The orbitofrontal cortex: reward, emotion, and depression

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Abbreviations: ADHD – attention deficit hyperactivity disorder; BA – Brodmann area; BOLD – blood oxygenation-level dependent; fMRI – functional magnetic resonance imaging; OFC – orbitofrontal cortex; VMPFC – ventromedial prefrontal cortex; VLPFC – ventrolateral prefrontal cortex
Abstract

The orbitofrontal cortex in primates including humans is the key brain area in emotion, and in the representation of reward value and in non-reward, that is not obtaining an expected reward. Cortical processing before the orbitofrontal cortex is about the identity of stimuli, i.e. ‘what’ is present, and not about reward value. There is evidence that this holds for taste, visual, somatosensory, and olfactory stimuli. The human medial orbitofrontal cortex represents many different types of reward, and the lateral orbitofrontal cortex represents non-reward and punishment. Not obtaining an expected reward can lead to sadness, and feeling depressed. The concept is advanced that an important brain region in depression is the orbitofrontal cortex, with depression related to over-responsiveness and over-connectedness of the non-reward-related lateral orbitofrontal cortex, and to under-responsiveness and under-connectivity of the reward-related medial orbitofrontal cortex. Evidence from large-scale voxel-level studies and supported by an activation study is described that provides support for this hypothesis. Increased functional connectivity of the lateral orbitofrontal cortex with brain areas that include the precuneus, posterior cingulate cortex, and angular gyrus is found in patients with depression, and is reduced towards the levels in controls when treated with medication. Decreased functional connectivity of the medial orbitofrontal cortex with medial temporal lobe areas involved in memory is found in patients with depression. Some treatments for depression may act by reducing activity or connectivity of the lateral orbitofrontal cortex. New treatments that increase activity or connectivity of the medial orbitofrontal cortex may be useful for depression. These concepts, and that of increased activity in non-reward attractor networks, have potential for advancing our understanding and treatment of depression. The focus is on the orbitofrontal cortex in primates including humans, because of differences of operation of the orbitofrontal cortex, and indeed of reward systems, in rodents. Finally, the hypothesis is developed that the orbitofrontal cortex has a special role in emotion and decision-making in part because as a cortical area it can implement attractor networks useful in maintaining reward and emotional states online, and in decision-making.
Introduction

Advances in our understanding of the orbitofrontal cortex are described here, and include the following. First, the orbitofrontal cortex includes the medial orbitofrontal cortex areas 13 and 11, and the lateral orbitofrontal cortex, area 12, as shown in Fig. 1. Conclusions about the functions of the orbitofrontal cortex cannot be established by considering only one part of it, the medial orbitofrontal cortex areas 13 and 11 (Rudebeck et al., 2013). Further, some authors have termed a region that includes the lateral orbitofrontal cortex area 12 the ‘ventrolateral prefrontal cortex’ (Rudebeck et al., 2017), and that terminology has clouded the issue in such studies of the functions of the lateral orbitofrontal cortex, area 12. Dividing the orbitofrontal cortex into a medial part (areas 13 and 11) and a lateral part (area 12) (based on its architectonics, Fig. 1) is useful, for connectivity-based parcellations show differences in the connectivity of these parts in humans (Du et al., 2020a, Hsu et al., 2020).

A second key point made is that this distinction between the human medial and lateral orbitofrontal cortex is important functionally: the lateral orbitofrontal cortex, area 12 shown in Fig. 1, is implicated in the effects of aversive and subjectively unpleasant stimuli, and in not receiving expected rewards (termed ‘non-reward’) when a reward choice must be reversed, and has increased functional connectivity in depression. In contrast, the medial orbitofrontal cortex, areas 13 and 11 in Fig. 1, is activated by rewarding and subjectively pleasant stimuli, and has reduced functional connectivity in depression. This difference is supported by recent investigations in for example a monetary Win vs NoWin task (Xie et al., 2020).

A third key advance is in understanding the connectivity of the human orbitofrontal cortex using both tractography (Hsu et al., 2020) and functional connectivity (Du et al., 2020a), showing for example that the medial orbitofrontal cortex is connected especially with the reward-related pregenual anterior cingulate cortex, and the lateral orbitofrontal cortex and its closely related orbitofrontal part of the inferior frontal gyrus is connected especially with the non-reward and punishment-related supracallosal part of the anterior cingulate cortex. This is relevant to increasing understanding that the orbitofrontal is a key brain region involved in reward value and its rapid updating in even one trial when the reward value changes, and sends this information to the anterior cingulate cortex for actions to be learned guided by the reward or non-reward outcomes received (Rolls, 2019b).

A fourth key advance included here is that the anterior cingulate cortex can be conceptualized as receiving information about reward outcomes from the orbitofrontal cortex, and the posterior cingulate cortex as receiving information from the parietal cortex about actions just performed, providing the signals needed for action-outcome goal-related learning, and sending outputs to premotor areas from the mid-cingulate cortex (Rolls, 2019b).

A fifth set of key advances described here is in understanding the functions of the orbitofrontal cortex in mental disorders including depression by using voxel-level analyses of functional connectivity in many recent large-scale studies. Indeed, it is a key aim of this paper to highlight the potential importance of the orbitofrontal cortex, as a key brain region involved in emotion, in understanding and treating depression.

A sixth key feature of this paper is the increasing evidence that the human and non-human primate orbitofrontal cortex, with its importance for reward representations and very rapid updating of these that is important to social behavior, is very different from the rodent orbitofrontal cortex, for the rodent orbitofrontal cortex, and the whole organization of reward processing in the rodent brain, is very different (Rolls, 2019c, Rolls, 2021a). Partly for his reason, a feature of this paper is that it focusses on the evidence from both humans and foundational studies in non-human primates, because of similarities in their orbitofrontal cortex systems, and their differences from the processing in rodents.

This paper refers to some of the key concepts developed in The Orbitofrontal Cortex (Rolls, 2019c), and has a different focus to an earlier paper published in 2017 (Rolls, 2019d).

We start by describing new evidence on the connections of the orbitofrontal cortex and its functions in reward and emotion, and then consider new evidence on how differences in orbitofrontal cortex function are related to depression.

The orbitofrontal cortex is a key brain region in reward value, mood and emotion

The connections of the orbitofrontal cortex

The orbitofrontal cortex cytoarchitectonic areas of the human brain are shown in Fig. 1 (left). The medial orbitofrontal cortex includes areas 13 and 11 (Öngür et al., 2003). The lateral orbitofrontal cortex includes area 12
The anterior cingulate cortex includes the parts shown in Fig. 1 (right) of areas 32, 25 (subgenual cingulate), and 24. The ventromedial prefrontal cortex includes areas 14 (gyrus rectus), 10m and 10r.

Some of the main connections of the orbitofrontal cortex in primates are shown schematically in Fig. 2 (Carmichael and Price, 1994, Barbas, 1995, Carmichael and Price, 1995, Petrides and Pandya, 1995, Pandya and Yeterian, 1996, Ongür and Price, 2000, Price, 2006, Barbas, 2007, Price, 2007, Saleem et al., 2008, Mackey and Petrides, 2010, Petrides et al., 2012, Saleem et al., 2014, Henssen et al., 2016, Rolls, 2017, Rolls, 2019d, Rolls, 2019c). The orbitofrontal cortex receives inputs from the ends of the ventral cortical streams that process the identity of visual, taste, olfactory, somatosensory, and auditory stimuli (Rolls, 2019c). At the ends of each of these cortical processing streams, the identity of the stimulus is represented independently of its reward value. This is shown by neuronal recordings in primates (Rolls, 2019c). For example, the inferior temporal cortex represents objects and faces independently of their reward value as shown by visual discrimination reversal and devaluation of reward tests by feeding to satiety (Rolls et al., 1977, Rolls, 2012a, Rolls, 2016a, Rolls, 2019c). Similarly, the insular primary taste cortex represents what the taste is independently of its reward value (Yaxley et al., 1988, Rolls, 2015, Rolls, 2016b, Rolls, 2019c).

Outputs of the orbitofrontal cortex reach the anterior cingulate cortex (Rolls, 2019b), the striatum, the insula, and the inferior frontal gyrus, and enable the reward value representations in the orbitofrontal cortex to influence behaviour (Fig. 2, green). The orbitofrontal cortex projects reward value information to the anterior cingulate cortex, where it is used to provide the reward outcomes for action-outcome learning (Rushworth et al., 2012, Rolls, 2019c, Rolls, 2019b). The orbitofrontal cortex projects reward-related information to the ventral striatum (Williams et al., 1993), and this provides a route, in part via the habenula, for reward-related information to reach the dopamine neurons (Rolls, 2017), which respond inter alia to positive reward prediction error (Bromberg-Martin et al., 2010, Schultz, 2016a, Schultz, 2017). The striatal / basal ganglia route is used for stimulus-response, habit, learning (Everitt and Robbins, 2013, Rolls, 2014), with dopamine used to provide reward prediction error in reinforcement learning (Schultz, 2016b, Cox and Witten, 2019). As that system uses dopamine in reinforcement learning of stimulus-response habits, it is much less fast to learn than the orbitofrontal cortex (reward or punishment outcome) with anterior cingulate cortex (action) system for action-outcome goal-based learning, and for emotion (Rolls, 2021a). The orbitofrontal cortex may also have direct connections to the ventral tegmental area in mice where dopamine neurons are located (Namboodiri et al., 2019). The orbitofrontal cortex outputs to the insula include a projection to the visceros-autonomic cortex in the antero-ventral insula (Hassanpour et al., 2018) that helps to account for why the insula is activated in some tasks in which the orbitofrontal cortex is involved (Rolls, 2016b, Rolls, 2019c). The lateral orbitofrontal cortex also projects to the inferior frontal gyrus (Du et al., 2020a, Hsu et al., 2020), to a region that on the right is implicated in stopping behavior (Aron et al., 2014), and to a region on the left that includes Broca’s area (Hsu et al., 2020, Rolls, 2021a).

New evidence on the connections of the orbitofrontal cortex in humans is shown in Fig. 3, based on resting state functional connectivity in 654 participants (Du et al., 2020a). First it is shown that a parcellation based on the voxel-wise functional connectivity of orbitofrontal cortex voxels with other brain areas reveals subdivisions (Fig. 3) that are very similar to the cytoarchitectural divisions of the human orbitofrontal cortex shown in Fig. 1. Second, the lateral orbitofrontal cortex (parcels 5 and 6 in Fig. 3) has connectivity with language-related areas not only in the inferior frontal gyrus (Broca’s area), but also with the angular and supramarginal gyri. Parts of the medial orbitofrontal cortex (parcels 2-4 in Fig. 3) have connectivity with the parahippocampal gyrus, hippocampus, the temporal cortex and fusiform gyrus, the insula, and the cingulate cortex. These connectivities, as shown below, are altered in opposite directions in depression.

The connectivity of the orbitofrontal cortex analysed in humans with functional connectivity is likely to include trans-synaptic effects, but direct connections have been investigated with diffusion tractography imaging in 50 participants (Hsu et al., 2020). The medial orbitofrontal cortex and ventromedial prefrontal cortex have direct connections with the pregenual and subgenual parts of the anterior cingulate cortex, all of which are reward-related areas. The lateral orbitofrontal cortex and its closely connected right inferior frontal gyrus, has direct connections with the supracallosal anterior cingulate cortex, all of which are punishment or non-reward-related areas (Hsu et al., 2020). This confirms findings based on functional connectivity for connections between the medial orbitofrontal cortex and the pregenual cingulate cortex; and the lateral orbitofrontal cortex and related right inferior frontal gyrus with the supracallosal anterior cingulate cortex (Rolls et al., 2019, Du et al., 2020a). The lateral orbitofrontal cortex and right inferior frontal gyrus also have direct connections with the right supramarginal gyrus and inferior parietal cortex, and with some premotor cortical areas, which may provide outputs for the lateral orbitofrontal cortex and right inferior frontal
gyrus. Direct connections of the human orbitofrontal cortex and inferior frontal gyrus with the temporal lobe were especially with the temporal pole (Hsu et al., 2020).

The medial orbitofrontal cortex represents reward value; and the lateral orbitofrontal cortex represents punishers and non-reward

The primate including human orbitofrontal cortex is the first stage of cortical processing that represents reward value (red in Fig. 2) (Rolls, 2019c). For example, in devaluation experiments, taste, olfactory, visual, and oral texture neurons in the macaque orbitofrontal respond to food when hunger is present, and not after feeding to satiety when the food is no longer rewarding (Rolls et al., 1989, Critchley and Rolls, 1996). In visual discrimination reversal experiments, neurons in the macaque orbitofrontal cortex reverse the visual stimulus in as little as one trial when the reward vs punishment taste received as an outcome for the choice reverses (Thorpe et al., 1983, Rolls et al., 1996). This is rule-based reversal, in that after a previously rewarded visual stimulus is no longer rewarded, the macaques choose the other stimulus on the very next trial, even though its previous reward association was with punishment, as illustrated in Fig. 4 which also illustrates a non-reward neuron active at the time of the reversal (Thorpe et al., 1983). (Non-reward refers here to not obtaining an expected reward.) This capability requires a rule to be held in memory and reversed by non-reward (Deco and Rolls, 2005, Rolls and Deco, 2016), is very appropriate for primates which in social situations may benefit from being very responsive to non-reward vs reward signals, and may not occur in rodents (Rolls, 2019c, Hervig et al., 2020, Rolls, 2021a). The human lateral orbitofrontal cortex is activated in this one-trial rule-based non-associative reversal (Rolls et al., 2020b). The macaque orbitofrontal cortex contains neurons that reflect face expression and face identity (both necessary to decode value and important in social behaviour) (Thorpe et al., 1983, Rolls et al., 2006), and also social categories such as young faces (Barat et al., 2018) and position in the social hierarchy (Munuera et al., 2018). Economic value is represented in the orbitofrontal cortex, in that for example single neurons reflect the trade-off between the quality of a reward and the amount that is available (Padoa-Schioppa and Conen, 2017). These investigations show that some orbitofrontal cortex neurons respond to outcome value (e.g. the taste of food), and others to expected value (or future rewards), and interestingly humans with ADHD have increased sensitivity to these future rewards (Tegelbeckers et al., 2018). The expected value neurons are not positive reward prediction error neurons, for they keep responding to the expected reward even when there is no prediction error (Rolls, 2021a). Consistent with this neurophysiological evidence, lesions of the macaque medial orbitofrontal cortex areas 13 and 11 make the animals less sensitive to reward value, as tested in devaluation experiments in which the animal is fed to satiety (Rudebeck et al., 2017). (These were described as OFC lesions, but in fact included primarily the medial OFC areas 13 and 11 shown in Fig. 1.)

Neuroimaging experiments in humans (see Technical Note) produce consistent evidence about reward value representations (de Araujo et al., 2003, Kringelbach et al., 2003, Kringelbach and Rolls, 2003, Grabenhorst and Rolls, 2008, Grabenhorst et al., 2008a), and allow the types of reward to be extended to include monetary reward (O’Doherty et al., 2001, Xie et al., 2020), face expressions (Kringelbach and Rolls, 2003), and face beauty (O’Doherty et al., 2003). In humans the medial orbitofrontal cortex is activated by many rewarding stimuli and reflects their subjective pleasantness (Grabenhorst and Rolls, 2011, Rolls, 2019c). This is found for odors (Rolls et al., 2003a), flavor (de Araujo et al., 2003, Kringelbach et al., 2003), pleasant touch (Rolls et al., 2003b, McCabe et al., 2008), monetary reward (O’Doherty et al., 2001, Xie et al., 2020), and amphetamine (Völlm et al., 2004). A recent study with 1,877 participants emphasizes these points, by showing that the medial orbitofrontal cortex is activated by reward (such as winning money or candies), and that the lateral orbitofrontal cortex is activated by not winning (Fig. 5) (Xie et al., 2020). Humans with orbitofrontal cortex lesions may also be less sensitive to reward, as shown by their reduced subjective emotional feelings and altered social and emotional behavior and problems with face and voice expression processing (Rolls et al., 1994, Hornak et al., 1996, Hornak et al., 2003, Rolls, 2021b).

The macaque orbitofrontal cortex has neurons that respond when an expected reward is not received (Thorpe et al., 1983), and these have been termed non-reward neurons (Rolls, 2014, Rolls, 2019c) (see example in Fig. 4C). They can be described as negative reward prediction error neurons, in that they respond when a reward outcome is less than was expected (Rolls, 2019c). These neurons do not respond to expected punishers (e.g. the discriminative stimulus for saline in Fig. 4C; (Thorpe et al., 1983)), but other neurons do respond to expected punishers (Rolls et al., 1996), showing that non-reward and punishment are represented by different neurons in the orbitofrontal cortex. The finding of non-
reward neurons is robust, in that 18/494 (3.6%) of the neurons in the original study responded to non-reward (Thorpe et al., 1983), consistent results were found in different tasks in a complementary study (10/140 non-reward neurons in the orbitofrontal cortex or 7.1%) (Rosenkilde et al., 1981), and an fMRI study has shown that the macaque lateral orbitofrontal cortex is activated when an expected reward is not obtained during reversal (Chau et al., 2015) (Fig. 4D). The hypothesis is that these non-reward neurons are computed in the orbitofrontal cortex, because this is the first brain region in primates at which expected value and outcome value are represented, and these two signals are those required to compute non-reward, that is, reward outcome < expected value (as summarized in Fig. 2 and with the evidence set out fully by Rolls (2019c, 2021a). Corresponding to this, the human lateral orbitofrontal cortex is activated when a reward is not obtained in a visual discrimination reversal task (Kringelbach and Rolls, 2003) (Fig 4a), and when money is not received in a monetary reward task (O'Doherty et al., 2001, Xie et al., 2020), and in a one-trial rule-based reward reversal task (Rolls et al., 2020b). Consistent with this, the human lateral orbitofrontal cortex is also activated by punishing, subjectively unpleasant, stimuli (Grabenhorst and Rolls, 2011, Rolls, 2019c). Examples include unpleasant odors (Rolls et al., 2003a), pain (Rolls et al., 2003b), losing money (O'Doherty et al., 2001), and receiving an angry face expression indicating that behavior should change in a reversal (Kringelbach and Rolls, 2003). The human right lateral orbitofrontal cortex / inferior frontal gyrus is also activated when behavioural correction is required in the stop-signal task (Fig. 4B) (Deng et al., 2017). These discoveries show that one way in which the orbitofrontal cortex is involved in decision-making is by representing rewards, punishers, and errors made during decision-making. This is supported by the problems that orbitofrontal cortex damage produces in decision-making, which include failing to respond correctly to non-reward, as described next.

Consistent with this neurophysiological and neuroimaging evidence, lesions of the orbitofrontal cortex can impair behavioural changes to non-reward. For example, reward reversal learning is impaired during decision-making in humans, who continue responding to the previously rewarded, now non-rewarded, stimulus (Rolls et al., 1994, Hornak et al., 2004, Fellows, 2011). The change in contingency between the stimulus and reward vs non-reward is not processed correctly. In macaques, damage to the lateral orbitofrontal cortex impairs reversal and extinction (Butter, 1969, Iversen and Mishkin, 1970). It has been a problem in some studies of the orbitofrontal in macaques that the orbitofrontal cortex lesions have been incomplete, with for example the lesions including only the medial areas 13 and 11, and not the lateral orbitofrontal cortex area 12, with one study reporting no reversal learning deficit after such a medial lesion, and suggesting that the orbitofrontal cortex was not involved in reversal (Rudebeck et al., 2013). In the light of the above, that does not address the role of the orbitofrontal cortex in reversal learning, as including the lateral orbitofrontal cortex area 12 is highly relevant. In a more recent study, damage to the lateral orbitofrontal cortex (mainly area 12 as illustrated in Fig. 1, and extending around the inferior convexity, but described as VLPFC - ventrolateral prefrontal cortex) was found to impair the ability to make choices based on whether reward vs non-reward had been received (Rudebeck et al., 2017, Murray and Rudebeck, 2018), which is the type of contingency learning in which this brain region is implicated (Rolls, 2019c, Rolls et al., 2020b). (Unfortunately the one-trial, rule based, reversal learning in which the orbitofrontal cortex is implicated (Rolls, 2019c), was not tested in that study (Rudebeck et al., 2017)). Further evidence that the lateral orbitofrontal cortex is involved in learning contingencies between stimuli and reward vs non-reward is that in humans, lateral orbitofrontal cortex damage impaired this type of ‘credit assignment’ (Noonan et al., 2017). This type of flexibility of behaviour is important in primate including human social interactions (Rolls, 2018a, Rolls, 2019c).

The ventromedial prefrontal cortex and reward-related decision-making

The ventromedial prefrontal cortex (VMPFC, which can be taken to include the gyrus rectus area 14 and parts of 10m and 10r, Fig. 1) receives inputs from the orbitofrontal cortex, and has distinct connectivity (with strong functional connectivity with the superior medial prefrontal cortex, cingulate cortex, and angular gyrus (Du et al., 2020a)). The VMPFC has long been implicated in reward-related decision-making (Bechara et al., 1997, Bechara et al., 2005, Glascher et al., 2012), this region is activated during decision-making contrasted with reward valuation (Grabenhorst et al., 2008b, Rolls and Grabenhorst, 2008), and it has the signature of a decision-making region of increasing its activation in proportion to the difference in the decision variables, which correlates with decision confidence (Rolls et al., 2010b, Rolls et al., 2010a, Rolls, 2019c). Consistently, single neurons in the macaque ventromedial prefrontal cortex signal the value of the chosen offer, suggesting that the network produces a choice (Strait et al., 2014), also consistent with the attractor model of decision-making (Rolls et al., 2010a, Rolls et al., 2010b, Rolls, 2014, Rolls, 2016a, Rolls, 2021a). The
The orbitofrontal cortex and emotion

One of the major theories of emotion is that emotions are states elicited by rewards and punishers, which are instrumental reinforcers (Rolls, 2000, Rolls, 2013b, Rolls, 2014, Rolls, 2018a) (Fig. 6). The evidence described above shows that the orbitofrontal cortex is involved in representing the reward value of stimuli (with an emphasis on the medial and mid orbitofrontal cortex areas 11 and 13); and is involved in learning associations between stimuli and rewards, and rapidly correcting these (with an emphasis on the lateral orbitofrontal cortex area 12 and the closely connected orbital part of the inferior frontal gyrus) (Rolls, 2018a, Rolls, 2019c). In this context, the theory of emotion holds that the role of the orbitofrontal cortex in emotion is to decode the reward / punishment goals for action, by representing reward value, and by learning about stimuli with reward vs non-reward contingencies, and then to transmit the resulting representations to further brain regions (such as the cingulate cortex) which implement the learning of actions to obtain the reward outcomes signaled by the orbitofrontal cortex (Rolls, 2019b, Rolls, 2019a, Rolls, 2021a). In accordance with this, the rewarding and punishing stimuli described above are all affective stimuli, and activate the orbitofrontal cortex; and orbitofrontal cortex damage impairs subjective emotional states (Hornak et al., 2003, Rolls, 2019c), emotional responses to stimuli such as face and voice expression (Hornak et al., 1996, Hornak et al., 2003), and emotional and social behaviour with the neurological evidence described in more detail elsewhere (Rolls, 2019c, Rolls, 2021b). Further, activations in the orbitofrontal cortex are linearly related to the subjective pleasantness (i.e. affective experience) of stimuli, as described above, and elsewhere in more detail (Rolls, 2019c). The brain bases of subjective experience are a topic of considerable current interest, not only with higher order thought (HOT) theories (Rosenthal, 2004, Brown et al., 2019), but also with the higher order syntactic thought (HOST) theory of consciousness (Rolls, 2007, Rolls, 2012b, Rolls, 2014, Rolls, 2016a, Rolls, 2018a, Rolls, 2020) which is more computationally specific and addresses the adaptive value of the type of processing related to consciousness. The point made here is that the orbitofrontal cortex is at least on the route to human subjective experience of emotion and affective value (Rolls, 2019c).

Although the amygdala has many of the same connections as the orbitofrontal cortex (see Fig. 2), it is an evolutionarily old brain region, and appears to be overshadowed by the orbitofrontal cortex in humans, in that the effects of damage to the human amygdala on emotion and emotional experience are much more subtle (Whalen and Phelps, 2009, Delgado et al., 2011, LeDoux and Pine, 2016, LeDoux et al., 2018) than of damage to the orbitofrontal cortex (Rolls et al., 1994, Hornak et al., 1996, Hornak et al., 2003, Hornak et al., 2004, Camille et al., 2011, Fellows, 2011, Rolls, 2019c). Indeed, LeDoux and colleagues have emphasized the evidence that the human amygdala is rather little involved in subjective emotional experience (LeDoux and Pine, 2016, LeDoux and Brown, 2017, LeDoux et al., 2018). That is in strong contrast to the orbitofrontal cortex, which is involved in subjective emotional experience, as shown by the evidence just cited. The orbitofrontal cortex provides the answer to LeDoux’s conundrum: if not the amygdala for subjective emotional experience, then what? Further, consistent with the poor rapid reversal learning found by amygdala neurons (Sanghera et al., 1979, Rolls, 2014) compared to orbitofrontal cortex neurons, it has been found that neuronal responses to reinforcement predictive cues in classical conditioning update more rapidly in the macaque orbitofrontal cortex than amygdala, and activity in the orbitofrontal cortex but not the amygdala was modulated by recent reward history (Saez et al., 2017). Neurons that are sensitive to the rank of the individual being viewed in the social hierarchy are found not only in the macaque amygdala, but also in the closely connected orbitofrontal cortex, and anterior cingulate cortex (Munuera et al., 2018). In addition, it has been shown in the macaque that amygdala neurons are involved in social, observational learning in a reversal learning task, and that some neurons even predicted the choices of the partner monkey (Grabenhorst et al., 2019). These processes - assessing the social rank of individuals, learning from social partners, anticipating their behaviour - are critical for social life. However, the balance may shift towards the orbitofrontal cortex in humans, in that it is orbitofrontal cortex damage in humans that produces profound changes in social and emotional behavior, and subjective emotional experience, as well as in reward reversal learning (Rolls et al., 1994, Hornak et al., 1996, Hornak et al., 2003, Berlin et al., 2004, Hornak et al., 2004, Berlin et al., 2005, Rolls, 2019c).
**The rodent orbitofrontal cortex, and reward systems**

The focus in this paper is on evidence from primates including humans. The reason for this focus is that the rodent orbitofrontal cortex (Schoenbaum *et al.*, 2009, Wilson *et al.*, 2014, Sharpe *et al.*, 2015, Izquierdo, 2017, Sharpe *et al.*, 2019), and the whole operation of reward systems in rodents, appears to be somewhat different from that in primates including humans (Rolls, 2019c, Rolls, 2021a), as follows.

First, the rodent orbitofrontal cortex contains only agranular cortex, which corresponds to only a small region of the primate orbitofrontal cortex, posteriorly (Wise, 2008, Passingham and Wise, 2012, Passingham, 2021), and these authors provide evidence that there is no equivalent in rodents of most of the primate orbitofrontal cortex.

Second, the connectivity of the rodent reward systems including the orbitofrontal cortex is so different from that of primates that the principles of operation appear to be very different. One example is the taste system, which in primates proceeds mainly via thalamo-cortical processing through a primary taste cortex in the insula to the orbitofrontal cortex, whereas instead rodents have a pontine taste area which projects taste information to many subcortical areas (Scott and Small, 2009, Small and Scott, 2009, Rolls, 2015, Rolls, 2016b, Rolls, 2019c). A second example is that with the great development of the temporal lobe in primates, visual processing becomes highly elaborated and transmits information about face identity and face expression to the orbitofrontal cortex, where it can be used in emotional and social behaviour appropriate for different individuals given the face expression and gestures (including face view) of each individual (Rolls, 2016b, Rolls, 2019c). A third example is that because the visual representation in primates includes processing to the level of view-invariant representations of objects and faces, reward value-related learning in the orbitofrontal cortex is efficient, for after a value association is made to one view, it generalizes to other views or transforms (Rolls, 2012a, Rolls, 2016b, Rolls, 2021a).

Third, in rodents, reward value as indicated in devaluation (satiety) studies involves reward processing even far peripherally in the first central relay, the nucleus of the solitary tract for taste (Giza and Scott, 1983, Giza and Scott, 1987, Giza *et al.*, 1992), and the olfactory bulb for odor (Pager *et al.*, 1972) making these complex systems as reward and identity processing about taste and odor are entangled throughout the system with each other. In another example, in reward reversal in mice, the orbitofrontal cortex has reward-related top-down effects on the primary somatosensory cortex (Banerjee *et al.*, 2020). This makes reward processing in rodents difficult to analyse. In contrast, in primates and humans, there is a clear separation between perceptual representations (Tier 1 in Fig. 2), and reward value representations in the orbitofrontal cortex and amygdala (Tier 2 in Fig. 2) (Rolls, 2015, Rolls, 2016a, Rolls, 2019c, Rolls, 2021a).

Fourth, although reward value is represented in the rodent (agranular) orbitofrontal cortex, so also apparently are behavioural responses (Schoenbaum *et al.*, 2009, Wilson *et al.*, 2014, Sharpe *et al.*, 2015, Izquierdo, 2017, Sharpe *et al.*, 2019), which makes the rodent orbitofrontal cortex very different to the primate orbitofrontal cortex. The primate orbitofrontal cortex in contrast appears to specialize in reward (and of course punishment and non-reward) value representations, but not in interfacing these value representations to actions (which occurs in the primate cingulate cortex (Rolls, 2019b, Rolls, 2021a)) or to responses (which occurs in the striatum and other parts of the basal ganglia), for actions and responses are poorly if at all represented in the primate orbitofrontal cortex (Thorpe *et al.*, 1983, Padoa-Schioppa and Assad, 2006, Grattan and Glimcher, 2014, Rolls, 2019c). In contrast, in rodents, the orbitofrontal cortex seems much more heterogeneous with behavioural responses also represented in it (Wilson *et al.*, 2014, Sharpe *et al.*, 2015, Sharpe *et al.*, 2019), and again, the system is more complex because different computations are apparently intermingled in the same brain region. Although it is interesting that in the mouse, neurons in LO represent the values of individual options, the binary choice outcome, and the chosen value, this is in the context of spatial responses (Kuwabara *et al.*, 2020), not of the value of goods as in primates.

Fifth, although reward reversal learning is studied in rodents (Hervig *et al.*, 2020), it does not so far appear to be of the same powerful type as the rule-based system present in primates, which allows switching to a different stimulus even previously associated with punishment when no reward is received when it was expected by a behavioural choice on a single trial (Thorpe *et al.*, 1983, Rolls *et al.*, 1996, Rolls, 2019c, Rolls *et al.*, 2020b). This type of rapid, rule-based, reversal provides a foundation for rapid changes in social behaviour whenever feedback is received, and a similar rule-based system is not known to be present in rodents. This is consistent with the great development of cortical processing for these functions provided by the primate orbitofrontal cortex, given that the cortex provides a computational basis in its attractor networks for holding information online, and therefore producing behaviour that depends on ‘hidden’ internal
states, rather than being more dominated by sensory input (Rolls, 2016a, Rolls, 2021a). However, it is of interest that neurons in the rodent lateral orbitofrontal cortex respond in reward reversal, and that silencing these neurons impairs the reversal (Banerjee et al., 2020).

Because we wish the advances described here to be relevant to understanding the functions of the orbitofrontal cortex in humans, we focus here on findings in primates including humans, but further evidence on research in rodents is provided elsewhere (Izquierdo, 2017, Rolls, 2019c, Rolls, 2021a).

A theory of depression

Better understanding of the functions of the orbitofrontal cortex in major depressive disorder is important, for it 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). Moreover, the economic cost of depression is enormous, with an estimated 350 million people affected globally. For example, the cost to Europe of work-related depression was estimated to be Euro 617 billion annually in 2013 and rising (Matrix, 2013).

A theory of depression has been developed based on our understanding of the brain processes involved in emotion, reward, and non-reward described above (Rolls, 2016c, Rolls, 2018a). Given that not receiving expected rewards is a reinforcement contingency that can lead to sadness, or in the extreme case such as the loss of a loved one, depression, the theory was proposed that the lateral orbitofrontal cortex, implicated in non-reward and learning contingencies between stimuli and reward vs non-reward, over-responds to non-reward in people with depression; and that a major non-reward event that activated the lateral orbitofrontal cortex might lead to depression (Rolls, 2016c, Rolls, 2018a). Because non-reward neurons in the lateral orbitofrontal cortex can maintain their activity for at least many seconds (see Fig. 4) (Thorpe et al., 1983), and because this persistent activity is needed to ensure that after non-reward, the behavior changes even if the same stimuli are not received for some time, the theory is that there is a non-reward attractor network in the lateral orbitofrontal cortex, and that this is more sensitive or persistent in depression (Rolls, 2016c, Rolls, 2018a). It is postulated that the effects of the non-reward can be prolonged by rumination of sad thoughts which is supported by a long loop attractor involving language areas in the angular gyrus and related regions, which receive inputs from the lateral orbitofrontal cortex, and project back to it. The theory thus is that some aspects of depression may be related to over-responsiveness of the lateral orbitofrontal to non-reward and punishment (Rolls, 2016c, Rolls, 2018a, Rolls, 2021a). Consistent with this, increased sensitivity to non-reward (not winning in a monetary incentive delay task) of the lateral orbitofrontal cortex is associated with the severity of depressive symptoms measured in hundreds of adolescents (Xie et al., 2020).

Given that the activations of the lateral and medial orbitofrontal cortex often appear to be reciprocally related (O'Doherty et al., 2001, Rolls et al., 2003a, Xie et al., 2020), the other part of the theory is that in depression there may be underactivity, under-sensitivity, or under-connectivity of the (reward-related) medial orbitofrontal cortex in depression (Rolls, 2016c, Rolls, 2018a). The theory is further that under-responsiveness of the medial orbitofrontal cortex could contribute to other aspects of depression, such as anhedonia.

There is now much evidence that supports this theory of depression, as described in the following sections. This approach based on advances in understanding the functions of the primate including human orbitofrontal cortex also provides an approach to understanding how other brain systems such as the subgenual / subcallosal anterior cingulate cortex are implicated in depression (Mayberg et al., 2016), in that they receive inputs from the orbitofrontal cortex. This approach also adds to previous approaches relating to reward and punishment systems (Eshel and Roiser, 2010, McCabe et al., 2012, Satterthwaite et al., 2015), by being based on the theory of emotion described above and on the understanding of brain systems involved in emotion in primates including humans described above. Other contributing factors to depression are considered elsewhere (Rolls, 2018a).

Increased functional connectivity of the non-reward related lateral orbitofrontal cortex, and decreased functional connectivity of the reward-related medial orbitofrontal cortex, in depression.

This section describes many new large-scale voxel-level analyses of differences in the connectivity of the orbitofrontal cortex in depression, and this is the first review in which this new evidence is brought together. An overview of many of the new discoveries is provided in Fig. 8.
There is considerable interest in functional connectivity differences between people with major depressive disorder and controls, for increased functional connectivity could reflect increased communication between brain regions, and decreased connectivity the opposite. Functional connectivity studies have typically been performed with resting state fMRI, and the functional connectivity is measured by the correlation of the BOLD signals between pairs of brain regions. A number of studies have provided evidence for different functional connectivity that may include the orbitofrontal cortex, anterior cingulate cortex, amygdala, and hippocampus, but many of these studies have involved relatively small numbers of participants, and whole brain regions (Helm et al., 2018). Indeed, power analyses show that resting state functional connectivity for individual links in people is not robust with small samples (Button et al., 2013, Poldrack, 2019), especially in populations with psychiatric disorders, as we also have found. The studies described next have therefore focused on large numbers of participants to provide robust results, and on voxel-level analysis to enable separation of connectivity of nearby brain areas such as the medial and lateral orbitofrontal cortex. In addition, the studies considered next also have the advantage that in several it was possible to perform neuroimaging in a large sample of unmedicated patients, and to compare the functional connectivity with that in medicated patients. Descriptions of some of the studies in which this has been possible are provided next.

**A brain-wide analysis of voxel-level differences in functional connectivity implicates the lateral and medial orbitofrontal cortex in depression**

In the first brain-wide voxel-level resting state functional connectivity neuroimaging analysis of depression (with 421 patients with major depressive disorder and 488 controls), we found that one major circuit with altered functional connectivity involved the medial orbitofrontal cortex BA 13, which had reduced functional connectivity in depression with memory systems in the parahippocampal gyrus and medial temporal lobe (Cheng et al., 2016) (Fig. 7). 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 connectivity with the medial temporal lobe memory system.

A second major circuit change was that the lateral orbitofrontal cortex area BA 47/12 had increased functional connectivity with the precuneus, the angular gyrus, and the temporal visual cortex BA 21 (Cheng et al., 2016) (Fig. 7). This enhanced functional connectivity of the non-reward/punishment system (BA 47/12) with the precuneus (involved in the sense of self and agency (Rolls, 2021a)), and the angular gyrus (involved in language (Rolls, 2021a)) is thus related to the explicit affectively negative sense of the self, and of self-esteem, in depression.

The differences in orbitofrontal connectivity with these brain regions was related to the depression by evidence that the symptoms of depression were correlated with these differences of functional connectivity; and that the lateral orbitofrontal cortex functional connectivity links described were less high if the patients were receiving antidepressant medication (Cheng et al., 2016).

Because the lateral orbitofrontal cortex responds to many punishing and non-rewarding stimuli that are likely to elicit autonomic/visceral responses via the anteroventral insula (see above), 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, which it is (Drevets, 2007, Hamilton et al., 2013, Ma, 2015).

These advances were made possible because we performed whole-brain voxel-level functional connectivity, enabling clear separation and localization of differences between the lateral and medial orbitofrontal cortex. Further analyses which focused instead on voxel-level functional connectivity of particular brain systems has revealed much more about the different systems involved, as described next, and have provided cross-validation in a cohort from the USA (Cheng et al., 2018d).

**Precuneus: higher connectivity with the lateral orbitofrontal cortex**

The precuneus is a medial parietal cortex region implicated in the sense of self and agency, autobiographical memory, spatial function, and navigation (Cavanna and Trimble, 2006, Freton et al., 2014). The retrosplenial cortex provides connections to and receives connections from the hippocampal system, connecting especially with the parahippocampal gyrus areas TF and TH, and with the subiculum (Kobayashi and Amaral, 2003, Kobayashi and Amaral,

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To further analyze the functioning of the precuneus in depression, resting state functional connectivity was measured in 282 patients with major depressive disorder and 254 controls (Cheng et al., 2018c). In 125 patients not receiving medication, voxels in the precuneus had significantly higher functional connectivity with the lateral orbitofrontal cortex (Fig. 8). In patients receiving medication, the functional connectivity between the lateral orbitofrontal cortex and precuneus was decreased back towards that in the controls (Cheng et al., 2018c). These findings support the theory that the non-reward system in the lateral orbitofrontal cortex has increased effects on areas in which the self is represented including the precuneus, which could relate to the low self-esteem in depressed patients (Rolls, 2016c).

**Parahippocampal gyrus / medial temporal lobe memory system, and temporal lobe visual cortex: lower connectivity with the medial orbitofrontal cortex**

We found that voxels in the medial orbitofrontal cortex had lower functional connectivity with the parahippocampal gyrus / medial temporal lobe memory system (Cheng et al., 2016) (Fig. 7), and interpreted this as resulting in fewer happy memories being recalled, as the medial orbitofrontal cortex has activations that correlate with subjective pleasantness, as described above, and the parahippocampal gyrus is a pathway in the hippocampal episodic memory system (Kesner and Rolls, 2015, Rolls, 2016a, Rolls, 2018b, Rolls and Wirth, 2018, Rolls, 2019b, Rolls, 2021a). The reduced connectivity with temporal cortex areas in which objects and faces are represented was interpreted as contributing to the reduced positive valuation of signals involve in emotion such as the sight of face expressions, and of people (Hasselmo et al., 1989, Critchley et al., 2000).

In a further analysis that also investigated the effects of antidepressant medication (Rolls et al., 2020a), medial orbitofrontal cortex voxels had lower functional connectivity with temporal cortex areas, the parahippocampal gyrus, fusiform gyrus, and supplementary motor area, and medication did not result in these functional connectivities being closer to controls. This is consistent with the anhedonia of depression and reduced happy memories being related to these low functional connectivities of the medial orbitofrontal cortex with temporal lobe and memory systems. What is especially interesting is that these low functional connectivities are not normalized by treatment with antidepressant drugs (Rolls et al., 2020a), suggesting that one goal of future treatment for depression might be to increase the functionality of the medial orbitofrontal cortex.

**Posterior cingulate cortex: higher functional connectivity with the lateral orbitofrontal cortex**

The posterior cingulate cortex is a region with strong connectivity in primates with the entorhinal cortex and parahippocampal gyrus (areas TF and TH), and thus with the hippocampal memory system (Vogt, 2009, Bubb et al., 2017, Rolls, 2018b, Rolls and Wirth, 2018, Rolls, 2019c, Rolls, 2019b, Rolls, 2021a). The posterior cingulate cortex also has connections with the orbitofrontal cortex (Vogt and Pandya, 1987, Vogt and Laureys, 2009), and the posterior cingulate cortex has high functional connectivity with the parahippocampal regions that are involved in memory (Cheng et al., 2018b, Rolls, 2019b). The posterior cingulate region (including the retrosplenial cortex) is consistently engaged by a range of tasks that examine episodic memory including autobiographical memory, and imagining the future; and also spatial navigation and scene processing (Auger and Maguire, 2013, Leech and Sharp, 2014). Self-reflection and self-imagery activate the ventral part of the posterior cingulate cortex (vPCC, the part with which we will be mainly concerned here) (Kircher et al., 2000, Johnson et al., 2002, Kircher et al., 2002, Sugiura et al., 2005).

A study with 15 patients and 15 controls had implicated functional connectivity of the posterior cingulate with the subgenual cingulate cortex to rumination in depression (Berman et al., 2011), but we find that functional connectivity in people with psychiatric disorders is not robust with small samples. Therefore to analyze the functioning of the posterior cingulate cortex in depression, we performed a fully voxel-level resting-state functional connectivity neuroimaging analysis of depression of the posterior cingulate cortex, with 336 patients with major depressive disorder and 350 controls (Cheng et al., 2018b). In depression, the posterior cingulate cortex had significantly higher functional connectivity with the lateral orbitofrontal cortex (Fig. 8). In patients receiving medication, the functional connectivity between the lateral orbitofrontal cortex and the posterior cingulate cortex was decreased back towards that in the controls. These findings are consistent with the hypothesis that the non-reward system in the lateral orbitofrontal cortex has increased effects on memory systems, which contribute to the rumination about sad memories and events in depression (Cheng et al., 2018b).

2007, Bubb et al., 2017). The precuneus provides access to the hippocampus for spatial information from the parietal cortex (given the rich connections between the precuneus and parietal cortex) (Rolls and Wirth, 2018, Rolls, 2021a).
Anterior cingulate cortex: reduced connectivity with the orbitofrontal cortex in depression

The orbitofrontal cortex projects to the anterior cingulate cortex (Vogt, 2009, Rolls, 2019b, Vogt, 2019). The supracallosal anterior cingulate cortex is activated by many aversive stimuli (Grabenhorst and Rolls, 2011, Rolls, 2014, Rolls, 2019b), and has strong connectivity with the lateral orbitofrontal cortex and adjoining part of the inferior frontal gyrus (Rolls et al., 2019, Du et al., 2020a, Hsu et al., 2020). The pregenual cingulate cortex is activated by many pleasant, rewarding, stimuli (Grabenhorst and Rolls, 2011, Rolls, 2014, Rolls, 2019b), and has strong functional connectivity with the medial orbitofrontal cortex (Rolls et al., 2019, Du et al., 2020a, Hsu et al., 2020). However, the anterior cingulate cortex appears to be involved in learning actions to obtain rewards (action-outcome learning), where the outcome refers to the reward or punisher for which an action is being learned (Rudebeck et al., 2008, Camille et al., 2011, Rushworth et al., 2011, Rushworth et al., 2012, Rolls, 2019c, Rolls, 2019b). In contrast, the medial orbitofrontal cortex is involved in reward-related processing and learning, and the lateral orbitofrontal cortex in non-reward and punishment-related processing and learning (Rolls, 2019c). These involve stimulus-stimulus associations, where the second stimulus is a reward (or its omission), or a punisher (Rolls, 2019c). Given that emotions can be considered as states elicited by rewarding and punishing stimuli, and that moods such as depression can arise from prolonged non-reward or punishment (Rolls, 2016c, Rolls, 2018a, Rolls, 2019c), the part of the brain that processes these stimulus-reward associations, the orbitofrontal cortex, is more likely to be involved in depression than the action-related parts of the cingulate cortex. However, the action-related parts of the cingulate cortex, and other regions related to action such as the right inferior frontal gyrus, could contribute to the motor-related slowing, fatigue, and decreased energy that are all symptoms commonly seen in depressed individuals (Rolls et al., 2020a).

The subgenual (or subcallosal) cingulate cortex has been implicated in depression, and electrical stimulation in that region may relieve depression (Mayberg, 2003, Hamani et al., 2009, Hamani et al., 2011, Lozano et al., 2012, Laxton et al., 2013, Lujan et al., 2013) (although it has not been possible to confirm this in a double-blind study (Holtzheimer et al., 2017)). However, the subgenual cingulate cortex is also implicated in autonomic function (Gabbott et al., 2003), and this could be related to some of the effects found in this area that are related to depression. Whether the subgenual cingulate cortex is activated because of inputs from the orbitofrontal cortex, or performs separate computations is not yet clear. Further, the possibility is considered that electrical stimulation of the subcallosal region, which includes parts of the ventromedial prefrontal cortex (Laxton et al., 2013), that may relieve depression, may do so at least in part by activating connections involving the orbitofrontal cortex, other parts of the anterior cingulate cortex, and the striatum (Johansen-Berg et al., 2008, Hamani et al., 2009, Lujan et al., 2013).

In a recent study of depression, overall the anterior cingulate cortex had significantly reduced functional connectivity with the orbitofrontal cortex, temporal lobe areas, the parahippocampal gyrus and hippocampus, and motor areas (Fig. 8) (Rolls et al., 2019). This is consistent with the hypothesis that the anterior cingulate cortex, with its representations of rewards and punishers received from the orbitofrontal cortex and which is involved in interfacing these to action systems (Rolls, 2019b), may relate to depression by a disconnection of rewards and punishers from their action-related and other outputs. The hypothesis is that this disconnection contributes to the insensitivity to the effects of rewards and punishers, amotivational states, and feelings of helplessness than can be present in depression (Rolls et al., 2019).

Inferior frontal gyrus: increased connectivity with the lateral orbitofrontal cortex in depression

The lateral orbitofrontal cortex projects to the inferior frontal gyrus, and, very interestingly, higher functional connectivity was found in depression of voxels in the right inferior frontal gyrus with voxels in the lateral and medial orbitofrontal cortex, cingulate cortex, inferior and middle temporal gyrus and temporal pole, the angular gyrus, precuneus, hippocampus and mid- and superior frontal gyrus (Rolls et al., 2020a) (Fig. 8). In medicated patients these functional connectivities of the inferior frontal gyrus were lower and towards those in controls.

The hypothesis was proposed that one way in which the orbitofrontal cortex influences behavior in depression is via the right inferior frontal gyrus, which projects in turn to premotor cortical areas (Du et al., 2020a). Consistent with the consequent hypothesis that the inferior frontal gyrus route may allow non-reward signals to have too great an effect to inhibit behavior in depression, lesions of the right inferior frontal gyrus impair stopping in the stop-signal task, and produce impulsiveness (Aron et al., 2004, Aron et al., 2014). Also consistent with the hypothesis, successful stopping in

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the stop-signal task is associated with high activation of the inferior frontal gyrus and lateral orbitofrontal cortex (Deng et al., 2017).

**Amygdala: reduced connectivity with the orbitofrontal cortex in depression**

The amygdala is involved in emotion, though as shown above it may be overshadowed in humans by the orbitofrontal cortex (LeDoux and Pine, 2016, Rolls, 2019c). Some relatively small-scale studies had shown different functional connectivity of the amygdala in depression (Connolly et al., 2017, Helm et al., 2018). In a large scale study of depression, amygdala voxels had decreased functional connectivity with the medial orbitofrontal cortex (involved in reward); the lateral orbitofrontal cortex (involved in non-reward and punishment); temporal lobe areas (involved in visual and auditory perception including face expression analysis (Perrett et al., 1982, Leonard et al., 1985, Rolls, 2011, Rolls, 2012a)); and the parahippocampal gyrus (involved in memory) (Fig. 8) (Cheng et al., 2018a). This disconnectivity of the amygdala may contribute to the depression.

**Sleep, depression, and increased lateral orbitofrontal cortex connectivity**

Sleep is frequently impaired in depression (Becker et al., 2017). To advance understanding of the brain regions involved in sleep and depression, the relation between functional connectivity, depressive symptoms (the Adult Self-Report Depressive Problems scores), and poor sleep quality was measured in 1,017 participants from the general population in the Human Connectome Project (Cheng et al., 2018d). The brain areas with increased functional connectivity of these common links related to both sleep and depressive scores included the lateral orbitofrontal cortex; the dorsolateral prefrontal cortex; the anterior and posterior cingulate cortex; the insula; the parahippocampal gyrus and hippocampus; the amygdala; the temporal cortex; and the precuneus. A mediation analysis showed that these functional connectivities in the brain contribute to the relation between depression and poor sleep quality.

Evidence was also found in this general population that the Depressive Problems scores were correlated with functional connectivities between areas that included the lateral orbitofrontal cortex, cingulate cortex, precuneus, angular gyrus, and temporal cortex (Cheng et al., 2018d). Part of the importance of this is that it provides strong support for a role of the lateral orbitofrontal cortex in depression in a general population in the U.S.A. in which a tendency to have depressive problems could be assessed. This cross-validation in a completely different population and in people not selected to have depression (Cheng et al., 2018d) provides support for the theory that the lateral orbitofrontal cortex is a key brain area that might be targeted in the search for treatments for depression (Rolls, 2016c). Low sleep duration and depression are also related to structural differences of the orbitofrontal cortex (Cheng et al., 2020). In particular, higher depressive problems’ scores were associated with reduced cortical areas or volumes of brain regions that included the lateral and medial orbitofrontal cortex, temporal cortex, precuneus, superior and middle frontal gyrus and superior medial frontal cortex, angular and supramarginal gyrus, and hippocampus (Cheng et al., 2020).

**Effective connectivity in depression**

Effective connectivity measures the effect of one brain region on another in a particular direction, and can in principle therefore provide information related to the causal processes that operate in brain function, that is, how one brain region influences another.

In a resting state fMRI investigation, effective connectivity directed to the medial orbitofrontal cortex from areas including the parahippocampal gyrus, temporal pole, inferior temporal gyrus, and amygdala was decreased in depression (Rolls et al., 2018). This implies less strong positive driving influences of these input regions on the medial and middle orbitofrontal cortex, regions implicated in reward, and thus helps to elucidate part of the decreased feelings of happy states in depression (Rolls, 2016c). The links from temporal cortical areas to the precuneus were increased in depression, and this may relate to representations of the sense of self (Cavanna and Trimble, 2006), which become more negative in depression (Cheng et al., 2016, Rolls, 2016c). The lateral orbitofrontal cortex, implicated in non-reward and punishment, had an increased level of activity as reflected in the model in the depressed group. In addition, activity in the model was also higher in the right and left hippocampus of patients with depression, implying heightened memory-related processing (Rolls et al., 2018).

**Orbitofrontal cortex activations to reward and non-reward in depression**

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Reinforcement learning approaches

Depression has been investigated in the framework of reinforcement learning, using in particular the learning rate coefficient and the sensitivity to reward. In earlier studies, it was reported that depression reduces prediction errors during reinforcement learning (Kumar et al., 2008, Gradin et al., 2011), but Rutledge et al (2017) found that prediction error was unchanged in the ventral striatum. On that basis, they suggested that depression does not affect the expression of dopaminergic reward prediction errors. Their study was consistent with evidence that reward sensitivity and not learning rates are reduced in anhedonic depression (Huys et al., 2013, Chen et al., 2015). Also within the reinforcement learning framework, it was found that positive reward prediction error in the medial orbitofrontal cortex is reduced in depression, and was correlated with anhedonia, but the learning was intact, in 28 drug naïve patients with depression (Rothkirch et al., 2017).

Increased activations to non-reward of the lateral orbitofrontal cortex, and decreased sensitivity to reward of the medial orbitofrontal cortex, are related to depression scores

In 1,140 adolescents at age 19 and 1,877 at age 14 in the monetary incentive delay task, the medial orbitofrontal cortex had graded increases in activation as the reward (Win) value increased (Xie et al., 2020). The lateral orbitofrontal cortex had graded increases of activation as the reward value dropped to zero (the No-Win condition) (Fig. 5).

In a subgroup with a high score on the Adolescent Depression Rating Scale at age 19 and 14, the medial orbitofrontal cortex activations had reduced sensitivity to the different reward conditions; and the lateral orbitofrontal cortex activation showed high activation to the No-Win (i.e. Non-reward) condition (Xie et al., 2020). These new findings provide support for the hypothesis that those with symptoms of depression have increased sensitivity to non-reward in the lateral orbitofrontal cortex, and decreased sensitivity for differences in reward of the medial orbitofrontal cortex. Moreover, these differences are evident at an age as early as 14 years old (Xie et al., 2020). This result thus supports the theory that depressive symptoms can be related to sensitivity to non-reward (Rolls, 2016c, Rolls, 2018a), that is, to not winning in this monetary reward task.

Possible structural differences in the orbitofrontal cortex in depression

For completeness, we note that there is some evidence for altered structure and function of the lateral orbitofrontal cortex in depression (Drevets, 2007, Price and Drevets, 2012, Ma, 2015). For example, reductions of grey-matter volume have been demonstrated specifically in the posterolateral OFC (BA 47, caudal BA 11 and the adjoining BA 45), and also in the subgenual cingulate cortex (BA 24, 25) (Nugent et al., 2006, Drevets, 2007, Griève et al., 2013). Meta-analyses revealed that depressed patients showed large volume reductions in frontal regions, especially in the anterior cingulate and orbitofrontal cortex (Koolschijn et al., 2009, Lorenzetti et al., 2009).

In recent large-scale studies with the Adolescent Brain Cognitive Developmental (ABCD) dataset, it has been found that a number of factors are associated with psychiatric problems including the depressive problems score, and with reduced brain volume. The brain regions with reduced volume include the orbitofrontal cortex, hippocampus, temporal cortex, and medial frontal cortex. The factors that are associated with these differences are low maternal age (Du et al., 2020b), problems in the family (Gong et al., 2020), severe nausea and vomiting in pregnancy (Wang et al., 2020), and low sleep duration (Cheng et al., 2020).

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), but convergence across studies is not strong (Gray et al., 2020).

The orbitofrontal cortex and possible treatments for depression, including new areas for brain stimulation

In research stimulated by the theory (Rolls, 2016c), it has been reported that transcranial magnetic stimulation of the right lateral orbitofrontal cortex, which may disrupt its activity, helps in the treatment of depression in a substantial proportion of patients (Feffer et al., 2018, Downar, 2019).

Treatment with antidepressant drugs decreases the activity (Ma, 2015) and functional connectivity (Cheng et al., 2016, Cheng et al., 2018b, Cheng et al., 2018c, Rolls et al., 2019, Rolls et al., 2020a) of the non-reward lateral
orbitofrontal cortex system. The research described suggests that a search for new treatments that would increase the connectivity of the reward-related medial orbitofrontal cortex could be helpful, because current medications do not ameliorate these reduced functional connectivities.

Deep brain stimulation of the orbitofrontal cortex may also be useful in the treatment of mood disorders and depression. The macaque orbitofrontal cortex is a key brain site at which deep brain electrical stimulation is rewarding (Rolls et al., 1980, Rolls, 2005, Rolls, 2019c). Electrical stimulation of the human orbitofrontal cortex can also produce reward and raise mood (Rao et al., 2018), and many of the sites were in the middle part of the orbitofrontal cortex, areas 13 and 11, which are categorised as medial orbitofrontal cortex, the area activated by rewards (Rolls, 2019c). It is likely that these medial orbitofrontal cortex sites will produce better reward in humans than stimulation in the lateral orbitofrontal cortex BA12/47, for these lateral sites are activated by unpleasant stimuli and by not obtaining expected rewards. The medial (/ middle) orbitofrontal cortex may for the reasons described here and elsewhere (Rolls, 2019c) be a key area of interest for deep brain stimulation to help relieve depression.

The anterior cingulate cortex, including the subcallosal cingulate cortex, is a key brain region to which the orbitofrontal cortex projects (Rolls, 2019b). It is possible that brain stimulation of the subcallosal cingulate cortex might be useful in the treatment of at least some patients with depression (Johansen-Berg et al., 2008, Lujan et al., 2013, Dunlop et al., 2017, Holtzheimer et al., 2017, Riva-Posse et al., 2018), and it is possible that the subcallosal cingulate stimulation affects pathways that connect with the orbitofrontal cortex (Johansen-Berg et al., 2008, Lujan et al., 2013, Dunlop et al., 2017, Riva-Posse et al., 2018). Given that the anterior cingulate cortex is an output region of the orbitofrontal cortex (see Fig. 1), it may be that treatments of the orbitofrontal cortex, where the emotion is implemented, may be a better target for potential treatments for depression.

The general approach to depression described here, that it relates to effects produced by increased non-reward or non-reward sensitivity, or decreased reward or reward sensitivity (Fig. 6), has implications for self-help and behavioural treatments for depression (Rolls, 2018a), as well as for medical interventions.

What are the special computational roles of the orbitofrontal cortex in reward, emotion, and decision-making?

It is important in terms of our understanding of brain function to consider what is special about the primate including human orbitofrontal cortex for reward, decision-making, and emotion, compared to other brain regions. This invites an answer about what is special about the computations performed by the orbitofrontal cortex compared to other brain regions (Rolls, 2016a, Rolls, 2019c, Rolls, 2021a).

First, the orbitofrontal cortex, as a neocortical area, has highly developed recurrent collateral connections between its pyramidal cells, which together with associative synaptic plasticity, provide the basis for autoassociation or attractor networks (Rolls, 2016a, Rolls, 2021a). (The amygdala in contrast has little recurrent collateral connectivity (Millhouse and DeOlmos, 1983).)

These attractor networks provide the basis for short-term memory functions, by maintaining neuronal firing in a stable attractor (Rolls, 2021a). These attractor networks can hold on-line which stimuli (and this could be other individuals) are currently rewarding, which is important for social interactions and economic decisions. This memory capability is an important component of rule-based one-trial reversal, in which the current rule must be held in short-term memory (Deco and Rolls, 2005). Short-term memory is also potentially very useful for holding mood online for some time, so that if for example a reward is not received, the non-reward state of frustration can lead to continuing attempts to regain the reward. Similar short-term memory processes might enable one to remember the recent reinforcement history of individuals, and again can be important in decision-making. The short-term memory aspects of these attractor networks are also important for holding the expected value online, until the reward outcome is received, after which non-reward neurons may be activated in ways for which there is a computational model (Rolls and Deco, 2016), and such computations may also contribute to reward prediction error, defined as the reward outcome value minus the expected reward. The short-term memory also provides the biasing system for top-down attention to reward value (Grabenhorst and Rolls, 2008, Rolls et al., 2008, Grabenhorst and Rolls, 2010, Ge et al., 2012, Luo et al., 2013), and attention by biased activation (Rolls, 2013a, Rolls, 2021a).

These attractor networks in the orbitofrontal cortex and ventromedial prefrontal cortex also provide the basis for reward-related decision-making, in which inputs to two competing attractor states in an attractor network lead to a bifurcation and to a decision (Rolls and Deco, 2010, Rolls et al., 2010b, Rolls et al., 2010a, Deco et al., 2013, Rolls,
2021a). Part of the utility of this approach to decision-making is that once the decision has been taken in the attractor network, the results of the decision are kept active in the decision-making attractor network to provide the goals for the selection of actions by the cingulate cortex to obtain the rewards (Rolls, 2019b, Rolls, 2019c, Rolls, 2021a).

Second, the primate and human orbitofrontal cortex as a neocortical area is beautifully connected anatomically to receive inputs from representations of ‘what’ stimulus is present from every sensory modality at the top of each sensory cortical hierarchy, independently of reward value (as shown in Fig. 2), and then to compute multimodal representations that are then represented in terms of their reward value. This is very different from the rodent, in which reward is represented throughout the processing systems (Rolls, 2019c, Rolls, 2021a).

Third, the primate orbitofrontal cortex specializes in reward value, rather than action. This separation allows the value of many stimuli in the high dimensional space of different rewards (Rolls, 2014) to be represented, and for competition between them to be useful for computing relative reward value (Grabenhorst and Rolls, 2009). Moreover, mood states can be maintained, independently of any actions being performed. In contrast, as described above, the rodent ‘orbitofrontal cortex’ is also involved in motor responses and actions (Wilson et al., 2014), so can be less specialized for representing reward value, and rapidly changing it.

Fourth, the primate orbitofrontal cortex projects reward value representations to the pregenual anterior cingulate cortex, and punishment value representations to the supracallosal anterior cingulate cortex (Du et al., 2020a, Hsu et al., 2020), where they can be associated with actions performed recently, received via the posterior cingulate cortex from the parietal cortex, to implement action-outcome learning. Outputs are then directed from mid-cingulate areas to the premotor cortical areas (Rolls, 2019b). The amygdala does not have similar connectivity.

Fifth, the human lateral orbitofrontal cortex has considerable connectivity with the inferior frontal gyrus areas 45 and 44 which in the left are Broca’s area, and this may be part of the route by which the orbitofrontal cortex, especially laterally, becomes functionally connected with language areas in the posterior temporal and parietal areas (Du et al., 2020a, Hsu et al., 2020, Rolls, 2021a). This provides a route for top-down influences of language-related processing on emotional and social behavior, and indeed is part of the long-loop interactions between attractor networks that are proposed to contribute to increased rumination in depression (Cheng et al., 2016, Rolls, 2016c, Rolls, 2021a).

Conclusions

The research described here provides evidence that the primate including human orbitofrontal cortex is a key brain region in reward value representation and in emotion (Rolls, 2019c). The primate orbitofrontal cortex represents values, but not actions. Instead, the orbitofrontal cortex sends reward outcome information to the cingulate cortex for use in action-outcome goal-directed learning, both of which are therefore key to understanding emotions and goal-directed actions (Rolls, 2019b). The case is also made that the orbitofrontal cortex is a source of reward-related information that reaches the dopamine neurons in the brainstem (Rolls, 2017, Namboodiri et al., 2019) (Fig. 2), which provide for reinforcement-based learning of stimulus-response habits in the basal ganglia.

This framework provides a foundation for the proposal that because of its importance in emotion, the orbitofrontal cortex is likely to be a key brain region in emotional disorders such as depression. The new evidence from large-scale voxel-level neuroimaging studies described here shows that the reward-related medial orbitofrontal cortex has reduced functional connectivity with a number of brain systems including the medial temporal lobe memory system. Interestingly, antidepressant medications do not normalize these functional connectivities, suggesting a new avenue for exploration for new treatments for depression. The new evidence also shows that the punishment / non-reward related lateral orbitofrontal cortex and its related nearby right inferior frontal gyrus areas have increased functional connectivity in depression, which may relate to increased non-reward processing in depression. These advances, and the way in which depression can be related to altered responsiveness to non-rewards, provide an approach to the better understanding and treatment of depression (Rolls, 2016c, Rolls, 2018a, Rolls, 2019c, Rolls, 2021a). Moreover, these new approaches relate to ideas that the subgenual cingulate cortex is involved in depression, for it receives major inputs from the orbitofrontal cortex.

The research described here provides a theory supported by much empirical evidence for why and how the orbitofrontal cortex is involved in depression, and provides a complementary approach to the strong focus there has been on the subgenual or subcommissural cingulate cortex in depression (Mayberg, 2003, Hamani et al., 2011, Lozano et al., 2012, Mayberg et al., 2016, Dunlop et al., 2017, Riva-Posse et al., 2018). We hope that the new concepts and evidence
presented here based on a fundamental understanding of the functions of the orbitofrontal cortex in emotion will help in developments of better understanding and treatments for depression (Rolls, 2018a).
Technical note
The orbitofrontal cortex is a difficult brain region for fMRI as sometimes signal dropout and distortion can occur due to inhomogeneities in the magnetic field being produced by the air-filled bony sinuses. For many of our investigations we utilized a protocol set up very helpfully by Prof Peter Jezzard (FMRIB, Oxford) for imaging in the coronal plane with the head angle optimised for each participant, and with imaging parameters that were carefully selected, as described in our papers before 2012. Since then, we have successfully used imaging in approximately the plane of the Sylvian fissure, which enables imaging of both the orbitofrontal cortex and medial temporal lobe, as set out in the following papers (Deichmann et al., 2002, Deichmann et al., 2003, Rolls et al., 2015b, Rolls et al., 2020b).

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The authors do not have conflicts of interest to report.

Data availability
Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Figure Legends.

Fig. 1. Maps of architectonic areas in the orbitofrontal cortex and medial prefrontal cortex of humans. Left, ventral view of the brain: The medial orbitofrontal cortex includes areas 13 and 11 (green). The lateral orbitofrontal cortex includes area 12 (red). (Area 12 is sometimes termed area 12/47 in humans. The figure shows two architectonic subdivisions of area 12.) Almost all of the human orbitofrontal cortex except area 13a is granular. Agranular cortex is shown in dark grey. The part of area 45 shown is the orbital part of the inferior frontal gyrus pars triangularis. Right: the anterior cingulate cortex (medial view) includes the parts shown of areas 32, 25 (subgenual cingulate), and 24. The ventromedial prefrontal cortex includes areas 14 (gyrus rectus) 10m and 10r. AON – anterior olfactory nucleus; Iai, Ial, Iam, Iapm – subdivisions of the agranular insular cortex. (After Öngür, Ferry and Price (2003) Journal of Comparative Neurology with permission of John Wiley & Sons, Inc., modified from a redrawn version by Passingham and Wise (2012).)

Fig. 2. Some of the connections of the taste, olfactory, somatosensory, visual and auditory pathways to the orbitofrontal cortex and amygdala in primates. V1, primary visual (striate) cortex; V2 and V4, further cortical visual areas. PFC, prefrontal cortex. The Medial PFC area 10 is part of the ventromedial prefrontal cortex (VMPFC). VPL, ventro-postero-lateral nucleus of the thalamus, which conveys somatosensory information to the primary somatosensory cortex (areas 1, 2 and 3). VPMpc, ventro-postero-medial nucleus pars parvocellularis of the thalamus, which conveys taste information to the primary taste cortex. For purposes of description, the stages can be described as Tier 1, representing what object is present independently of reward value; Tier 2 in which reward value and emotion is represented; and Tier 3 in which decisions between stimuli of different value are taken, and in which value is interfaced to behavioral output systems. A pathway for top-down attentional and cognitive modulation of emotion is shown in purple. Auditory inputs also reach the amygdala. (From Rolls 2019 The Orbitofrontal Cortex. Oxford University Press.)

Fig. 3. Connectivity of the human orbitofrontal cortex (OFC) based on parcellation of the functional connectivity of every OFC voxel with each of the 94 Automated Anatomical Labelling atlas 2 brain regions. Six divisions of the OFC are shown, with the approximate correspondence of each division with the cytoarchitectonic areas defined by Öngür, Ferry and Price (2003) shown in Fig. 1 indicated in brackets: 1 - the gyrus rectus (much of it area 14); 2 - medial OFC (area 13m); 3: posterior OFC (area 13l); 4 - anterior OFC (area 11l); 5 - lateral OFC, posterior (area 12m); 6 - lateral OFC, anterior (area 12r). Surface maps showing the cortical connectivity of each parcel are shown. The functional connectivities have been thresholded at 0.3, and were obtained in resting state fMRI with 654 participants. Quantitative evidence on the connectivity with different brain regions of each parcel is provided by Du, Rolls et al (2020) and Hsu, Rolls et al (2020). (After Du, Rolls, Cheng et al, 2020.)

Fig. 4. 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 Kringelbach,M.L. and Rolls,E.T. (2003) NeuronImage 20, Neural correlates of rapid reversal learning in a simple model of human social interaction, pp. 1371-1383.)

B Activations in the human lateral orbitofrontal cortex are related to a signal to change behavior 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 behavior, and stop the response. There is a larger response
on trials on which the participant successfully changes the behavior 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, Rolls et al, 2017).

C Non-reward error-related neurons maintain their firing after non-reward is obtained. 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, Rolls and Maddison 1983.)

D 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).

Fig. 5. The lateral orbitofrontal cortex is activated by not winning, and the medial orbitofrontal cortex by winning, in the monetary incentive delay task. The lateral orbitofrontal cortex region in which activations increased towards no reward (No Win) in the monetary incentive delay task are shown in red in 1140 participants at age 19 and in 1877 overlapping participants at age 14. The conditions were Large win (10 points) to Small Win (2 points) to No Win (0 points) (at 19; sweets were used at 14). The medial orbitofrontal cortex region in which activations increased with increasing reward from No Win to Small Win to High Win) is shown in green. The parameter estimates are shown from the activations for the participants (mean ± sem) with the lateral orbitofrontal in red and medial orbitofrontal cortex in green. The interaction term showing the sensitivity of the medial orbitofrontal cortex to reward and the lateral orbitofrontal cortex to non-reward was significant at p=10^-50 at age 19 and p<10^-72 at age 14. In a subgroup with depressive symptoms as shown by the Adolescent Depression Rating Scale, it was further found that there was a greater activation to the No Win condition in the lateral orbitofrontal cortex; and the medial orbitofrontal cortex was less sensitive to the differences in reward value. (Modified from Xie, Jia, Rolls et al, 2020.)

Fig. 6. Some of the emotions associated with different reinforcement contingencies. Intensity increases away from the centre of the diagram, on a continuous scale. The classification scheme created by the different reinforcement contingencies consists with respect to the action of (1) the delivery of a reward (S+), (2) the delivery of a punisher (S-), (3) the omission of a reward (S+) (extinction) or the termination of a reward (S+!) (time out), and (4) the omission of a punisher (S-) (avoidance) or the termination of a punisher (S-!) (escape). Note that the vertical axis describes emotions associated with the delivery of a reward (up) or punisher (down). The horizontal axis describes emotions associated with the non-delivery of an expected reward (left) or the non-delivery of an expected punisher (right). For the contingency of non-reward (horizontal axis, left) different emotions can arise depending on whether an active action is possible to respond to the non-reward, or whether no action is possible, which is labelled as the passive condition. In the passive condition, non-reward may produce depression. The diagram summarizes emotions that might result for one reinforcer as a result of different contingencies. Every separate reinforcer has the potential to operate according to contingencies such as these. This diagram does not imply a dimensional theory of emotion, but shows the types of emotional state that
might be produced by a specific reinforcer. Each different reinforcer will produce different emotional states, but the contingencies will operate as shown to produce different specific emotional states for each different reinforcer.

**Fig. 7. Resting state functional connectivity in depression.** 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. (From Cheng, Rolls et al, 2016.)

**Fig. 8. Functional connectivity (FC) differences of the medial and lateral orbitofrontal cortex in major depressive disorder.** Higher functional connectivity in depression is shown in red, and includes higher functional connectivity of the non-reward / punishment-related lateral orbitofrontal cortex with the precuneus, posterior cingulate cortex (PCC), pregenual anterior cingulate cortex (ACC), angular gyrus, and inferior frontal gyrus. Lower functional connectivity in depression is shown in blue, and includes lower functional connectivity of the medial orbitofrontal cortex with the parahippocampal gyrus memory system (PHG), amygdala, temporal cortex and supracallosal anterior cingulate cortex (ACC). The part of the medial orbitofrontal cortex in which voxels were found with lower functional connectivity in depression is indicated in green. The areas apart from the medial orbitofrontal cortex shown are as defined in the automated anatomical labelling atlas (Rolls et al., 2015a), although the investigations that form the basis for the summary were at the voxel level.
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Fig. 1

Human orbitofrontal cortex
ventral view, right hemisphere

Human medial prefrontal cortex
medial view, right hemisphere

187x97mm (300 x 300 DPI)
Fig. 2

209x163mm (300 x 300 DPI)
Fig. 4

203x174mm (300 x 300 DPI)
The Medial and Lateral Orbitofrontal Cortex (OFC) in the Monetary Incentive Delay Task

A
Coronal View, Y = 49

L
R

Axial View, Z = -13

Medial OFC
Lateral OFC

B
Age 14, Medial and Lateral OFC, Reward Anticipation in MID task

C
Age 19, Medial and Lateral OFC, Reward Anticipation in MID task

Fig. 5

157x122mm (300 x 300 DPI)
Emotions: states elicited by Rewards and Punishers

Fig. 6

206x158mm (300 x 300 DPI)
The functions of the orbitofrontal cortex in emotion, reward value, reward-related decision-making, and depression are described.
Abbreviated summary

The orbitofrontal cortex is involved in emotion, reward value, and reward-related decision-making. Rolls et al. describe how it implements these functions, and the effects of damage. In depression, the lateral orbitofrontal cortex has increased functional connectivity and sensitivity to non-reward; and the medial orbitofrontal cortex has decreased connectivity and sensitivity to reward.