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Disorders of Emotion in Neurologic Disease
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Chapter 1

The neuroscience of emotional disorders

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Abstract

Emotions can be defined as states elicited by rewards or punishments, and indeed the neurology of emotional disorders can be understood in terms of this foundation. The orbitofrontal cortex in humans and other primates is a critical area in emotion processing, determining the value of stimuli and whether they are rewarding or nonrewarding. The cortical processing that occurs before the orbitofrontal cortex primarily involves defining the identity of stimuli, i.e., "what" is present and not reward value. There is evidence that this holds true for taste, visual, somatosensory, and olfactory stimuli. The human medial orbitofrontal cortex is important in processing many different types of reward, and the lateral orbitofrontal cortex in processing nonreward and punishment. Humans with damage to the orbitofrontal cortex have an impaired ability to identify facial and voice expressions of emotions, and impaired subjective experience of emotion. They can have an altered personality and be impulsive because they are impaired at processing failures to receive expected rewards and at processing punishments. In humans, the role of the amygdala in the processing of emotions is reduced because of the great evolutionary development of the orbitofrontal cortex: amygdala damage has much less effect on emotion than does orbitofrontal cortex damage. The orbitofrontal cortex projects reward value information to the anterior cingulate cortex, which is involved in learning those actions required to obtain rewards and avoid punishments. The cingulate cortex thus provides an output route for emotional behavior. In depression, the medial orbitofrontal cortex has decreased connectivity and sensitivity to reward, and the lateral orbitofrontal cortex has increased connectivity and sensitivity to nonreward. The orbitofrontal cortex has major projections to the anterior cingulate cortex, including its subcommissural region, and the anterior cingulate cortex is also implicated in depression.

INTRODUCTION

The approach to be taken to understanding the neurology and neuroscience of emotional disorders in humans is as follows. First, emotions are defined and their functions are described. Then the key brain regions involved in emotional functions are considered, including the orbitofrontal cortex, amygdala, anterior cingulate cortex, insula, and ventral striatum. For each brain region, we consider its connections, evidence from neuronal recording and fMRI bearing on its functions, and within this context, the emotional and related disorders that arise from damage to brain regions—a key issue in neurology. Also to be considered for each brain region is how emotional disorders, including depression, may arise from abnormal function.

A definition of emotion

A clear working definition of emotion is helpful before we consider its brain mechanisms. Emotions can usefully be defined (operationally) as mental and physical states elicited by rewards and punishments, in which these states have particular functions (Rolls, 1999, 2013, 2014, 2018a). A reward is anything for which animals (including humans) will work to obtain. A punishment

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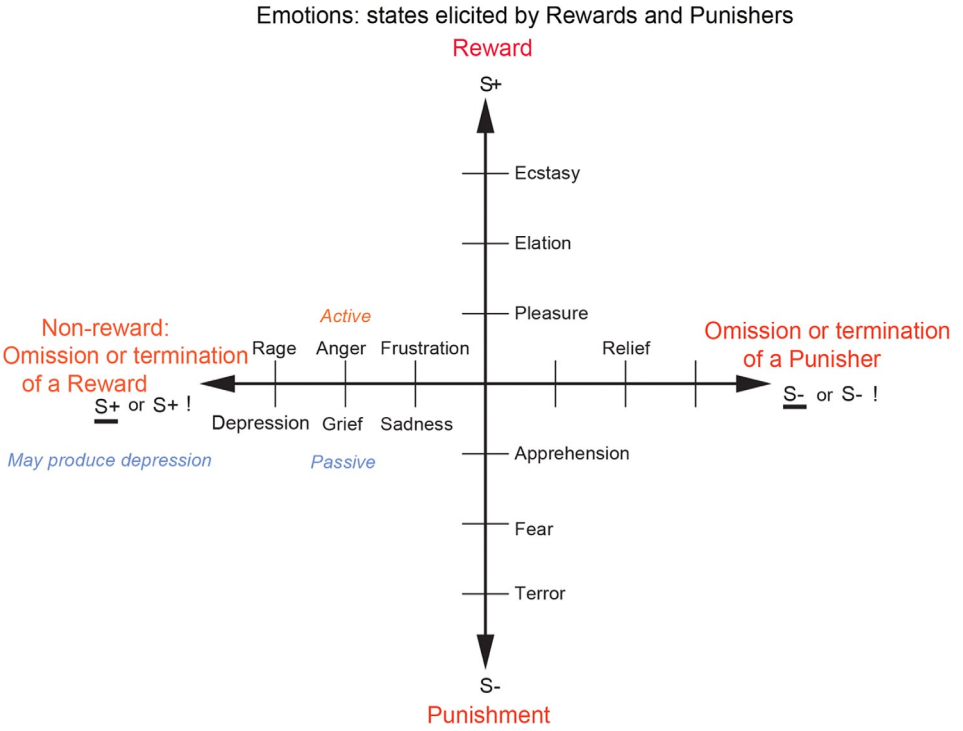

Fig. 1.1. Some of the emotions associated with different reinforcement contingencies are indicated. Intensity is proportional to the distance from the center of the diagram, on a continuous scale. The classification scheme created by the different reinforcement contingencies consists, with respect to the action being reinforced, of (1) the delivery of a reward (S+); (2) the delivery of a punishment (S −); (3) the omission of a reward (S+) (extinction) or the termination of a reward (S+!) (time out); and (4) the omission of a punishment (S −) (avoidance) or the termination of a punishment (S −!) (escape). Note that the vertical axis describes emotions associated with the delivery of a reward (up) or punishment (down). The horizontal axis describes emotions associated with the nondelivery of an expected reward (left) or the nondelivery of an expected punishment (right). For the contingency of nonreward (horizontal axis, left), different emotions can arise depending on whether an action is possible in response to the nonreward, or whether no action is possible (the passive condition). In the passive condition, nonreward 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 states 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.

is anything that animals will seek to escape from or avoid. (In other terminology, rewards have a positive valence, and punishments have a negative valence.) As shown in Fig. 1.1, different reward/punishment contingencies are associated with different types of emotion. An example of an emotion associated with a reward might be the happiness produced by being given a particular reward, such as a pleasant touch, praise, or winning a large sum of money. An example of an emotion produced by a punishment might be fear produced by the sound of a rapidly approaching bus or the sight of an angry expression on someone's face. We will work to avoid such punishing stimuli. An example of an emotion produced by the omission, termination, or loss of a reward is frustration or anger (if some action can be taken), or sadness (if no action can be taken). An example of an emotion produced by the omission or termination of a punishment (such as the removal of a painful stimulus or sailing out of danger) would be a relief. These examples illustrate the ways in which emotions can be produced by the delivery, omission, or termination of rewarding or punishing stimuli, and how different emotions can be produced and classified in terms of the rewards and punishments received, omitted, or terminated. A diagram summarizing some of the emotions associated with the delivery of a reward or punishment, a stimulus associated with one of them, or the omission of a reward or punishment is provided in Fig. 1.1.

The subjective feelings of emotions are part of the much larger problem of consciousness (Rolls, 2020a). The brain bases of subjective experience are a topic of considerable current interest, not only with higher-order thought theories (Rosenthal, 2004; Brown et al., 2019) but also with the higher-order syntactic thought theory

of consciousness (Rolls, 2007, 2012b, 2014, 2016a, 2018a, 2020a), which is more computationally specific and addresses the adaptive value of the type of processing related to consciousness. The orbitofrontal cortex is implicated in the human subjective experience of emotion and affective value (see later).

I consider elsewhere a slightly more formal definition than rewards and punishments, in which the concept of reinforcers is introduced and it is shown that emotions can be usefully seen as states produced by instrumental reinforcing stimuli (Rolls, 2014). Instrumental reinforcers are stimuli which, if their occurrence, termination, or omission is made contingent upon the making of a response, alter the probability of the future production of that response. Some stimuli are unlearned (innate) reinforcers (e.g., the taste of food if an animal is hungry, or pain). Others may become reinforcing by virtue of associative learning: because of their association with primary reinforcers, they become "secondary reinforcers." An example might be the sight of a painful stimulus. Understanding the brain systems that are responsible for learning and unlearning the associations between stimuli or environmental events and reinforcers is important to understanding the neuroscience and neurology of emotions, as we will see later.

This foundation has been developed (Rolls, 2014) for understanding how a very wide range of emotions can be accounted for in terms of the operation of a number of factors, including the following:

1. The *reinforcement contingency*, e.g., whether reward or punishment is given or withheld (see Fig. 1.1).
2. The *intensity* of the reinforcer (see Fig. 1.1).
3. Any environmental stimulus might have a *number of different reinforcement associations*. For example, a stimulus might be associated both with the presentation of a reward and of a punishment, allowing states such as conflict and guilt to arise.
4. Emotions elicited by stimuli associated with *different primary reinforcers* will be different.
5. Emotions elicited by *different secondary reinforcing stimuli* will be different from each other, even if their primary reinforcers are similar.
6. The emotion elicited can depend on whether an *active or passive behavioral response* is possible. For example, if there can be an active behavioral response to the omission of a positive reinforcer, then anger might ensue. However, if only a passive response is possible, then sadness, depression, or grief might occur.

By combining these six factors, it is possible to account for a very wide range of emotions (Rolls, 2014). It is also worth noting that emotions can be produced by the recall of reinforcing events. Cognitive processing (whether conscious or not) is important in many emotions. Very complex cognitive processing may be required to determine whether or not environmental events are reinforcing or punishing. Indeed, emotions normally consist of the cognitive processing involved in the analysis of the stimulus and determination of its reinforcing valence, followed by an elicited mood change if the valence is positive or negative. A mood or affective state may occur in the absence of an external stimulus, as in some types of depression, but normally the mood or affective state is produced by an external stimulus. The whole process of stimulus representation, evaluation in terms of reward or punishment value, and the resulting mood or affective state is referred to as emotion (Rolls, 2014).

The functions of emotions

The most important function of emotions relates to the processes of learning actions to obtain rewards or avoid punishments. The first process is *stimulus-reinforcer association learning*; emotional states are produced as a result (Rolls, 2014). An example might be learning that the sight of a person is associated with rewards, which might produce the emotion of happiness. This process is implemented in structures such as the orbitofrontal cortex and amygdala (Figs. 1.2 and 1.3) (Rolls and Grabenhorst, 2008; Grabenhorst and Rolls, 2011; Rolls, 2014). The second process is instrumental learning of an action to be made to approach and obtain the reward (an outcome) or to avoid or escape from the punishment (an outcome). This is *action-outcome learning*; it involves brain regions such as the cingulate cortex when the actions are being guided by the goals (Rushworth et al., 2011, 2012; Rolls, 2014, 2018a, 2019a, 2021a).

Emotion is an integral part of goal-directed learning. Emotion is the state elicited in the first stage by stimuli that are decoded as rewards or punishments. The emotional state has the property that it is motivating. The motivation is to obtain the reward or avoid the punishment (the goals for the action). Individuals must be built to learn to obtain certain rewards and avoid punishments (Rolls, 2014). In the second stage, actions are learned that are instrumental in obtaining the goals, which are the reinforcers. The first stage involves the orbitofrontal cortex, and the second stage the cingulate cortex (Rolls, 2019a). The striatum and rest of the basal ganglia can become involved when the behavior becomes automatic and habit-based, that is, engages more direct stimulus–response connections (Fig. 1.2).

Other functions of emotion include the elicitation of autonomic and endocrine responses, via pathways, for

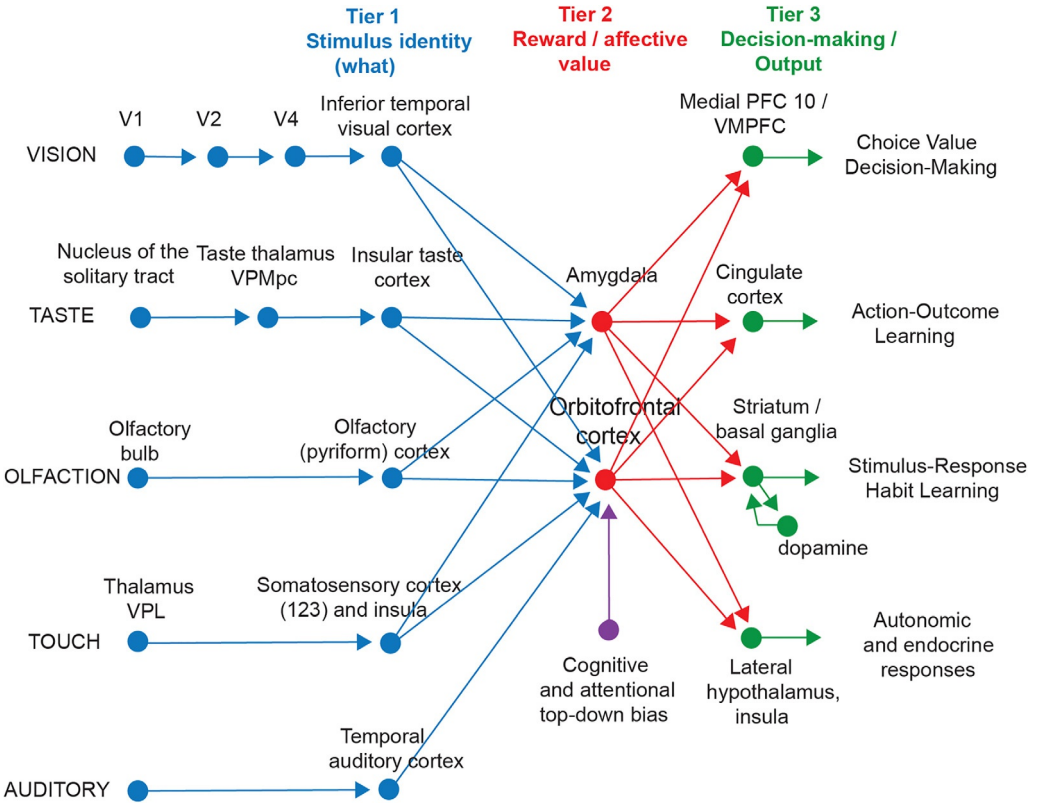

Fig. 1.2. The systems-level organization of the brain for emotion in human and nonhuman primates. In Tier 1, representations are built of visual, taste, olfactory, and tactile stimuli that are independent of reward value and therefore of emotion. In Tier 2, reward value and emotion are represented. A pathway for top-down attentional and cognitive modulation of emotion is shown in *purple*. In Tier 3, actions to obtain rewards, values of which are signaled by the orbitofrontal cortex and amygdala, are learned in the cingulate cortex. Decisions regarding stimuli of different reward value and costs can also be made. In Tier 3, stimulus–response habits can also be acquired through reinforcement learning. In Tier 3, autonomic responses can also be produced in response to emotion-provoking stimuli. Auditory inputs also reach the amygdala. *V1*, primary visual (striate) cortex; *V2, V4*, visual association cortices; *PFC*, prefrontal cortex; *medial PFC 10*, 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.

example, from the orbitofrontal cortex to the anteroventral visceral/autonomic insula and to the subgenual cingulate cortex (Rolls, 2013, 2014, 2019a,b).

A framework for understanding the neuroscience and neurology of emotion in humans and other primates

A framework is shown in Fig. 1.2, which is built on evidence from neuronal recordings, the effects of brain damage, and fMRI in humans and macaques, some of which is summarized later (Rolls, 2014, 2018a, 2019a, 2021a; Rolls et al., 2020b). Part of the evidence for what is shown in Fig. 1.2 comes from studies of reward devaluation, in which, when the reward value is changed, for example, by feeding to satiety, neural responses to stimuli are little affected in Tier 1 but decrease to zero in Tier 2. Part of the evidence comes from studies of the learning of associations between stimuli and reward value, which occurs mainly in Tier 2. Part of the evidence comes from studies of the effects of brain damage on emotion, particularly damage to the orbitofrontal cortex and amygdala in Tier 2, and the cingulate cortex in Tier 3. The organization of reward value processing and therefore emotion in the rodent brain is very different (Rolls, 2019b, 2021a) and is not therefore considered further here.

In the context of what is shown in Fig. 1.2, the focus next is on key brain areas involved in emotion in humans and other primates: the orbitofrontal cortex, the amygdala, and the cingulate cortex.

THE ORBITOFRONTAL CORTEX

The connections of the orbitofrontal cortex

The orbitofrontal cortex cytoarchitectonic areas of the human brain are shown in Fig. 1.3 (left). The medial orbitofrontal cortex includes areas 13 and 11 (Öngür et al., 2003). The lateral orbitofrontal cortex includes area

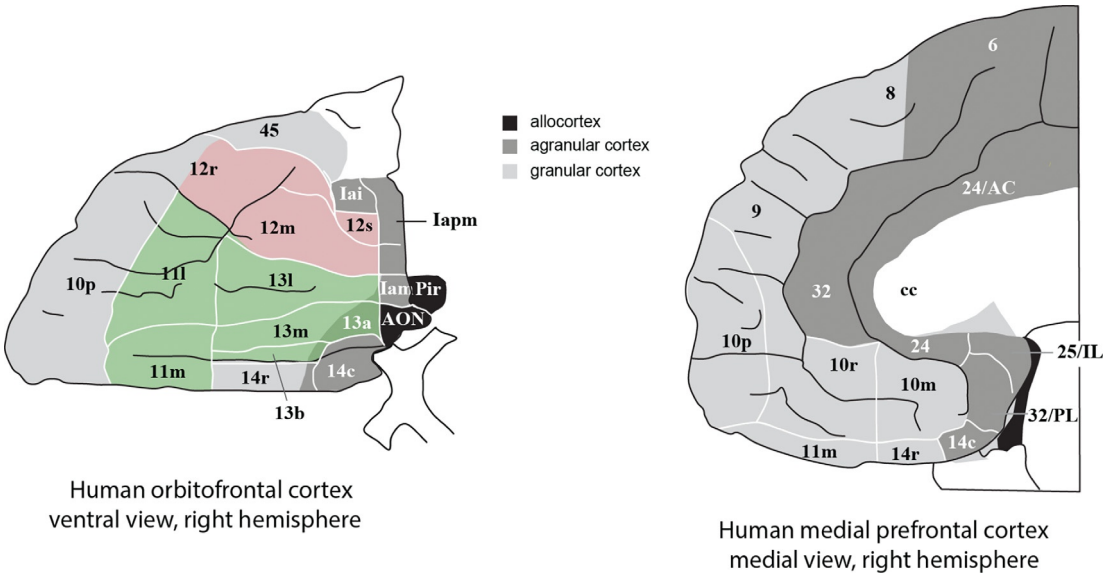

Fig. 1.3. Maps of architectonic areas in the orbitofrontal cortex (left, ventral view of the brain) and medial prefrontal cortex (right, medial view of the brain) of humans. Left: The medial orbitofrontal cortex includes areas 13 and 11 (*green*). The lateral orbitofrontal cortex includes area 12 (*red*). 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. The agranular cortex is shown in *dark gray*. The part of area 45 shown is the orbital part of the inferior frontal gyrus pars triangularis. Right: the anterior cingulate cortex includes the parts shown of areas 32, 25 (subgenual cingulate), and 24. The ventromedial prefrontal cortex includes areas 14 (gyrus rectus), 10 m, and 10r. *AON*, anterior olfactory nucleus; *Iai, Ial, Iam, Iapm*—subdivisions of the agranular insular cortex. After Öngür D, Ferry AT, Price JL (2003). Architectonic division of the human orbital and medial prefrontal cortex. J Comp Neurol 460: 425–449. with permission of John Wiley & Sons, Inc.Modified from a redrawn version by Passingham REP & Wise SP (2012). The neurobiology of the prefrontal cortex. Oxford University Press, Oxford.

12 (sometimes in humans termed 12/47). The anterior cingulate cortex includes the parts shown in Fig. 1.3 (right) of areas 32, 25 (subgenual cingulate), and 24. The ventromedial prefrontal cortex includes areas 14 (gyrus rectus), 10 m, and 10r.

Some of the main connections of the orbitofrontal cortex in primates are shown schematically in Fig. 1.2 (Carmichael and Price, 1994, 1995; Barbas, 1995, 2007; Petrides and Pandya, 1995; Pandya and Yeterian, 1996; Ongür and Price, 2000; Price, 2006, 2007; Saleem et al., 2008, 2014; Mackey and Petrides, 2010; Petrides et al., 2012; Henssen et al., 2016; Rolls, 2017, 2019b,c; Rolls et al., 2020b). The orbitofrontal cortex receives inputs from the ends of every ventral cortical stream that processes the identity of visual, taste, olfactory, somatosensory, and auditory stimuli (Rolls, 2019b, 2021a). The ends of these cortical-processing streams provide a representation of the identity of the stimulus, independent of its reward value. This is shown by neuronal recordings in primates (Rolls, 2019b). For example, the inferior temporal cortex represents objects and faces independent of their reward value, as shown by visual discrimination reversal and devaluation of reward tests employing feeding to satiety (Rolls et al., 1977, 2020b; Rolls, 2012a, 2016a, 2019b, 2021a). Similarly, the insular primary taste cortex represents what the taste is independent of its reward value (Yaxley et al., 1988; Rolls, 2015b, 2016b, 2019b).

Outputs of the orbitofrontal cortex reach the anterior cingulate cortex (Rolls, 2019a), the striatum, the insula, and the inferior frontal gyrus and enable the reward value representations in the orbitofrontal cortex to influence behavior (Fig. 1.2, green). The orbitofrontal cortex projects reward value information to the anterior cingulate cortex, where that information generates the reward outcomes for action–outcome learning (Rushworth et al., 2012; Rolls, 2019a,b). 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 midbrain dopamine neurons (Rolls, 2017), which respond inter alia to positive reward prediction error (Bromberg-Martin et al., 2010; Schultz, 2016a). The basal ganglia support stimulus–response, habit learning (Everitt and Robbins, 2013; Rolls, 2014). Dopaminergic activity signals reward prediction error in the process of reinforcement learning (Schultz, 2016b; Cox and Witten, 2019). As the basal ganglia system depends upon dopamine in reinforcement learning of stimulus–response habits, it learns much more slowly than the orbitofrontal cortex (outcome)–anterior cingulate cortex (action) system for action–outcome

goal-based learning, and for emotion (Rolls, 2021a). The orbitofrontal cortex projects to the viscero-autonomic cortex in the anteroventral insula (Hassanpour et al., 2018). Autonomic output helps to account for insular engagement in some emotion-related tasks in which the orbitofrontal cortex is involved (Rolls, 2016b, 2019b). The orbitofrontal cortex also projects to the inferior frontal gyrus, a region that on the right is implicated in stopping behavior and which, if damaged, can lead to impulsivity (Aron et al., 2014; Dalley and Robbins, 2017).

New evidence bearing on the connections of the orbitofrontal cortex in humans is shown in Fig. 1.4, which maps resting-state functional connectivity in 654 participants (Du et al., 2020). This functional connectivity is measured by the correlation between the signals in each pair of brain regions and suggests how much one brain region may influence another, or how they have a common input. First, a parcellation of voxel-wise functional connectivity of the orbitofrontal cortex with other brain areas reveals subdivisions (Fig. 1.4) that parallel the cytoarchitectural divisions of the human orbitofrontal

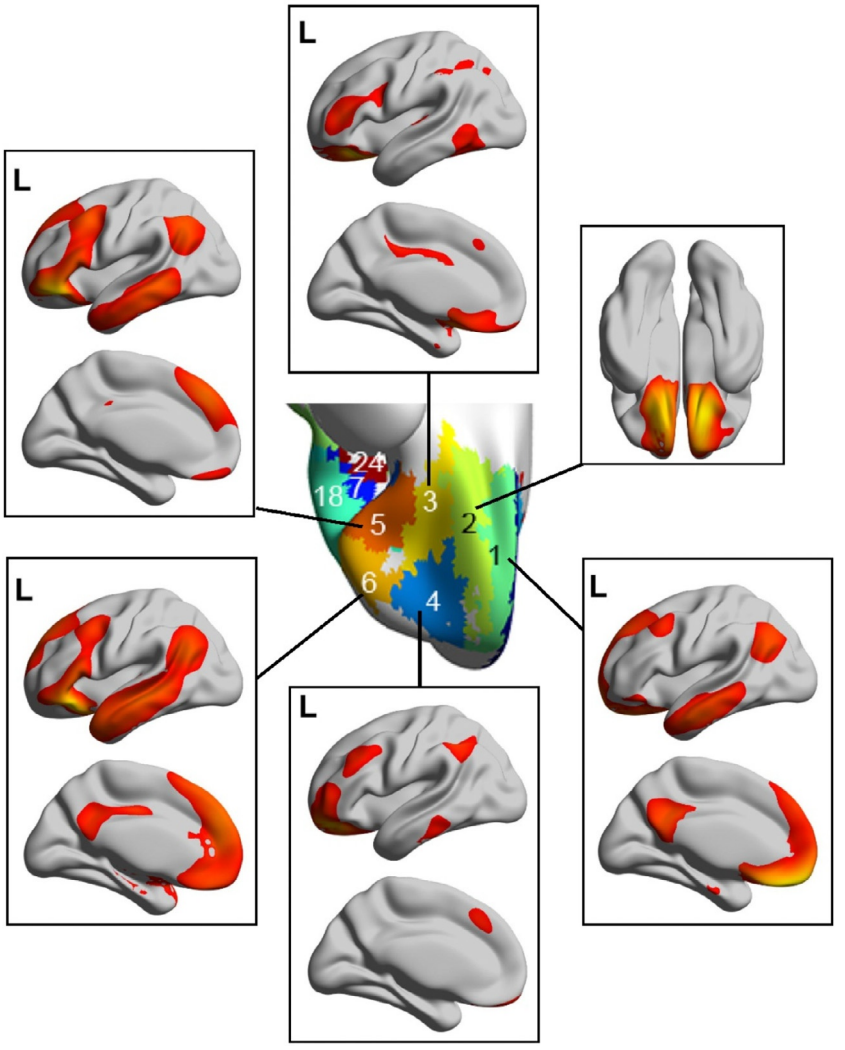

Fig. 1.4. Connectivity of the human orbitofrontal cortex (OFC) based on parcellation of the functional connectivity of every OFC voxel with each of the 94 automated anatomical labeling atlas 2 brain regions. At the center, six divisions of the OFC are shown, with the approximate correspondence of each division with the cytoarchitectonic areas defined by Öngür et al. (2003): 1, the gyrus rectus (much of it area 14); 2, medial OFC (area 13 m); 3, posterior OFC (area 13 L); 4, anterior OFC (area 11 L); 5, lateral OFC, posterior (area 12 m); 6, lateral OFC, anterior (area 12r). Surface maps showing the cortical connectivity of each parcel are shown. The functional connectivities in these maps are shown using a threshold of $r = 0.3$ and were obtained in a resting-state fMRI study involving 654 participants. Quantitative evidence on the connectivity with different brain regions of each parcel is provided by Du et al. (2020) and Hsu et al. (2020). After Du J, Rolls ET, Cheng W, et al. (2020). Functional connectivity of the orbitofrontal cortex, anterior cingulate cortex, and inferior frontal gyrus in humans. Cortex 123: 185–199.

cortex shown in Fig. 1.3. Second, the lateral orbitofrontal cortex (parcels 5 and 6 in Fig. 1.4) has functional 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. 1.4) have functional connectivity with the parahippocampal gyrus, the hippocampus, the temporal cortex, the fusiform gyrus, the insula, and the cingulate cortex. These functional connectivities, as shown later, are altered in opposite directions in depression.

The connectivity of the orbitofrontal cortex analyzed in humans through functional connectivity mapping 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 four are reward-related areas. The lateral orbitofrontal cortex and its closely connected right inferior frontal gyrus have direct connections with the supracallosal anterior cingulate cortex; all three are punishment or non-reward-related areas. This confirms findings based on functional connectivity studies that have suggested connections between the medial orbitofrontal cortex and the pregenual cingulate cortex and connections between the lateral orbitofrontal cortex, as well as related right inferior frontal gyrus, and the supracallosal anterior cingulate cortex (Rolls et al., 2019). 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 provide further routes to influence behavior. Direct connections of the human orbitofrontal cortex and inferior frontal gyrus with the temporal lobe extensively involve the temporal pole (Hsu et al., 2020).

The human medial orbitofrontal cortex represents reward value

The human and nonhuman primate orbitofrontal cortex is the first stage of cortical processing that represents reward value (red in Fig. 1.2) (Rolls, 2019b). For example, in devaluation experiments, taste, olfactory, visual, and oral texture neurons in the macaque orbitofrontal cortex respond to food when hunger is present but not after feeding to satiety, when the food is no longer rewarding (Rolls et al., 1989; Critchley and Rolls, 1996). This does not happen at earlier stages of processing (Rolls, 2019b,c). Consistent with this, 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). In visual discrimination reversal experiments, neurons in the macaque lateral orbitofrontal cortex reverse their response to a visual stimulus in as little as one trial when the reward/punishment taste received as an outcome of the choice reverses (Thorpe et al., 1983; Rolls et al., 1996). This is a 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 association was with punishment. Thus these neurons in the orbitofrontal cortex update their reward value representations very rapidly. The ability to update reward value representations very rapidly, in as little as one trial, has great adaptive value in human and nonhuman primates in facilitating social interaction.

The macaque orbitofrontal cortex contains neurons that encode face expression and face identity (both necessary to decode reward value) (Thorpe et al., 1983; Rolls et al., 2006), and also socially relevant categories such as young faces (Barat 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). Some orbitofrontal cortex neurons respond to outcome value (e.g., the taste of food), and others to the expected value (or future rewards). The expected value neurons are not positive reward prediction error neurons, for they keep responding to the expected reward even when, after learning, there is no longer a reward prediction error (Rolls, 2021a).

The results of neuroimaging experiments in humans (de Araujo et al., 2003; Kringelbach et al., 2003; Kringelbach and Rolls, 2003; Grabenhorst and Rolls, 2008; Grabenhorst et al., 2008a) are consistent with these neurophysiological data from nonhuman primate studies showing reward value representations in the orbitofrontal cortex. Human studies allow extension to other types of reward value, including monetary rewards (O'Doherty et al., 2001; Xie et al., 2021), face expressions (Kringelbach and Rolls, 2003), and facial beauty (O'Doherty et al., 2003). Further, in humans, activations of the medial orbitofrontal cortex are linearly related to the subjective (conscious) pleasantness of stimuli (Grabenhorst and Rolls, 2011; Rolls, 2019b). These reward-related effects are 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., 2021), and amphetamine (Völlm et al., 2004). A recent study involving 1140 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. 1.6) (Xie et al., 2021).

Further, humans with orbitofrontal cortex lesions may also be less sensitive to reward, as reflected in a reduction in subjective emotional feelings (Hornak et al., 2003), their difficulty in identifying face and voice emotion-related expressions, which are important for emotional and social behavior (Hornak et al., 1996, 2003), and their difficulty with reward reversal (Rolls et al., 1994; Hornak et al., 2004; Fellows, 2011).

The human lateral orbitofrontal cortex represents punishments and nonreward and is involved in changing emotional behavior

The macaque orbitofrontal cortex has neurons that respond when an expected reward is not received (Thorpe et al., 1983). These have been termed *nonreward neurons* (Rolls, 2014, 2019b) (see example in Fig. 1.5C). They can be described as negative reward prediction error neurons in that they respond when a reward outcome is less than was expected (Rolls, 2019b).

Nonreward neurons do not respond to expected punishments (e.g., the discriminative stimulus for saline in Fig. 1.5C; Thorpe et al., 1983), but other neurons do respond to expected punishments (Rolls et al., 1996). Thus nonreward and punishment are represented by different neurons in the orbitofrontal cortex.

The finding of nonreward neurons is robust in that 18/494 (3.6%) of the neurons in the original study responded to nonreward (Thorpe et al., 1983). Consistent results were found in different tasks in a complementary study (10/140 nonreward 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. 1.5D).

The hypothesis is that the activity of nonreward neurons reflects a computation in the orbitofrontal cortex, as shown by the following. The orbitofrontal cortex is the first brain region in primates at which expected value and outcome value are represented, as summarized in Fig. 1.2 (Rolls, 2019b), and these two signals are required to compute nonreward, that is, that rewarding outcome is less than the expected value of the outcome. These nonreward neurons may be part of the mechanism that helps rewarded behavior to change very rapidly in emotional and social situations (Deco and Rolls, 2005; Rolls and Deco, 2016).

Consistent with these neurophysiological discoveries, in macaques damage to the lateral orbitofrontal cortex impairs reversal and extinction (Butter, 1969; Iversen and Mishkin, 1970), and damage to the lateral orbitofrontal cortex area 12 extending around the inferior convexity impairs the ability to make choices based on whether reward vs nonreward had been received (Rudebeck et al., 2017; Murray and Rudebeck, 2018).

The results of functional neuroimaging studies in humans are consistent with the neurophysiological discoveries made in macaques. The human lateral orbitofrontal cortex is activated when a reward is not obtained in a visual discrimination reversal task (Kringelbach and Rolls, 2003) (Fig. 1.5A), when money is not received in a monetary reward task (O'Doherty et al., 2001; Xie et al., 2021), and in a one-trial reward reversal task (Rolls et al., 2020c). The human orbitofrontal cortex has an affective or hedonic organization, in that the human lateral orbitofrontal cortex is also activated by punishing, subjectively unpleasant stimuli (Grabenhorst and Rolls, 2011; Rolls, 2019b). Examples include unpleasant odors (Rolls et al., 2003a), pain (Rolls et al., 2003b), losing money (O'Doherty et al., 2001), and receiving an angry facial 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 behavioral correction is required in the stop-signal task (Fig. 1.5B) (Aron et al., 2014; Deng et al., 2017). These discoveries show that one way in which the orbitofrontal cortex is involved in decision making and emotion is by representing rewards, punishments, and errors made during decision making.

Consistent with this neurophysiological and neuroimaging evidence, lesions of the human orbitofrontal cortex can impair reward reversal learning during decision making (Rolls et al., 1994; Berlin et al., 2004; Hornak et al., 2004; Fellows, 2011). Patients with orbitofrontal cortex lesions continue to respond to the previously rewarded, now nonrewarded, stimulus. This indicates that the change in contingency between the stimulus and reward vs nonreward was not processed correctly. The difficulty that patients with orbitofrontal cortex damage have in responding appropriately to their changed circumstances, and their personality changes, which include impulsivity, can be related to these impairments in responding to nonreward and punishment (Rolls et al., 1994; Berlin et al., 2004; Berlin and Rolls, 2004; Hornak et al., 2004; Rolls, 2018a, 2019b).

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 10 m and 10r, Fig. 1.3) receives inputs from the orbitofrontal cortex and has strong connectivity with the superior medial prefrontal cortex and cingulate cortex (Hsu et al., 2020; Du et al., 2020). The VMPFC has long been implicated in reward-related decision making

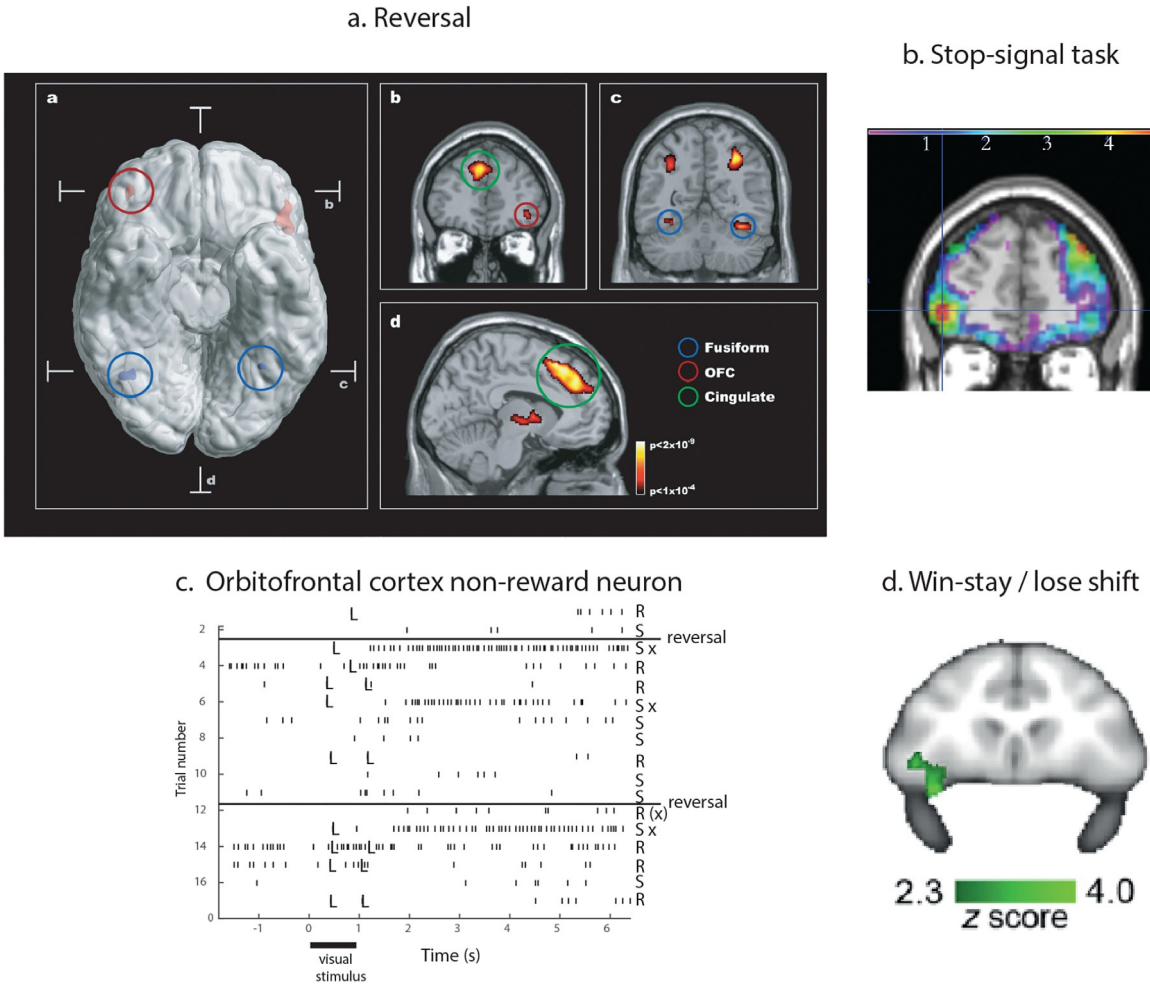

Fig. 1.5. (A) Reversal. Evidence that the human lateral orbitofrontal cortex is activated by nonreward. Activation of the lateral orbitofrontal cortex (*red circles*) in a visual discrimination reversal task on reversal trials, when a face was selected but the expected reward was not obtained, indicating that the subject should select the other face in future to obtain the reward. (a) A ventral view of the human brain indicating the location of the two coronal slices (b,c) and the transverse slice (d). The activations designated by the *red circles* in the lateral orbitofrontal cortex (OFC, peaks at [42 42 –8] and [−46 30 –8]) correspond to reversal trials compared to nonreversal trials. For comparison, the activations designated by the *blue circles* correspond to the engagement of the fusiform face area produced just by facial 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. (The right side of the brain is shown on the right, the convention used in neuroscience.) Activation is also shown in the supracallosal anterior cingulate region (*green circles*, b and d) that is also known to be activated by many punishing, unpleasant, stimuli (see Grabenhorst and Rolls, 2011). (B) Stop-signal task. 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 left lateral orbitofrontal cortex, with peak at [−42 50 –2] indicated by the cross-hairs, measured in 1709 participants. There were corresponding, though smaller, effects in the right lateral orbitofrontal cortex [42 52 –4]. Some activation in the left dorsolateral prefrontal cortex in an area implicated in attention is also shown. (C) Orbitofrontal cortex non-reward neuron. Nonreward error-related neurons maintain their firing after nonreward is obtained. Responses of an orbitofrontal cortex neuron that responded only when the macaque licked in response to a visual stimulus during reversal, expecting to obtain fruit juice reward, but actually obtaining 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

(Continued)

(Bechara et al., 1997, 2005; Glascher et al., 2012). It is activated during decision making more than in representing reward value (Rolls and Grabenhorst, 2008; Grabenhorst et al., 2008b). It has the signature of a decision-making region in that its activation increases in proportion to the difference in the decision variables, which in turn correlates with decision confidence (Rolls et al., 2010a,b; Rolls, 2019b). Consistently, in macaques, single neurons in the ventromedial prefrontal cortex rapidly signal the value of the chosen offer, suggesting that the circuit serves to select a choice (Strait et al., 2014). These findings are consistent with an attractor model of decision making (Rolls et al., 2010a,b; Rolls, 2014, 2016a). This attractor model of decision making is a neuronal network with associatively modifiable recurrent collateral synapses between the neurons of the type prototypical of the cerebral cortex (Wang, 2002; Rolls and Deco, 2010). Inputs for each of the decision variables are applied simultaneously and the network, after previous training with these decision variables, reaches a state in which the population of neurons representing one of the decision choices has a high firing rate (Rolls and Deco, 2010; Deco et al., 2013; Rolls, 2016a, 2021a).

THE AMYGDALA

Although the amygdala has many of the same connections as the orbitofrontal cortex (Fig. 1.2), it is an evolutionarily older brain region and its role in processing human emotions appears to be overshadowed by that of the orbitofrontal cortex, which has strong connections with the amygdala (Rolls, 2014, 2019b, 2021a; Rolls et al., 2020b). For example, 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 the effects of damage to the orbitofrontal cortex (Rolls et al., 1994; Hornak et al., 1996, 2003, 2004; Camille et al., 2011; Fellows, 2011; Rolls, 2019b). 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). This is in strong contrast to the orbitofrontal cortex, which is definitively involved in subjective emotional experience, as discussed in the foregoing. 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 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 in the amygdala and activity in the orbitofrontal cortex but not the amygdala is modulated by recent reward history (Saez et al., 2017).

Nevertheless, amygdala damage in humans does appear to influence the processing of emotions. Consistent with the discovery of face neurons in macaques (Leonard et al., 1985), human amygdala neurons respond to faces (Rutishauser et al., 2015). Face expression but not face identity impairments were described in a patient (SM) with bilateral damage to the amygdala (Adolphs et al., 1994), and this has been found in other patients (Calder et al., 1996; Adolphs et al., 2002). SM was especially impaired at recognizing the facial expression of fear and she also rated expressions of fear, anger, and surprise as having less intensity than did control participants. It has been shown that SM's impairment in judging emotions stems from an inability to make normal use of information from the eye region of faces, which in turn is related to a lack of spontaneous fixations on the eyes during free viewing of faces (Kennedy and Adolphs, 2011). Although SM fails to look normally at the eye region in all facial expressions, her selective impairment in recognizing fear is explained by the fact that the eyes are the most important feature for identifying this emotion. Indeed, SM's recognition of fearful faces became entirely normal when she was instructed explicitly to look at the eyes. This finding provides a mechanism to explain the amygdala's role in fear recognition and points to new approaches for the possible rehabilitation of patients with defective emotion perception.

Patients with amygdala lesions show other signs of difficulty with processing emotion in that they are

Fig. 1.5—Cont'd reversed are indicated. After responding to nonreward, 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 nonrewarded stimulus. This shows that rapid reversal can be performed by a nonassociative process and must be rule-based. (D) Win-stay/lose shift. Bold signal in the macaque lateral orbitofrontal cortex related to win-stay/lose-shift performance, that is, to reward reversal performance. Panel (A) From Kringelbach ML, Rolls ET (2003). Neural correlates of rapid reversal learning in a simple model of human social interaction. NeuroImage 20: 1371–1383. Panel (B) After Deng WL, Rolls ET, Ji X et al. (2017). Separate neural systems for behavioral change and for emotional responses to failure during behavioral inhibition. Human Brain Mapp 38: 3527–3537. Panel (C) After Thorpe SJ, Rolls ET, Maddison S (1983). Neuronal activity in the orbitofrontal cortex of the behaving monkey. Exp Brain Res 49: 93–115. Panel (D) After Chau BK, Sallet J, Papageorgiou GK et al. (2015). Contrasting roles for orbitofrontal cortex and amygdala in credit assignment and learning in macaques. Neuron 87: 1106–1118.

impaired at acquiring conditioned skin conductance responses when a blue square is associated with a shock. They are also impaired in acquiring this autonomic response to fear when learning by observation or verbal instruction (Phelps, 2006; Whalen and Phelps, 2009). The human amygdala has been described as being important mainly for some fear responses to some stimuli, such as whether an individual backs off in a social encounter (Feinstein et al., 2011; Wang et al., 2017). In a complementary approach, if emotion-related memories are too intense, interference with the process of memory reconsolidation has been suggested (Kroes et al., 2016).

THE CINGULATE CORTEX

A recent synthesis of the functions of the cingulate cortex showed how the functions of its different parts are related to both emotion and memory (Rolls, 2019a). The subgenual cingulate cortex (area 25) may link rewards and punishments to autonomic output (Rolls, 2019a). The anterior cingulate cortex receives information from the orbitofrontal cortex about reward and nonreward outcomes. The posterior cingulate cortex receives spatial and action-related information from parietal cortical areas. It is argued that these inputs allow the cingulate cortex to perform action–outcome learning, with outputs from the mid-cingulate motor area to premotor areas including the supplementary motor area. In addition, because the anterior cingulate cortex links rewards to actions, it is involved in emotion, and because the posterior cingulate cortex has outputs to the hippocampal system, it is involved in memory (Rolls, 2019a). Some of the evidence is as follows.

In humans, by virtue of anatomical connectivity (Vogt, 2009, 2019; Hsu et al., 2020; Du et al., 2020), the pregenual anterior cingulate cortex receives information related to reward from the medial orbitofrontal cortex, and the supracallosal anterior cingulate receives information related to punishment and not receiving an expected reward from the lateral orbitofrontal cortex (Fig. 1.7). The human pregenual cingulate cortex is activated by many of the same rewards as the medial orbitofrontal cortex and the supracallosal anterior cingulate cortex are activated by many of the same punishments (and nonreward during reward reversal) as the lateral orbitofrontal cortex (Grabenhorst and Rolls, 2011; Rolls, 2019a; Rolls et al., 2020c) (see, e.g., Fig. 1.5A). The value representations received by the anterior cingulate cortex include information about reward outcomes received as a result of actions that have been performed, and the cingulate cortex can thereby learn which actions to perform in future to obtain the goal outcomes (Rushworth et al., 2012; Kolling et al., 2016; Rolls, 2019b). This is termed "action-outcome learning." The anterior cingulate cortex is implicated in emotion because it is involved in processing reward and punishment outcome information and associating actions with this reward outcome information. This reward processing incorporates information reflecting emotional expression in the face and voice, responses to which are impaired in patients with anterior cingulate cortex damage (Hornak et al., 2003).

The posterior cingulate cortex is relevant to this action–outcome learning, for it receives information about actions from the parietal cortex, including areas 7a, VIP and LIP laterally, and area 7 m medially (as well as some inputs from ventral stream temporal lobe areas) (Vogt and Laureys, 2009; Rolls, 2019a, 2020b, 2021a). The posterior cingulate cortex is therefore implicated in processing relevant to actions in space. A concept is that the posterior cingulate action-related information is interfaced with the anterior cingulate cortex outcome-related information and, via the midcingulate cortex, can thereby influence premotor areas that receive information from the midcingulate cortex (Fig. 1.7) (Rolls, 2019a). The posterior cingulate cortex in addition has major connectivity with parahippocampal areas TF and TH, which in turn project spatial information to the entorhinal cortex and thereby into the hippocampal episodic memory system. The posterior cingulate cortex provides a route for spatial information to reach the hippocampus, where it can be combined with an object and reward-related information to form episodic memories that may have emotional components because they incorporate reward information (Rolls, 2016a, 2018b, 2021a; Rolls and Wirth, 2018).

EMOTION AND AUTONOMIC RESPONSES

The expression of emotion also involves the autonomic nervous system and endocrine systems. The orbitofrontal cortex projects to the antero-ventral insula, which is a part of the insula involved in autonomic functions (Critchley and Harrison, 2013; Rolls, 2016b; Hassanpour et al., 2018; Mulcahy et al., 2019). Consistent with this concept, the anterior insula is often activated in emotion-related tasks (Menon and Uddin, 2010; Mulcahy et al., 2019; Rolls et al., 2020c). The anterior dorsal part of the insula is the primary taste cortex (Rolls, 2016b). The orbitofrontal cortex also projects to the subgenual cingulate cortex (Hsu et al., 2020), which is involved in autonomic output (Gabbott et al., 2003; Alexander et al., 2019). The amygdala can also influence autonomic output, via connections with the hypothalamus (Quirk et al., 1996). In addition, the periaqueductal area of the midbrain appears to be important in mediating defensive behaviors and the amygdala can

influence freezing behavior via its connections with the periaqueductal gray matter (Quirk et al., 1996).

The James–Lange theory of emotion proposed that feedback from the viscera of changes elicited by autonomic output produces emotional experiences (Rolls, 2014). The related somatic marker hypothesis postulated that emotional decision making is facilitated by peripheral feedback from, for example the autonomic nervous system (Damasio, 1994). There is evidence, however, from studies of the effects of artificial elicitation of autonomic effects and studies of the effects of disconnection or pharmacological blockade of the autonomic system that feedback from autonomic output is not needed for emotional behavior and emotional feelings (Rolls, 2014). There is also clear evidence (Maia and McClelland, 2004; Rolls, 2014) against the somatic marker hypothesis (Damasio, 1994; Bechara et al., 2005). In a direct test of the somatic marker hypothesis and James–Lange theory, emotional decision making was measured using the Iowa Gambling Task (Bechara et al., 2005) in patients with pure autonomic failure (Heims et al., 2004). In this condition, there is degeneration of the peripheral autonomic system and thus autonomic responses are severely impaired and autonomic feedback to the brain is markedly reduced. It was found that performance on the Iowa Gambling Task was not impaired (Heims et al., 2004). Nor was performance impaired on many other tests of emotion and emotional performance, including face expression identification, theory of mind tasks, and social cognition tasks (Heims et al., 2004). Thus emotional decision making does not depend on ongoing feedback from somatic markers related to autonomic function. Further, feelings and sentience persist after bilateral damage of the insula (Damasio et al., 2013), a key brain region in receiving input from the periphery.

THE "LIMBIC SYSTEM" AND EMOTION

The term limbic lobe was coined by Broca to refer to structures that are at the border or edge (the literal meaning of limbic) of the hemispheres (when seen in medial view) (Broca, 1878). This neuroanatomic designation was followed by the development of the concept of the limbic lobe as a functional system (Papez, 1937; Pessoa and Hof, 2015). Limbic structures include the hippocampus, the amygdala (which has major connections with the orbitofrontal cortex), and the cingulate cortex, as well as structures connected to them, including the anterior thalamic nuclei, hypothalamus, and septal region. However, it has been argued that there is no single "limbic system" (Rolls, 2015a), with the hippocampus and its connected structures involved primarily in episodic memory (Kesner and Rolls, 2015; Rolls, 2018b, 2021a) and navigation (Rolls and Wirth, 2018; Rolls, 2021b), and the amygdala and its connected structures, particularly the orbitofrontal cortex, involved in emotion (Rolls, 2014, 2018a, 2019b,c). The cingulate cortex spans both of these computational systems, with the anterior cingulate cortex receiving reward outcome information, the posterior cingulate cortex receiving information about spatial actions, and the merging of these signals within the cingulate cortex to implement action–outcome learning (Rolls, 2019a). Thus the concept of a "limbic system" is no longer useful (Rolls, 2015a) and we should instead consider what computations are performed by different brain systems, and how the computations are performed (Rolls, 2021a).

EMOTIONAL DISORDERS: DEPRESSION

A theory of depression

Neurological findings on the emotional disorders related to damage to brain systems have been described previously. In addition, other emotional disorders, including depression, can be linked to atypical function of brain systems involved in emotion, especially the orbitofrontal cortex (Rolls, 2016c, 2018a; Rolls et al., 2020b), and subgenual (subcommissural) cingulate cortex (Mayberg, 2003; Mayberg et al., 2005, 2016; Laxton et al., 2013; Dunlop et al., 2017; Holtzheimer et al., 2017; Riva-Posse et al., 2018, 2019, 2020).

A theory of depression has been developed based on our understanding of the brain processes involved in emotion, reward, and nonreward described previously (Rolls, 2016c, 2018a). Given that not receiving expected rewards is a reinforcement contingency that can lead to sadness or, in an extreme case, such as the loss of a loved one, depression, the theory was proposed that the lateral orbitofrontal cortex, implicated in nonreward and learning contingencies between stimuli and reward vs nonreward, overresponds to nonreward in people with depression (Rolls, 2016c, 2018a). Because nonreward neurons in the lateral orbitofrontal cortex can maintain their activity for at least many seconds (see Fig. 1.5C) (Thorpe et al., 1983), and because this persistent activity is needed to ensure that after nonreward, the behavior changes even if the same stimuli are not received for some time, the theory is that there is a nonreward attractor network in the lateral orbitofrontal cortex and that this network is more sensitive or its activity more persistent in depression (Rolls, 2016c, 2018a). It is postulated that the effects of the nonreward can be prolonged by

rumination over sad thoughts, supported by a long loop attractor involving language areas in the angular gyrus and related regions with reciprocal connections to the lateral orbitofrontal cortex. The theory thus is that some aspects of depression may be related to overresponsiveness of the lateral orbitofrontal cortex to nonreward and punishment. Consistent with this, in a study involving hundreds of adolescents (Xie et al., 2021), increased activation of the lateral orbitofrontal cortex to nonreward (not winning in a monetary incentive delay task) was associated with the severity of depressive symptoms. The differences in the lateral orbitofrontal cortex could be related in part to genetic factors and in part to environmental factors, including pathological learning, in lateral orbitofrontal cortex nonreward attractor networks, which might be driven into overactivity by severe events in the life of the individual and influenced by factors such as stress (Rolls, 2018a).

Given that 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., 2021), I have also proposed that in depression, there may be underactivity, undersensitivity, or underconnectivity of the (reward-related) medial orbitofrontal cortex in depression (Rolls, 2016c, 2018a). The theory is further that underresponsiveness of the medial orbitofrontal cortex could contribute to other aspects of depression, such as anhedonia. Other contributing factors to depression are considered elsewhere (Rolls, 2018a).

Increased functional connectivity of the nonreward related lateral orbitofrontal cortex and decreased functional connectivity of the reward-related 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 (BA13), which, in the state of depression, had reduced functional connectivity with memory systems in the parahippocampal gyrus and medial temporal lobe (Cheng et al., 2016) (Fig. 1.8). On the other hand, the lateral orbitofrontal cortex (BA 47/12), which is involved in nonreward and punishing events, did not have this reduced functional connectivity with memory systems. Thus there was evidence of an imbalance between the lateral and medial orbitofrontal regions reflected in relatively decreased reward-related connectivity with the medial temporal lobe memory system.

A second major circuit change observed in depression consisted of increased functional connectivity between the lateral orbitofrontal cortex area BA 47/12 and the precuneus, the angular gyrus, and the temporal visual cortex BA 21 (Cheng et al., 2016) (Fig. 1.8). This enhanced functional connectivity of the nonreward/punishment system (BA 47/12) with the precuneus (involved in the sense of self and agency) and the angular gyrus (involved in language) is thus related to the explicit affectively negative sense of the self and poor self-esteem in depression.

The concept that the differences described above in orbitofrontal connectivity with other brain regions are related to depression is supported by the fact that symptoms of depression correlate with these alterations of functional connectivity, and that the lateral orbitofrontal cortex functional connectivity links described were partially normalized by treatment with antidepressant medication (Cheng et al., 2016).

Because the lateral orbitofrontal cortex responds to many punishing and nonrewarding stimuli in a way that is likely to elicit autonomic/visceral responses (see above), and in view of connections from the lateral orbitofrontal cortex 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 analyses, enabling clear separation and localization of differences between the lateral and medial orbitofrontal cortices. Further analyses that have focused on voxel-level functional connectivity with other brain systems have revealed much more about the systems involved (as described next), provided cross validation on a cohort from the United States (Cheng et al., 2018d), and defined alterations in effective connectivity associated with depression (Rolls et al., 2018), as described next with a summary provided in Fig. 1.9.

Precuneus: Higher connectivity with the lateral orbitofrontal cortex in depression

The precuneus is a medial parietal cortical 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, 2007; Bubb et al., 2017). The precuneus can be

conceptualized as providing access to the hippocampus for spatial and related information from the parietal cortex (given the rich connections between the precuneus and parietal cortex) (Rolls and Wirth, 2018).

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 relative to controls (Fig. 1.9). In patients receiving medication, the functional connectivity between the lateral orbitofrontal cortex and precuneus was closer to that of the controls (Cheng et al., 2018c). These findings support the theory that in depression, the nonreward system in the lateral orbitofrontal cortex has relatively increased interaction with areas in which the self is represented (Freton et al., 2014), including the precuneus, which could relate to low self-esteem in depressed patients (Rolls, 2016c). The concept (Rolls et al., 2020b) is that connections between the orbitofrontal cortex and the precuneus (Hsu et al., 2020) may provide emotion-related information for the autobiographical memory system (Freton et al., 2014).

Parahippocampal gyrus/medial temporal lobe memory system and temporal lobe visual cortex: Lower connectivity with the medial orbitofrontal cortex in depression

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) (Figs. 1.8 and 1.9) and interpreted this as a basis for recall of fewer happy memories, as activation of the medial orbitofrontal cortex correlates with subjective pleasantness, as described above, and the parahippocampal gyrus is a component of the hippocampal episodic memory system (Kesner and Rolls, 2015; Rolls, 2016a, 2018b, 2019a; Rolls and Wirth, 2018). The reduced connectivity of the medial orbitofrontal cortex with the temporal cortical areas in which objects and faces are represented is interpreted as contributing to the reduced positive valuation of signals involved in emotion, such as the sight of known people and their facial expressions (Hasselmo et al., 1989; Critchley et al., 2000).

Treatment of depressed participants with antidepressants did not alter the lower functional connectivity, relative to controls, between medial orbitofrontal cortex voxels and temporal cortical areas, the parahippocampal gyrus, the fusiform gyrus, and the supplementary motor area (Rolls et al., 2020a). The depression-related reduction in these functional connectivities is consistent with the anhedonia of depression and the related reduction in happy memories. What is especially interesting in these results is that these low functional connectivities are not normalized by treatment with antidepressant drugs (Rolls et al., 2020a). This suggests that one goal of future treatment studies of depression might be finding a means of increasing the functionality of the medial orbitofrontal cortex.

Posterior cingulate cortex: Higher functional connectivity with the lateral orbitofrontal cortex in depression

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 and Wirth, 2018; Rolls, 2018b, 2019a,b). The posterior cingulate cortex also has connections with the orbitofrontal cortex (Vogt and Pandya, 1987; Vogt and Laureys, 2009). It also has high functional connectivity with the parahippocampal regions that are involved in episodic memory formation and retrieval (Cheng et al., 2018b; Rolls, 2019a). The posterior cingulate region (including the retrosplenial cortex) is consistently engaged by a range of tasks, including the encoding and retrieval of episodic memories and the retrieval of autobiographical memories, as well as imagining the future. It is also implicated in 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, 2002; Johnson et al., 2002; Sugiura et al., 2005).

To analyze the functioning of the posterior cingulate cortex in depression, we performed a voxel-based resting-state functional connectivity neuroimaging analysis of the posterior cingulate cortex in 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. 1.9). In patients receiving medication, the functional connectivity between the lateral orbitofrontal cortex and the posterior cingulate cortex declined toward control levels. These findings are consistent with the hypothesis that, in depression, the nonreward system in the lateral orbitofrontal cortex has increased effects on memory systems, thereby contributing to rumination about sad memories and events (Cheng et al., 2018b).

Anterior cingulate cortex: Reduced connectivity with the orbitofrontal cortex in depression

The subgenual (subcallosal) anterior cingulate cortex has been implicated in depression and electrical stimulation in this region may relieve depression (Mayberg, 2003; Hamani et al., 2009, 2011; Lozano et al., 2012; Laxton et al., 2013; Lujan et al., 2013) (although this was not confirmed in a randomized double-blind study (Holtzheimer et al., 2017)). However, the subgenual anterior cingulate cortex is also implicated in autonomic function (Gabbott et al., 2003; Alexander et al., 2019), and this could account for 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. It is also possible that electrical stimulation of the subcallosal region, which includes parts of the ventromedial prefrontal cortex (Laxton et al., 2013), may relieve depression, at least in part by activating connections involving the orbitofrontal cortex, other parts of the anterior cingulate cortex, or the striatum (Johansen-Berg et al., 2008; Hamani et al., 2009; Lujan et al., 2013).

In a study of the functional connectivity of the anterior cingulate cortex in depression, it was found in unmedicated patients that the lateral orbitofrontal cortex adjacent to the anteroventral insular cortex had increased functional connectivity with the subgenual/subcallosal anterior cingulate cortex (see fig. S2B in Rolls et al., 2019) (Fig. 1.9). This may reflect increased effects of unpleasant states represented in the lateral orbitofrontal cortex on autonomic output in which the anteroventral insula and subgenual cingulate cortex are implicated (Rolls, 2021a). Increased functional connectivity was also found between the medial orbitofrontal cortex and a region including parts of the supracallosal anterior cingulate cortex (see fig. S2A in Rolls et al. (2019)) (Fig. 1.9). This may reflect reward inputs reaching a supracallosal anterior cingulate cortex region typically involved in representing aversive stimuli.

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

The lateral orbitofrontal cortex has extensive connectivity with the inferior frontal gyrus (Du et al., 2020). In depression, increased functional connectivity (relative to controls) was found between the right inferior frontal gyrus and both lateral and medial orbitofrontal cortices, as well as the cingulate cortex, inferior and middle temporal gyri, the temporal pole, the angular gyrus, the precuneus, the hippocampus, and mid- and superior frontal gyri (Rolls et al., 2020a) (Fig. 1.9). In medicated patients, these functional connectivities of the inferior frontal gyrus with other brain regions were closer to those of controls.

We (Du et al., 2020) proposed that one mechanism by which the orbitofrontal cortex may influence behavior in depression is via the right inferior frontal gyrus, which projects in turn to premotor cortical areas. Thus inferior frontal gyrus-lateral orbitofrontal connectivity may enable the elevated lateral orbitofrontal activity associated with depression to exert an excessive inhibitory effect on behavior. Lesions of the right inferior frontal gyrus are disinhibitory: they impair stopping in the stop-signal task and produce impulsiveness (Aron et al., 2014). Successful stopping in 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

In a large-scale study of depression, there was decreased functional connectivity in patients with depression, relative to controls, between the amygdala and the medial orbitofrontal cortex (involved in reward); the lateral orbitofrontal cortex (involved in nonreward 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, 2012a)); and the parahippocampal gyrus (involved in memory) (Fig. 1.9) (Cheng et al., 2018a). These alterations in the functional connectivity of the amygdala may contribute to the low emotional state in depression, given that the amygdala has some functions in emotion, and is relatively disconnected in 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 relationship between functional connectivity, depressive symptoms (the Adult Self-Report Depressive Problems scores), and poor sleep quality was measured in 1017 participants from the general population in the Human Connectome Project (Cheng et al., 2018d). The brain areas with increased functional connectivities 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 relationship between depression and poor sleep quality. The implication is that there is considerable overlap between the brain systems involved in sleep duration and depression. This has implications for better understanding and treating depression.

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 the role of the lateral orbitofrontal cortex in depression in a general population in the United States in which a tendency to have depressive problems could be assessed. This crossvalidation 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).

A summary of some of the differences in functional connectivity in depression is shown in Fig. 1.9 (Rolls et al., 2020b).

Effective connectivity in depression

Effective connectivity measures the effect of one brain region on another in a particular direction and can, in principle, provide information related to the causal processes that operate in brain function, that is, how one brain region influences another. It is possible to measure effective connectivity in resting-state fMRI by using the time series from different brain regions and utilizing time lags of 0 vs 1 repetition time (Rolls et al., 2018).

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 weaker driving influences of these regions on the medial orbitofrontal cortex, regions implicated in reward, and thus it may help to elucidate, at least in part, reduced happiness in depression (Rolls, 2016c). The effective connectivity between temporal cortical areas and the precuneus was increased in depression; this may relate to representations of the sense of self (Cavanna and Trimble, 2006; Freton et al., 2014), which become more negative in depression (Cheng et al., 2016; Rolls, 2016c). The lateral orbitofrontal cortex, implicated in nonreward and punishment, had an increased level of activity as reflected in the analysis in the depressed group. In addition, activity in the analysis was also higher in the right and left hippocampus of patients with depression, implying heightened memory-related processing (Rolls et al., 2018).

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

In a functional imaging study of 1877 adolescents aged 14 and 1140 adolescents aged 19 employing a monetary incentive delay task, as the reward value was increased (Win condition), there was a graded increase in signal in the medial orbitofrontal cortex (Xie et al., 2021). As the reward value was reduced to zero (the No-Win condition), there was a graded increase in signal in the lateral orbitofrontal cortex (Fig. 1.6).

In a subgroup of these adolescents that had a high score on the Adolescent Depression Rating Scale, the medial orbitofrontal cortex activations in response to the different reward conditions were blunted and the lateral orbitofrontal cortex activations in the No-Win (i.e. Nonreward) condition were consistently high (Xie et al., 2021). These new findings provide support for the hypothesis that depression is associated with decreased sensitivity of the medial orbitofrontal cortex to differences in reward and increased sensitivity of the lateral orbitofrontal cortex to nonreward. Moreover, these differences are evident as early as 14 years of age (Xie et al., 2021). This result thus supports the theory that depressive symptoms can be related to sensitivity to nonreward, that is, to not winning in this monetary reward task.

Possible structural and activity level differences in the orbitofrontal cortex in depression

There is some evidence for altered structure as well as the function of the lateral orbitofrontal cortex in depression (Drevets, 2007; Price and Drevets, 2012; Ma, 2015). For example, reductions of gray-matter volume have been demonstrated in the posterolateral orbitofrontal cortex (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; Grieve et al., 2013). Meta-analyses have revealed that depressed

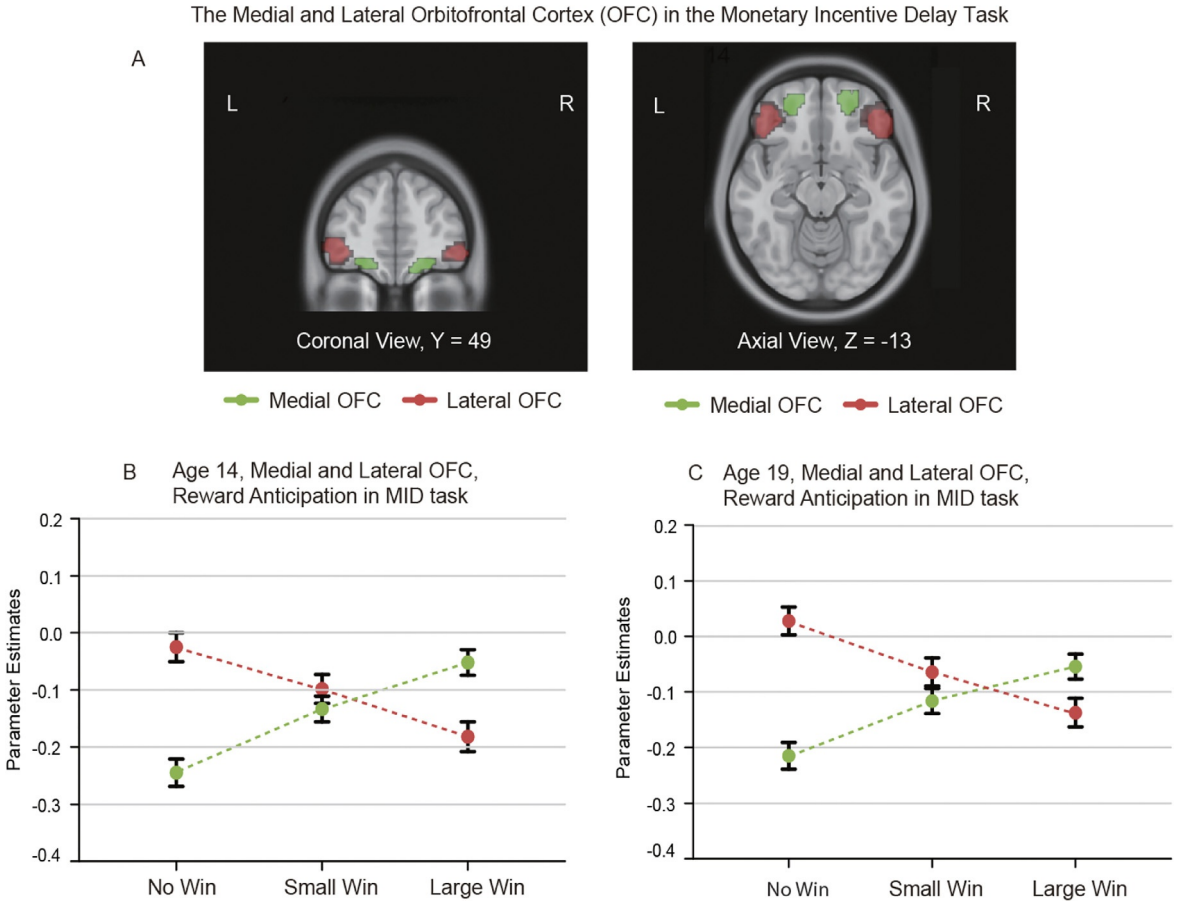

Fig. 1.6. In the monetary incentive delay task, the lateral orbitofrontal cortex is activated by not winning and the medial orbitofrontal cortex by winning. The lateral orbitofrontal cortex region in which activations increased with no reward (No Win) are shown in *red* in 1140 participants at age 19 and in 1877 participants at age 14. The conditions were: Large win (10 points); Small Win (2 points); and No Win (0 points) (at age19; sweets were used instead of points at age 14). The medial orbitofrontal cortex region in which activations increased with increasing reward from No Win to Small Win to Large Win is shown in *green*. The parameter estimates are shown from the activations for the participants (mean ± sem) with the lateral orbitofrontal cortex 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 nonreward 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 that the medial orbitofrontal cortex was less sensitive to the differences in reward value. Modified from Xie C, Jia T, Rolls ET et al. (2021). Reward vs non-reward sensitivity of the medial vs lateral orbitofrontal cortex relates to the severity of depressive symptoms. Biol Psychiatry Cogn Neurosci Neuroimaging 6: 259-269. doi: 10.1016/j.bpsc.2020.1008.1017.

patients exhibit 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 of the Adolescent Brain Cognitive Developmental data set, psychiatric problems, including depression, have been associated with reduced volume of the orbitofrontal cortex, hippocampus, temporal cortex, and medial frontal cortex. These psychiatric disorders, and associated reductions in brain volume, have been linked to problems in the family (Gong et al., 2021), severe nausea and vomiting in pregnancy (Wang et al., 2020), low parental age (Du et al., 2021), 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,

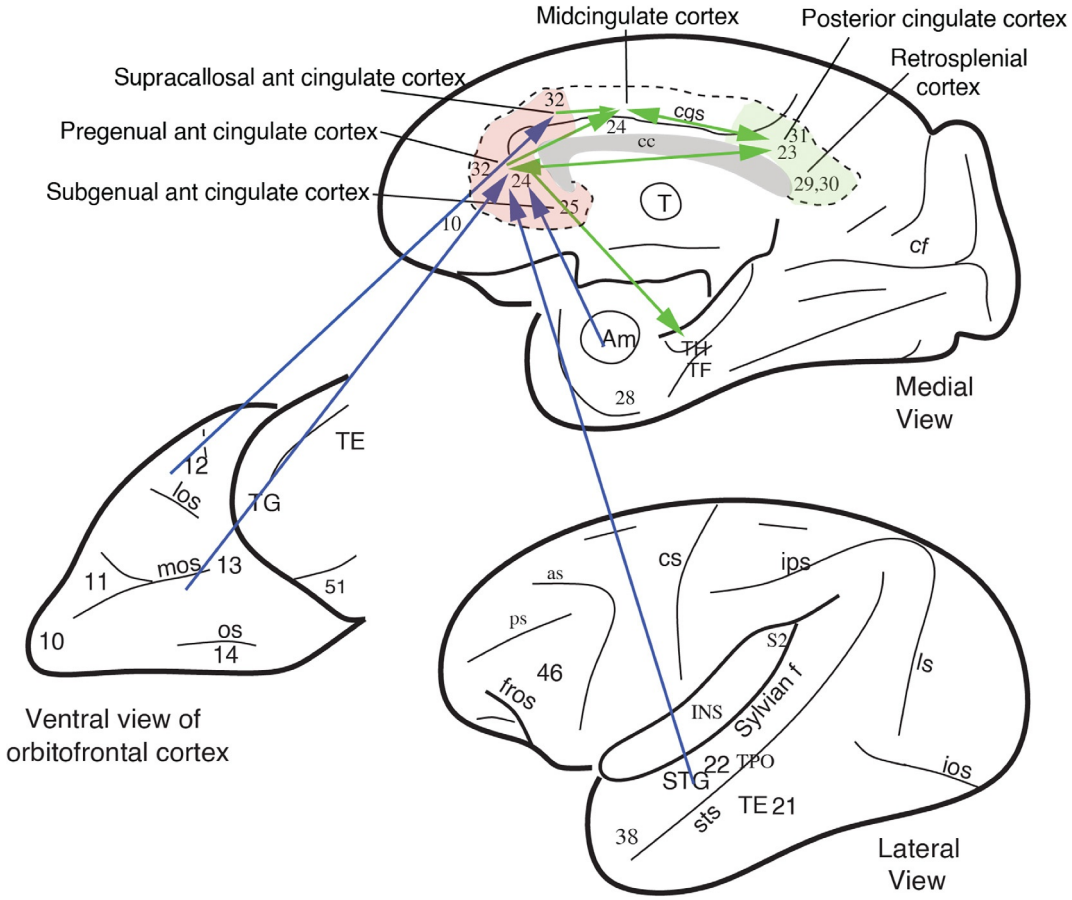

Fig. 1.7. Connections of the anterior cingulate cortex shown on views of the nonhuman primate brain. The *arrows* show the main direction of connectivity, but there are connections in both directions. The supracallosal anterior cingulate cortex is also termed the anterior part of the midcingulate cortex and is distinct from the posterior part of the midcingulate cortex (pMidcingulate). Connections predominantly from the medial/mid-orbitofrontal cortex reach the pregenual cingulate cortex, and connections predominantly from the lateral orbitofrontal cortex reach the supracallosal anterior cingulate cortex. Connections to the anterior cingulate cortex from the temporal lobe are from the (auditory) superior temporal gyrus (STG), the visual and auditory cortex in the superior temporal sulcus, and the amygdala. Abbreviations: *Am*, amygdala; *as*, arcuate sulcus; *BA 12*, lateral orbitofrontal cortex; *BA 13 and 11*, medial orbitofrontal cortex; *BA 23 and 31*, posterior cingulate cortex; *BA 29 and 31,* retrosplenial cortex; *BA 38, TG*, temporal pole cortex; *BA 51*, olfactory (prepyriform and periamygdaloid) cortex; *cc*, corpus callosum; *cf.*, calcarine fissure; *cgs*, cingulate sulcus; *cs*, central sulcus; *INS*, insula; *ios*, inferior occipital sulcus; *ls*, lunate sulcus; *mos*, medial orbital sulcus; *os*, orbital sulcus; *ps*, principal sulcus; *STG (BA 22)*, superior temporal gyrus auditory association cortex; *sts*, superior temporal sulcus; *Sylvian f*, Sylvian (or lateral) fissure (which has been opened to reveal the insula)*; TE (BA 21)*, inferior temporal visual cortex; *TF and TH*, parahippocampal cortex; *TPO*, multimodal cortical area in the superior temporal sulcus.

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 reviewed above (Rolls, 2016c), it has been reported that transcranial magnetic stimulation of the right lateral orbitofrontal cortex, which may disrupt its activity, ameliorates 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, 2018b,c; Rolls et al., 2019, 2020a) of the nonreward lateral orbitofrontal cortex system. The research described here suggests that a search for new treatments that would increase the connectivity of the reward-related medial orbitofrontal

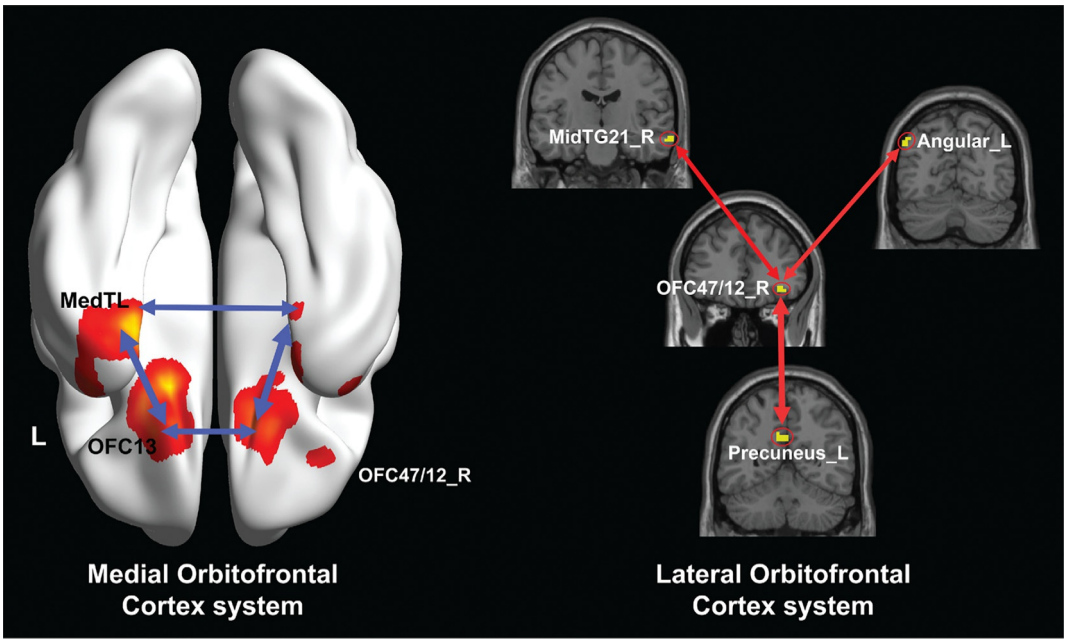

Fig. 1.8. Resting-state functional connectivity in depression. The medial and lateral orbitofrontal cortex networks show different functional connectivity in patients with depression. A decrease in functional connectivity is shown by *blue arrows* (on the left); and an increase in functional connectivity is shown by *red arrows* (on the right). The *red/yellow* color on the brain on the left shows the voxels with decreased functional connectivity in depression. 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; and 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 W, Rolls ET, Qiu J et al. (2016). Medial reward and lateral non-reward orbitofrontal cortex circuits change in opposite directions in depression. Brain 139: 3296–3309.

cortex could be helpful because current medications do not alter the reduced functional connectivities of this region.

Deep brain stimulation of the orbitofrontal cortex might 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, 2019b). Electrical stimulation of the human orbitofrontal cortex can also produce reward and raise mood (Rao et al., 2018), and many of the sites stimulated in this study were in areas 13 and 11, which are categorized as medial orbitofrontal cortex, the area activated by rewards (Rolls, 2019b). 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 orbitofrontal cortex may, for the reasons described here and elsewhere (Rolls, 2019b), 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, 2019a). 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. 1.1), it may be that treatments of the orbitofrontal cortex, where distributed representations of emotion are generated, would be a better target for potential treatments for depression.

The general approach to depression described here, insofar as it relates to effects of increased nonreward or nonreward sensitivity, or decreased reward or reward sensitivity, also has implications for self-help and behavioral treatments for depression (Rolls, 2018a), as well as for medical interventions.

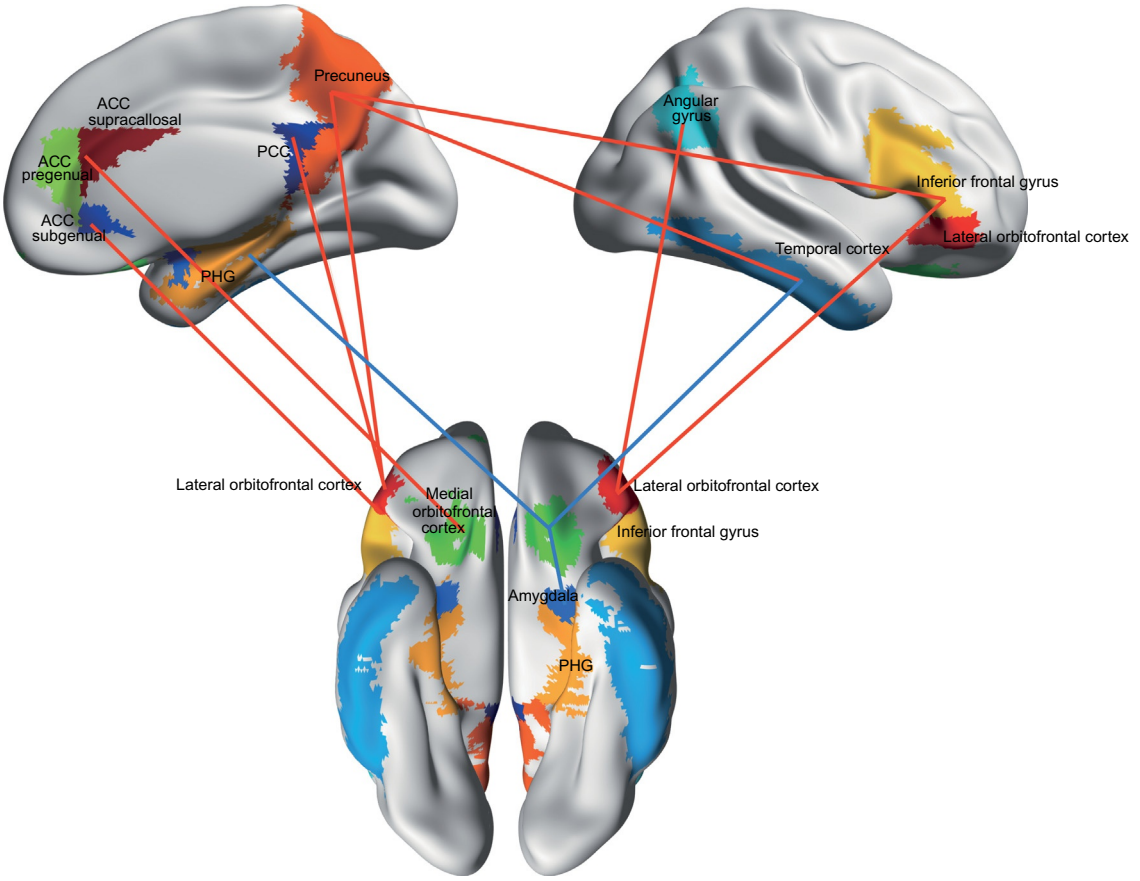

Fig. 1.9. Functional connectivity (FC) differences of the medial and lateral orbitofrontal cortex in major depressive disorder. Higher functional connectivity in depression is shown by *redlines* and includes higher functional connectivity of the nonreward/punishment-related lateral orbitofrontal cortex 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 with *blue-lines* 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. Other colors on the brain indicate other regions with altered functional connectivity in depression. The areas apart from the medial orbitofrontal cortex shown are as defined in the automated anatomical labeling atlas (Rolls et al., 2015), although the investigations that form the basis for the summary were at the voxel level.

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