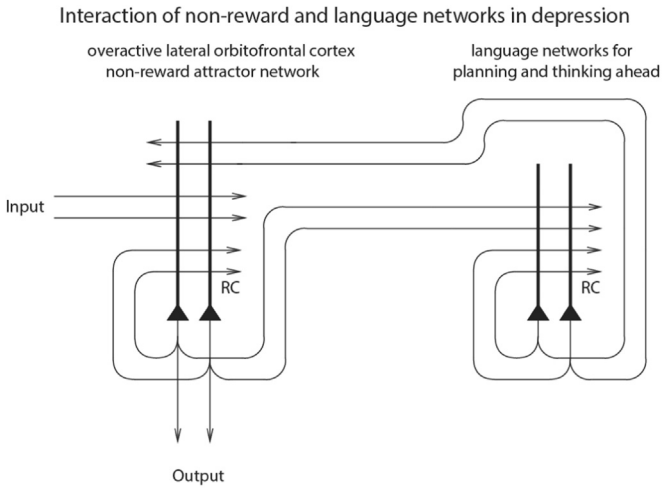

Fig. 14. Interaction of orbitofrontal cortex non-reward networks with language networks in depression. Illustration of how an overactive non-reward attractor network in the lateral orbitofrontal cortex could send information forward to networks for language and planning ahead which could in turn send top-down feedback back to the orbitofrontal non-reward network to maintain its over-activity. It is suggested that such a system contributes to the persistent ruminating thoughts in depression.

The theory is that one way in which depression could result from over-activity in this lateral orbitofrontal cortex non-reward system is if there is a major negatively reinforcing life event that produces reactive depression and activates this system, which then becomes self-re-exciting based on the cycle between the lateral orbitofrontal cortex non-reward/punishment attractor system and the cognitive system, which together operate as a systems-level attractor (Fig. 14). The theory is that a second way in which depression might arise is if this lateral orbitofrontal cortex non-reward/punishment system is especially sensitive in some individuals. This might be related for example to genetic predisposition; or to the effects of chronic stress which influences cortical regions including the orbitofrontal cortex (Gold, 2015; Radley et al., 2015). In this case, the orbitofrontal system would over-react to normal levels of non-reward or punishment, or even become active in the absence of a stimulus, and start the local attractor circuit in the lateral orbitofrontal cortex, which in turn would activate the cognitive system, which would feed back to the over-reactive lateral orbitofrontal cortex system to maintain now a systems-level attractor with ruminating thoughts (Fig. 14). In the theory, an oversensitive or over-responding short-term non-reward system in the lateral orbitofrontal cortex can produce long-lasting depression (a) because it activates the dorsolateral prefrontal cortex and related cognitive including language systems that continue thinking about the non-reward and re-excite the orbitofrontal cortex by top-down influences (see illustration in Fig. 14); and (b) because the orbitofrontal cortex non-reward system is activated whenever the human memory system retrieves a memory associated with a sad event (Rolls, 2015b), re-activating the positive feedback system between the orbitofrontal and dorsolateral prefrontal cortex. In that the lateral orbitofrontal cortex connects to the supracallosal part of the anterior cingulate cortex, this is also expected to be over-active or to have increased functional connectivity in depression.

A complementary part of the theory is that the medial orbitofrontal cortex reward-related areas are underactive in depression (Rolls, 2016c). There is evidence for reciprocal interactions between the lateral and medial orbitofrontal cortex. For example, monetary loss activates the lateral orbitofrontal cortex and deactivates the medial orbitofrontal cortex; and monetary gain activates the medial orbitofrontal cortex and

deactivates the lateral orbitofrontal cortex (O'Doherty et al., 2001a). This relationship is supported by evidence from resting-state functional connectivity (Rolls et al., 2017a), as follows. All the medial orbitofrontal cortex areas in the automated anatomical labelling atlas specially revised for the orbitofrontal cortex (Rolls et al., 2015) (OFCmed, OFCant, OFCpost, Rectus, and OLF) had a high functional connectivity (correlation) with each other that is on average 0.58 (std 0.13) (in the control group). Similarly, the two lateral orbitofrontal cortex areas (OFClat and IFG_Orb) have high functional connectivity with each other that is on average 0.68 (std 0.08). However, the mean FC between the medial orbitofrontal cortex areas and lateral orbitofrontal cortex areas was much lower, 0.36 (std 0.16), and the difference was significant (*t*-test, $p < 10^{-12}$). Further, this relates to an average functional connectivity value across all pairs in the brain of 0.35. This evidence provides an indication that the medial and lateral orbitofrontal cortex areas are not positively coupled to each other, but can operate in opposite directions, and even could operate reciprocally (Rolls et al., 2017a). The putative reciprocity between the lateral (non-reward-related) and medial (reward-related) parts of the orbitofrontal cortex is supported by the finding that there is strong effective (resting-state) connectivity directed from the medial orbitofrontal cortex to the lateral orbitofrontal cortex, and that this is increased in depression (Rolls et al., 2017a). The low value for functional connectivity (between these two areas) indicates that this is likely to reflect a reciprocal relationship between the medial and lateral orbitofrontal cortex. The anhedonia of depression is very likely to reflect decreased activity in the medial orbitofrontal cortex.

16.3. Evidence consistent with the theory

There is some evidence for altered structure and function of the lateral orbitofrontal cortex in depression (Drevets, 2007; Ma, 2015; Price and Drevets, 2012). For example, reductions of gray-matter volume and cortex thickness have been demonstrated specifically in the posterolateral orbitofrontal cortex/ventrolateral prefrontal cortex (BA 47, caudal BA 11 and the adjoining BA 45), and also in the subgenual cingulate cortex (BA 24, 25) (Drevets, 2007; Nugent et al., 2006). In depression, there is increased cerebral blood flow in areas that include the ventrolateral orbitofrontal cortex (which is a prediction of the theory), and also in regions such as the subgenual cingulate cortex and amygdala, and these increases appear to be related to the mood change, in that they become more normal when the mood state remits (Drevets, 2007).

Because the lateral orbitofrontal cortex responds to many punishing and non-rewarding stimuli (Grabenhorst and Rolls, 2011; Rolls, 2014a, 2014b) that are likely to elicit autonomic/visceral responses, as does the supracallosal anterior cingulate cortex, and in view of connections from these areas to the anterior insula which is implicated in autonomic/visceral function (Critchley and Harrison, 2013; Rolls, 2016b), the anterior insula would also be expected to be overactive in depression, and that prediction is confirmed (Drevets, 2007; Hamilton et al., 2013; Ma, 2015).

Evidence from the first brain-wide voxel-level resting state functional-connectivity neuroimaging analysis of depression with 421 patients with major depressive disorder and 488 controls Cheng et al. (2016) provides support for and helps to refine the theory of depression. Resting state functional connectivity between different voxels reflects correlations of activity between those voxels and is a fundamental tool in helping to understand the brain regions with altered connectivity and function in depression.

One major circuit with altered functional connectivity involved the medial orbitofrontal cortex BA 13, which is implicated in reward, and which had reduced functional connectivity in depression with memory systems in the parahippocampal gyrus and medial temporal lobe (Fig. 15). The lateral orbitofrontal cortex BA 47/12, involved in non-reward and punishing events, did not have this reduced functional connectivity with memory systems, so that there is an imbalance in depression towards decreased reward-related memory system functionality. The reduced functional connectivity of the medial orbitofrontal cortex, implicated in reward, with memory systems (relative to the lateral orbitofrontal cortex) provides a new way of understanding how memory systems may be biased away from pleasant events in depression (Cheng et al., 2016). Consistent with this two other areas connected to the orbitofrontal cortex and involved in emotion, the amygdala and anterior cingulate cortex have reduced functional connectivity with the orbitofrontal cortex and with temporal lobe memory systems in depression (Cheng et al., 2017; Rolls et al., 2017b).

Second, the lateral orbitofrontal cortex BA 47/12 had increased functional connectivity with the precuneus, the angular gyrus, and the temporal visual cortex BA 21 (Fig. 15). This enhanced functional connectivity of the non-reward/punishment system (BA 47/12) with the precuneus (involved in the sense of self and agency), and the angular gyrus (involved in language) may it is suggested be related to the explicit affectively negative sense of the self, and of self-esteem, in depression. The increased functional connectivity of the lateral orbitofrontal cortex, implicated in non-reward and punishment, with areas of the brain implicated in representing the self, language, and inputs from face and related perceptual systems (Fig. 15) (Cheng et al., 2016) provides a new way of understanding how unpleasant events and thoughts, and lowered self-esteem, may be exacerbated in depression. The increased connectivity between the lateral orbitofrontal cortex and the angular gyrus system involved in language (Fig. 15) directly supports the hypothesis illustrated in Fig. 14. It is of considerable interest that this lateral orbitofrontal cortex region is primarily on the right of the brain, and extends round the inferior frontal convexity to the ventral parts of the inferior frontal gyrus pars triangularis (BA45), anteriorly (and to some extent pars opercularis (BA44) posteriorly), both of which share the same type of functional connectivity differences in depression as the lateral orbitofrontal cortex. These areas have increased functional connectivity with the temporal cortex, precuneus, and angular (BA39) and supramarginal gyri (BA40) bilaterally (Cheng et al., 2016). The region is sometimes known as the inferior frontal gyrus, pars orbitalis. In the left hemisphere BA45 and BA44 are Broca's area (Amunts and Zilles, 2012; Clos et al., 2013), but in the right hemisphere the ventral parts of these areas may serve as a route for the lateral orbitofrontal cortex to connect with motor-related cortical areas. It is notable that this same right lateral orbitofrontal cortex area is activated in the stop-signal task (Deng et al., 2017), consistent with the hypothesis that this area is involved in detecting non-reward, punishers, and other signals that need to reverse reward-based and related processing to change behaviour (Rolls, 2016c). The extension of this lateral orbitofrontal cortex area BA47/12 round the inferior frontal convexity to the ventral parts of the inferior frontal gyrus BA45 and BA44 is consistent with resting-state functional connectivity parcellation studies (Goulas et al., 2017; Samara et al., 2017). Moreover and consistently, this same lateral orbitofrontal cortex region has functional connectivity that is negatively related to happiness / subjective well-being (Liu et al., 2017). Further, as a follow-up to my lateral orbitofrontal cortex non-reward attractor theory of depression (Rolls, 2016c), it is now being shown that inhibitory rTMS (repetitive transcranial magnetic stimulation) of the right lateral orbitofrontal cortex can relieve depression in at least some patients (Fettes et al., 2017a, b). Interestingly, the subcallosal cingulate cortex, implicated in depression (Hamani et al., 2011; Laxton et al., 2013), has increased functional connectivity with the lateral orbitofrontal cortex in depression (Rolls et al., 2017b).

Some of these differences in functional connectivity in depression were related to the depression in that there were significant correlations between some of the different functional links in depression and the symptom severity scores and illness duration (Cheng et al., 2016). One finding was that the Hamilton and Beck depression scores were correlated with some of the weakened functional connectivities of the medial

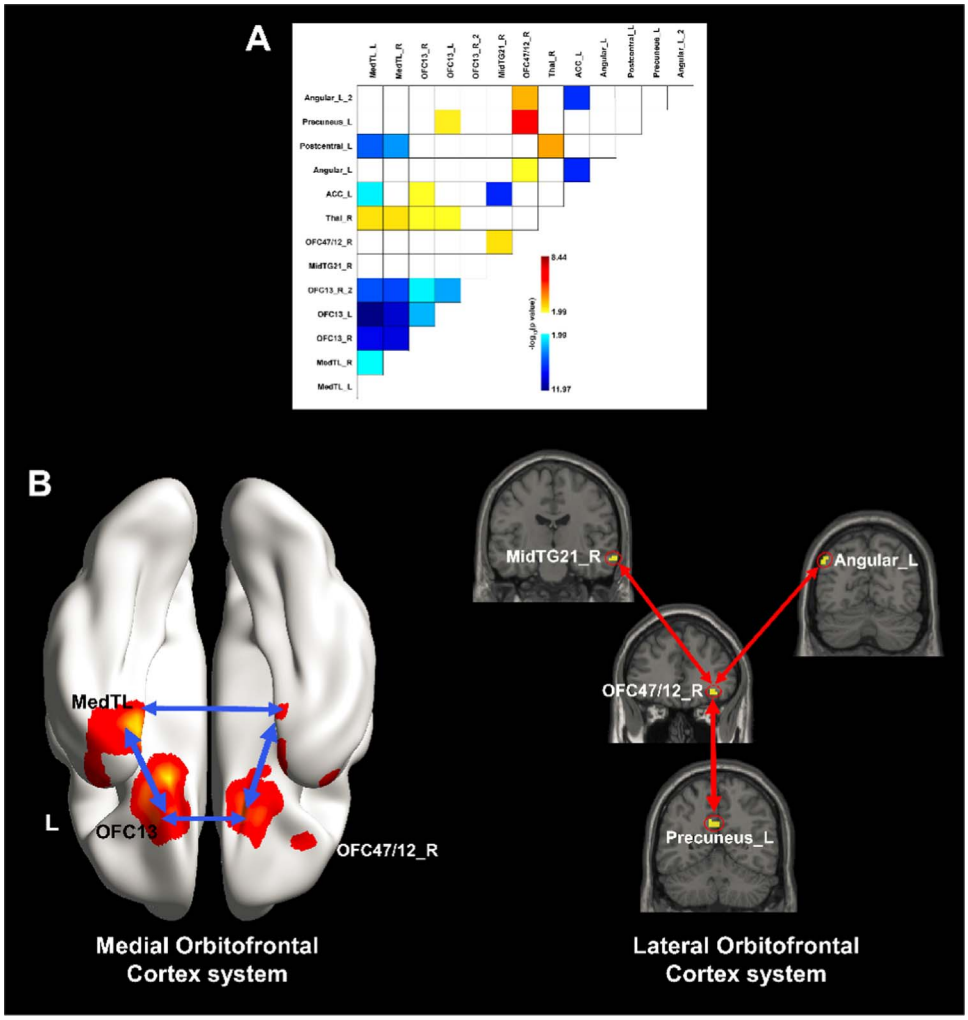

Fig. 15. Resting state functional connectivity in depression. A. Cluster functional connectivity matrix. The color bar shows the -log$_{10}$ of the p value for the difference of the functional connectivity. Blue indicates reduced functional connectivity, and yellow/orange/red increased functional connectivity. The matrix contains rows and columns for all cases in which there were 10 or more significant voxels within a cluster. ACC – anterior cingulate cortex; MedTL – medial temporal lobe, including parts of the parahippocampal gyrus; Thal – thalamus. The abbreviations are from the AAL2 (Rolls et al., 2015) (see also (Cheng et al., 2016)). B. The medial and lateral orbitofrontal cortex networks that show different functional connectivity in patients with depression. A decrease in functional connectivity is shown in blue, and an increase in red. MedTL – medial temporal lobe from the parahippocampal gyrus to the temporal pole; MidTG21R – middle temporal gyrus area 21 right; OFC13 – medial orbitofrontal cortex area 13; OFC47/12R – lateral orbitofrontal cortex area 47/12 right. The lateral orbitofrontal cortex cluster in OFC47/12 is visible on the ventral view of the brain anterior and lateral to the OFC13 clusters. (After Cheng et al., 2016.) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

orbitofrontal cortex. Another finding was that medication reduced the increased functional connectivity of some lateral orbitofrontal cortex links in depression. These findings provide further evidence that the orbitofrontal cortex functioning is related to depression (Cheng et al., 2016).

To provide evidence of some of the possible causal routes by which brain connectivity is altered in depression, the first brain-wide resting state effective-connectivity neuroimaging analysis of depression, with 353 healthy individuals, and 347 patients with major depressive disorder (Rolls et al., 2017a) has used a new algorithm for going beyond functional connectivity (which reflects correlations) to effective connectivity, which measures how one brain area influences another brain area (Gilson et al., 2016). Key discoveries were as follows. The medial cortex has reduced effective connectivity from temporal lobe input areas in depression. This could account for lower activity in the medial orbitofrontal cortex in depression. In turn, the temporal cortical visual areas receive increased effective connectivity from the precuneus, implicated in the sense of self. (Self-esteem is low in depression.) The lateral orbitofrontal cortex has increased activity (variance) in depression; and increased effective connectivity from the medial orbitofrontal cortex in depression, as described above (Rolls et al., 2017a). This investigation makes a start towards understanding some of the causal circuitry that operates differently in depression.

Treatments that can reduce depression such as a single dose of ketamine (Iadarola et al., 2015) may act in part by quashing the attractor state in the lateral orbitofrontal cortex/ventrolateral prefrontal cortex at least temporarily (though there is also evidence that ketamine's effect on depression may be related to blocking by blocking NR2B glutamatergic synapses onto GABA neurons). Evidence consistent with the possibility that ketamine depresses activity in the lateral orbitofrontal cortex is that glucose metabolism in the ventrolateral prefrontal cortex is decreased by a single dose of ketamine that ameliorates depression (Carlson et al., 2013), and in the lateral orbitofrontal cortex the decrease is related to the increase in hedonia produced by the ketamine (Lally et al., 2015). This NMDA receptor blocker may act at least in part by decreasing the high firing rate state of attractor networks by reducing transmission in the recurrent collateral excitatory connections between the neurons (Deco et al., 2013; Rolls, 2012a; Rolls and Deco, 2010, 2015; Rolls et al., 2008d). Another NMDA receptor blocker, nitrous oxide, has also been shown to have an antidepressant effect, though the therapeutic use of nitrous oxide is not recommended because it produces vitamin B12 depletion (Nagele et al., 2015). Electroconvulsive therapy (ECT), which may have antidepressant effects, may also knock the non-reward system out of its attractor state, and this may contribute to any antidepressant effect. It has been shown that successful ECT for major depressive disorder is associated with reduced activation of the orbitofrontal cortex in emotional tasks (Beall et al., 2012).

Electrical stimulation of the brain that may relieve depression (Hamani et al., 2009, 2011; Lujan et al., 2013) may act in part by providing reward that reciprocally inhibits the non-reward system, and/or by knocking the lateral orbitofrontal cortex and connected systems out of their attractor state. Treatment with antidepressant drugs decreases the activity of this lateral orbitofrontal cortex system

(Ma, 2015).

Antidepressant drugs such as Selective Serotonin Reuptake Inhibitors (SSRIs) may treat depression by producing positive biases in the processing of emotional stimuli (Harmer and Cowen, 2013), increasing brain responses to positive stimuli and decreasing responses to negative stimuli (Ma, 2015). These drugs may act on brainstem systems influenced by the orbitofrontal cortex via the habenula (Rolls, 2017c). The reward and non-reward systems are likely to operate reciprocally, so that facilitating the reward system, or providing rewards, and thus activating the medial orbitofrontal cortex (Grabenhorst and Rolls, 2011; Rolls, 2014a), may operate in part by inhibiting the overactivity in the lateral orbitofrontal cortex non-reward/punishment system. Reciprocal activations of the medial orbitofrontal cortex reward systems and lateral orbitofrontal cortex non-reward systems are evident in a monetary reward/loss task (O'Doherty et al., 2001a). The generally decreased functional connectivity of the medial orbitofrontal cortex in depression and the increased functional connectivity of the lateral orbitofrontal cortex illustrated in Fig. 15 (Cheng et al., 2016) also provides support for the theory that these systems operate in different directions in depression.

16.4. Implications of the orbitofrontal cortex non-reward attractor theory of depression

The implications can be understood and further explored in the context of investigations of the factors that influence the stability of attractor neuronal networks with integrate-and-fire neurons with noise introduced by the close to Poisson spiking times of the neurons (Deco et al., 2013, 2009; Loh et al., 2007; Rolls, 2016a; Rolls and Deco, 2010, 2011, 2015; Rolls et al., 2010c, 2008c, 2008d; Wang, 2002). One is that interventions such as deep brain stimulation, rTMS, or transcranial direct current inactivation (tDCS) of the lateral orbitofrontal cortex may be useful to explore further for the treatment of depression. A second is that it might be possible to produce agents that decrease the efficacy of NMDA (or other excitatory) receptors in the lateral orbitofrontal cortex, or increase the efficacy of GABA transmission, thereby reducing the stability of the depression-related attractor state. A third is that anti-anxiety drugs, by increasing inhibition, might reduce the stability of the high firing rate state of the non-reward attractor, thus acting to quash the depression-related attractor state. A fourth is that the whole concept of attractor states has many implications for the treatment of depression, for rewards and other environmental changes and activities that tend to compete with the non-reward attractor state and quash it may be useful in the treatment of depression (Rolls, 2016c). These cognitive approaches might include diverting thought and attention away from the negative stimuli and influences that may contribute to the depression; and directing thought and attention towards rewards, which may help to quash the activity of the non-reward system by the reciprocal interactions.

16.5. Relation of the orbitofrontal cortex to the anterior cingulate cortex in depression

There is considerable evidence that the anterior cingulate cortex is involved in emotion, with a pregenual part activated by many rewards, and a supracallosal part activated by non-reward and punishers (Grabenhorst and Rolls, 2011; Rolls, 2009a, 2014a; Vogt, 2009). The subcallosal anterior cingulate cortex (with a smaller region referred to previously as subgenual cingulate cortex) has been implicated in depression, and stimulation in the subcallosal cingulate cortex has been used to treat depression (Drevets et al., 2004; Drevets et al., 1997; Drysdale et al., 2017; Dunlop et al., 2017; Hamani et al., 2009, 2011; Johansen-Berg et al., 2008; Kang et al., 2016; Laxton et al., 2013; Lujan et al., 2013; Mayberg, 2003; Mayberg et al., 2016; McGrath et al., 2014, 2013; McInerney et al., 2017; Price and Drevets, 2010, 2012; Ramirez-Mahaluf et al., 2017; Riva-Posse et al., 2017). What then is the relation between the roles of the orbitofrontal cortex and the anterior cingulate cortex, in depression, and in the context that the orbitofrontal cortex has major projections to the anterior cingulate cortex?

In a voxel-level functional connectivity study in 336 patients with major depressive disorder and 350 controls, parcellation of the anterior cingulate cortex in the controls based on its functional connectivity with voxels in other brain regions, followed by tests of how this connectivity was different in depression, showed the following (Rolls et al., 2017b). A supracallosal anterior cingulate cluster had relatively reduced functional connectivity in depression with the right lateral orbitofrontal cortex. This is interesting, for both areas are activated by non-reward and punishers (Grabenhorst and Rolls, 2011; Rolls, 2014a).

A pregenual cingulate cortex cluster had especially relatively weak functional connectivity with the ventromedial prefrontal cortex (VMPFC) in patients with depression; and also with temporal lobe areas including the parahippocampal gyrus and hippocampus, the angular and supramarginal gyri, the precuneus, and middle and superior frontal gyri.

A subcallosal cingulate cortex cluster 3 had especially strong functional connectivity with voxels in the right lateral orbitofrontal cortex (IFGorb) and its two nearby areas, the right inferior frontal gyrus pars triangularis (BA45) and pars opercularis (BA44) in patients with depression.

This casts a new light on the functions of the anterior cingulate cortex in depression which relates it to the orbitofrontal cortex, for it divides the anterior cingulate cortex into these three divisions, each of which is related functionally to the medial or lateral orbitofrontal cortex, and each of which has different functional connectivity in depression (Rolls et al., 2017b).

16.6. Summary of the roles of the orbitofrontal cortex in depression

Increased understanding of the right lateral orbitofrontal cortex is advancing our understanding of this as a key region in changing behaviour when reward is no longer being received, or a punisher or signal to change behaviour is received (Chau et al., 2015; Deng et al., 2017; Grabenhorst and Rolls, 2011; Kringelbach and Rolls, 2003; O'Doherty et al., 2001a; Thorpe et al., 1983). Much such evidence, and the understanding that non-reward can lead to sadness and potentially depression (Rolls, 2014a), led to my lateral orbitofrontal cortex non-reward attractor theory of depression (Rolls, 2016c). In relation to this, we discovered that in depression the right lateral orbitofrontal cortex, and the ventral part of the right inferior frontal gyrus (ventral BA45) have increased functional connectivity with the temporal cortex, precuneus, and angular (BA39) and supramarginal gyri (BA40) bilaterally (Cheng et al., 2016). As a follow-up to this attractor theory of depression it is now being shown that inhibitory rTMS of the right lateral orbitofrontal cortex can relieve depression in at least some patients (Fettes et al., 2017a, 2017b). It has also been suggested that the orbitofrontal cortex and related brain areas involved in emotion such as the anterior cingulate cortex and amygdala (Rolls, 2014a) influence via the ventral striatum and habenula the brainstem monoamine systems including serotonin and dopamine via which some current pharmacological treatments for depression may act (Rolls, 2017c). This non-reward attractor theory of depression also has many complementary implications for cognitive treatments of depression, including developing further ways to help those with depression to focus on other thoughts and actions that will compete with and quash the non-reward attractor states that include ruminating negative thoughts (Rolls, 2016c). By combining understanding of the computations performed in each cortical area (Rolls, 2016a), and how alterations in the stability of local cortical circuits can impair the function of cortical attractor networks (Rolls, 2016a; Rolls and Deco, 2010), we may be at the start of a generational shift in our understanding and treatment of depression (Rolls, 2016c).

Further research on the relative roles of the orbitofrontal cortex, and

other areas such as the cingulate cortex and amygdala that are also involved in emotion, and of how treatments that influence the orbitofrontal cortex may be useful for depression, are key areas for future research. It will also be important to address further the relative contributions of the key components of the theory: that there is increased activity in a lateral orbitofrontal cortex non-reward attractor system in depression; that there is decreased activity of a medial orbitofrontal cortex reward-related system in depression; and that these two systems are reciprocally related.

Given that emotions can be considered as states elicited by rewards and punishers (Rolls, 2013b, 2014a, 2014b), a key contribution of the orbitofrontal cortex in depression is likely to be very important, given that rewards tend to decrease in depression and the medial orbitofrontal cortex is involved in rewards, and that depression involves much focus on non-rewards and punishers, in which the lateral orbitofrontal cortex is involved.

17. Conclusions and future directions

17.1. Representations of affective value vs intensity and identity

An important principle that emerges from research on the brain mechanisms of emotion is that there is a specialized system that provides representations of the reward or reinforcing value of stimuli, and that this is separate from brain systems that represent the physical properties of a stimulus such as its identity (e.g. that it is sweet, independently of hunger and whether we want it and it is currently rewarding; what object we are looking at, independently of whether we want it and it is currently rewarding, etc). The separation of affective processing from processing about the identity and intensity of stimuli in primates including humans (Rolls, 2017b) is highly adaptive, and a fundamental principle of brain design revealed by these investigations, for it enables us to see and learn about stimuli independently of whether we currently want them and find them rewarding. This enables goal-directed, emotional and motivational, behaviour to be separated from other types of learning that are independent of the current emotional and motivational value of stimuli (Rolls, 2014a).

17.2. Attention to affective value vs intensity

These concepts have been extended to the effects of attention. For example, when subjects are instructed to pay attention to the pleasantness of taste stimuli (monosodium glutamate), activations were larger in the orbitofrontal and pregenual cingulate cortex; and when paying attention to intensity, activations were larger in the taste insula (see Fig. 12) (Grabenhorst and Rolls, 2008). Further, when subjects are instructed to pay attention to the pleasantness of olfactory stimuli, activations were larger in brain areas such as the orbitofrontal and pregenual cingulate cortex and hypothalamus; and when paying attention to intensity, activations were larger in brain areas such as the pyriform cortex and inferior frontal gyrus (Rolls et al., 2008a). These interesting effects are related to the fact that the processing of affective value and intensity are separable processes, and indicate that the exact way in which we respond to stimuli depends on whether we are engaged in processing their affective value or their physical properties. This has important implications for sensory testing, as well as for emotional responsiveness more generally.

17.3. Cognitive modulation of affective value

It has also been possible to extend these concepts to the cognitive modulation of the affective and reward value of stimuli and emotion-related states. For example, it has been shown that highly cognitive, word-level, descriptions of olfactory (de Araujo et al., 2005), taste (Grabenhorst et al., 2008a), flavor (Grabenhorst et al., 2008a; Plassmann et al., 2008), and somatosensory stimuli (McCabe et al., 2008) can alter activations produced by these stimuli in brain areas that represent the pleasantness of these stimuli such as the orbitofrontal and pregenual cingulate cortex, and in a region to which these project, the ventral striatum. The implication of these findings is again fascinating, for it shows that cognition can descend into the first stage of processing at which affective value is made explicit in the representation, to alter the representations that are related to affective value in these areas.

17.4. Identity, affective, and decision-making tiers of processing

Fig. 3 is designed to draw out these issues in terms of processing hierarchies. The level of the tiered structure that forms a column including inferior temporal visual cortex, primary taste cortex, pyriform cortex, and somatosensory cortex is the level at which intensity, physical properties, and the identity of stimuli are represented, and in an affect-neutral way. The next tier of processing, including the orbitofrontal cortex, amygdala, and pregenual cingulate cortex, represents the reward/reinforcing value of stimuli and their corresponding subjective affective value. The next tier of processing provides a stage at which responses are organised to the stimuli, including autonomic responses via the lateral hypothalamus (and visceral insula not shown in Fig. 3); habit responses by brain regions that include the basal ganglia; and action-outcome learning to enable the goals represented at the second tier to be obtained.

17.5. Affective value, consciousness, and the affective tier

The reward value of stimuli, operationally defined, is represented in the orbitofrontal cortex. But it is a feature of our human functional neuroimaging studies that the subjective, conscious, ratings of pleasantness are correlated with activations in the orbitofrontal cortex, typically linearly. Rolls has argued that there are dual routes to action, and that one, concerned with simple reinforcers such as taste, can in some cases be implemented implicitly, that is unconsciously (Rolls, 1999a, 2004b, 2007a, 2008a, 2014a). The conjecture is that the conscious route is needed for rational (i.e. reasoning) thought about plans that may have multiple steps, and that the processing in this system happens to feel like something. Why then might activations of simple reinforcers such as taste or warmth have their subjective affective value represented at all? The suggestion that is made is that reasoning may have to occur about the advantages of different rewards (e.g. deferring an immediate taste reward for a longer term financial reward), and that the simple rewards, such as taste or warmth, become conscious by virtue of entering this reasoning processing system (Rolls, 1999a, 2004b, 2007a, b, 2008a, 2014a). (If the limited capacity reasoning system is not engaged in reasoning about something else, then simple rewards may, while it is monitoring events in the world, enter it and become conscious.) In any case, the activations in the orbitofrontal cortex are clearly closely related to the subjectively experienced affective value, and may thus provide inputs to the reasoning system. In an analogous way, the activity in the first tier of processing, at which intensity and identity are represented, is closely correlated with the subjective intensity of the stimuli, showing how the properties of what is represented in conscious experience reflects processing in different cortical areas. We have seen in this paper that processing in two particular brain areas, the orbitofrontal and pregenual cingulate cortex, is closely related to subjectively experienced affective value.

17.6. Specific reward representations using a common scale

The representations in the orbitofrontal cortex provide evidence about the exact nature of each reward, as shown most clearly by the single neuron recording studies. These show that different and overlapping populations of neurons provide representations of combinations of the taste, texture, odor, temperature and visual appearance of stimuli (e.g. Fig. 3). Other orbitofrontal cortex neurons provide

representations of which expression is present on a face, and of face identity (Rolls et al., 2006). Thus it is not general reward or affect that is represented (Rolls, 2014a). The computational reason for this is that to guide behaviour adaptively and correctly, each reinforcer must be represented separately. When we are hungry, we should eat food; when thirsty, we should drink water; etc. Moreover, social behaviour to an individual may require representations not only of face expression, but also of face identity, and both are involved in typical social behaviour.

All these different rewards have to be in a common scale, that is, one type of reward (e.g. food reward) should not dominate all other types of reward, for this would be maladaptive. Making different rewards approximately equally rewarding makes it likely that a range of different rewards will be chosen over time (and depending on factors such as need state in some cases), which is adaptive and essential for survival (Rolls, 2014a).

There are special mechanisms that help this common scale to operate gracefully. One is sensory-specific satiety, the decrease in the reward value of a stimulus that typically occurs over several minutes. This is an elegant way of ensuring that different rewards are selected at different times, and helps to keep the rewards competing evenly in a common currency.

17.7. Blind emotion

In blindsight, patients with damage to the primary visual cortex may deny having any subjective conscious experience of seeing a stimulus, but may be able to guess better than chance what the stimulus is, or what the expression is on a face, and may show signs of emotional responses (de Gelder et al., 1999; Tamietto et al., 2009, 2012; Weiskrantz, 1997, 1998). With subliminal stimuli, or in split brain patients, emotional responses may also be produced in the absence of consciousness awareness (Gazzaniga and LeDoux, 1978). I term these phenomena in which emotional stimuli may be processed but without consciousness awareness 'blind emotion'. We have shown that in backward masking experiments, when neurons in the macaque inferior temporal visual cortex fire for approximately 30 ms and represent substantial information about which stimulus was shown, then humans do not report seeing them. When the stimulus onset asynchrony is increased to allow the inferior temporal cortex neurons to fire for 50 ms, then humans do report conscious awareness of the stimuli (Rolls, 2003; Rolls et al., 1999b, 1994b; Tovee and Rolls, 1995). Given these findings, I have suggested that the threshold for conscious awareness is greater than the threshold for the representation of substantial information in the visual system (Rolls, 2003). I have argued that the adaptive value of this is that the cortical computations related to consciousness are serial, involving higher order syntactic thought, and that the threshold is set slightly above that for information representation because it is inefficient to interrupt serial syntactic thought unless there is a reasonable probability that there is a new stimulus or event to which that computational processor must be switched (Rolls, 2004b, 2007a, 2007b, 2008a, 2010a, 2011a, 2014a, 2016a).

My own theory of consciousness is that a higher order syntactic thought (HOST) system is needed to perform credit assignment to correct lower order syntactic multiple-step plans, and that when the HOST processing system is active and dealing with symbols grounded in the word, then subjective consciousness is a property of the operation of that system (Rolls, 2004b, 2007a, 2007b, 2008a, 2010a, 2011a, 2012c, 2014a, 2016a). (The syntax may not be as complex as that required for human language.) Larry Weiskrantz' view may not be too far from part of my theory of consciousness, in that he believes that reflection is involved in consciousness. Indeed, whenever I met Larry for the first time each day, he would ask me how I was, I would reply "Fine", and Larry would say: "You have no right to say that, Edmund, as you have not reflected on it."

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