CHAPTER 8

The Anterior and Midcingulate Cortices and Reward

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Chapter contents

The anterior cingulate cortex (ACC) occupies approximately the anterior one third of the cingulate cortex and is implicated in emotion. Figure 8.1 shows areas 24 and 32 in the pregenual ACC and area 25 in the subgenual ACC. The ACC is distinguished from the midcingulate cortex (MCC) which occupies approximately the middle third of the cingulate cortex and is comprised of areas 24a´b´ and 24d; the latter of which contains part of the caudal cingulate motor area (Chapters 1, 3, and 5) and may be involved in response selection (Rushworth *et al*., 2004). In what follows, I will distinguish the anterior or perigenual cingulate cortex (ACC) from the midcingulate cortex (MCC).

Vogt *et al*. (1996) showed that pain produced an increase in regional cerebral blood flow (rCBF), measured with positron emission tomography (PET) in an area of ACC which included parts of areas 25, 32, 24a, 24b, and/or 24c. They suggested that activation of this region is related to the affective aspect of pain. There are direct projections to the cingulate cortex from medial thalamic nuclei that relay pain inputs, including the parafascicular nucleus. In terms of other connections (Van Hoesen *et al*., 1993; Vogt and Pandya, 1987; Vogt *et al*., 1987), the ACC is connected to the medial orbitofrontal areas, parts of lateral orbitofrontal area 12 (Carmichael and Price, 1995), the amygdala (which projects strongly to cingulate area 25), and the temporal pole cortex, and also receives somatosensory inputs from the insula and other somatosensory cortical areas (Fig. 8.1). The ACC has output projections to the periaqueductal gray in the midbrain which is implicated in the descending control of pain processing, to the nucleus of the solitary tract and dorsal motor nucleus of the vagus through which autonomic effects can be elicited, and to the ventral striatum and caudate nucleus through which behavioural responses could be produced. Consistent with the ACC being involved in affect, the subgenual area 25 was activated by the induction of a sad mood in the study by Mayberg (1997; Chap. 24).

Goals of This Chapter

In this Chapter, I focus on reward-related circuits and activity in the anterior cingulate cortex, and refer to inputs produced by aversive stimuli in order to assess to what extent there is a segregation in the ACC and MCC of effects produced by rewards and punishers. The specific goals include the following:

1 Summarize circuits essential to reward processing in the ACC and MCC.

2 Evaluate the differentiation of pleasant somatosensory, noxious, oral, and olfactory responses in the cingulate gyrus.

3 Demonstrate cingulate activity that codes the reward value for food and water.

4 Present links between cognitive and emotional activations in anterior cingulate and orbitofrontal cortices.

5 Show the role of midcingulate cortex in reward reversal.

The ACC and Reward: Effects of Lesions in Animals

In macaques, ACC lesions can produce a type of social apathy (Hadland *et al*., 2003), including diminished social vocalisation, and also emotional and social changes. Although the exact homology of rodent ACC to that in primates is difficult (Chapter 3), it is of interest that ACC lesions in rodents impair stimulus-reinforcer association learning in tasks in which subjects must learn which stimulus to select in each of eight pairs in order to obtain reward (Bussey *et al*., 1997). ACC lesions also impair the Pavlovian associative stimulus-reward learning involved in autoshaping in rodents, but seem to have their effects only when multiple conditioned stimuli must be distinguished, and perhaps when there is some conflict (Cardinal *et al*., 2002).

The ACC and Reward: Functional Neuroimaging Studies

Functional neuroimaging studies in humans are showing that there appear to be partly separate representations of aversive and positive-valenced affective responses in the ACC. Comparison will also be made with activations in the same studies in the orbitofrontal cortex, for the orbitofrontal cortex has representations of affect (Rolls, 2005), and projects to the ACC.

Pleasant touch versus pain

Experiments have been performed to investigate where in the human touch-processing system tactile stimuli are decoded and represented in terms of their rewarding value or the pleasure they produce. In order to investigate where the reward-related or positively affective value of tactile stimulation is represented, Rolls *et al*. (2003b) performed functional magnetic resonance imaging (fMRI) of humans who were receiving pleasant, neutral, and painful tactile stimuli. They found that a weak but very pleasant touch of the hand with velvet produced much stronger activation of the orbitofrontal cortex than a more intense but affectively neutral touch of the hand with wood. In contrast, the pleasant stimuli produced much less activation of the primary somatosensory cortex S1 than the neutral stimuli as shown in Figure 8.2. It was concluded that part of the orbitofrontal cortex is concerned with

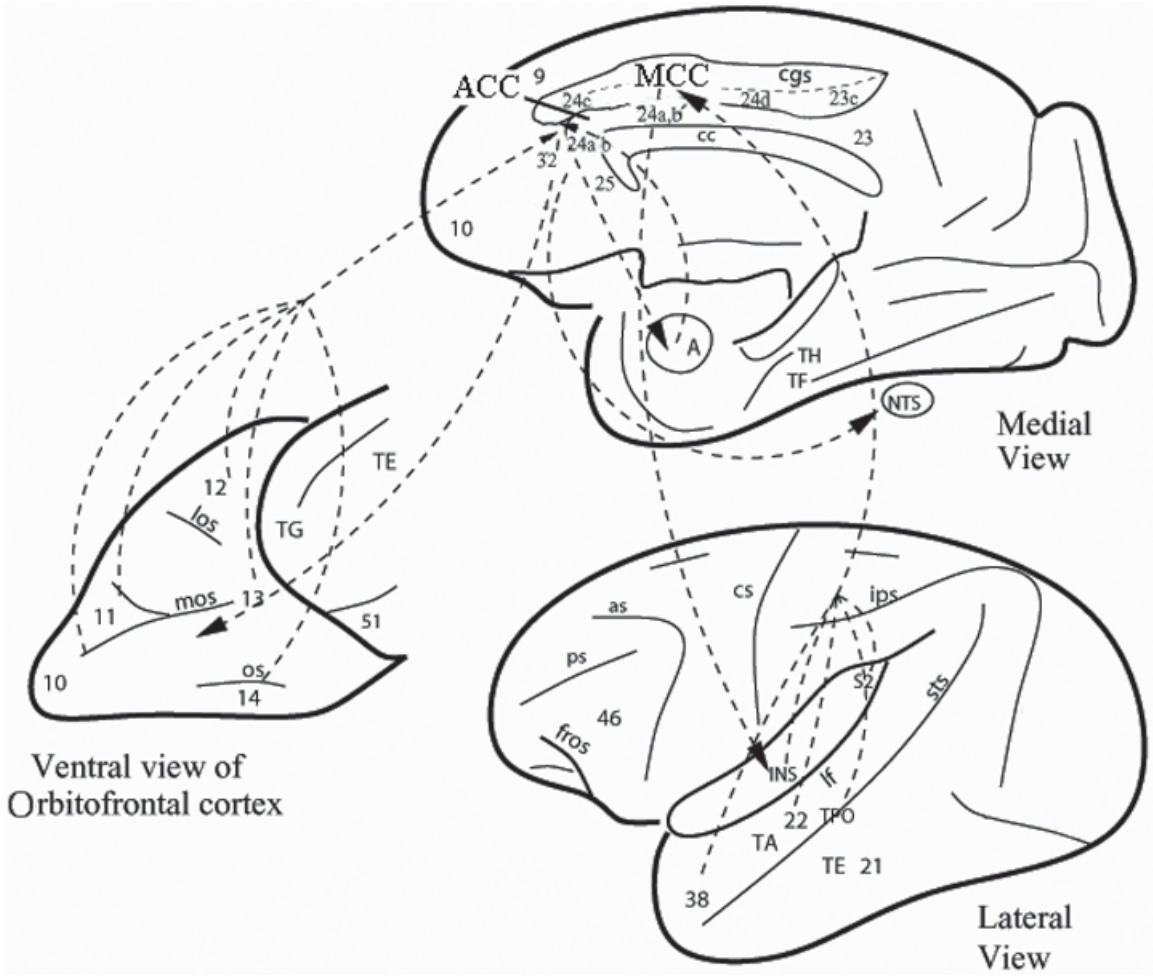

Fig. 8.1 Summary of connections of the pregenual ACC and midcingulate cortical regions. The cingulate sulcus (cgs) has been opened to reveal the cortex in the sulcus, with the dashed line indicating the fundus of the sulcus. The cingulate cortex is in the lower bank of this sulcus, and in the cingulate gyrus hooks above the corpus callosum (cc) and around the genu and splenium of the cc. The ACC has connections with the amygdala and orbitofrontal cortex, whereas area 24c has connections with the somatosensory insula (INS), the auditory association cortex (area 22, TA), and with temporal pole area 38. The MCC areas include area 24d, which is part of the caudal cingulate motor area. Abbreviations: as, arcuate sulcus; cs, central sulcus; mos, medial orbital sulcus; os, orbital sulcus; ps, principal sulcus; sts, superior temporal sulcus. lf, Lateral (or Sylvian) fissure (which has been opened to reveal the insula); A, amygdala; INS, insula; NTS, autonomic areas in the medulla, including the nucleus of the solitary tract and the dorsal motor nucleus of the vagus; TE (21), inferior temporal visual cortex; TA (22), superior temporal auditory association cortex; TF and TH, parahippocampal cortex; TPO, multimodal cortical area in the superior temporal sulcus; 38, TG, temporal pole cortex; 12, 13, 11, orbitofrontal cortex; 51, olfactory (prepyriform and periamygdaloid) cortex.

representing the positively affective aspects of somatosensory stimuli. This part of the orbitofrontal cortex probably receives its somatosensory inputs via the somatosensory cortex both via direct projections and via the insula (Mesulam and Mufson, 1982a, b). In contrast, the pleasantness of a tactile stimulus does not appear to be represented explicitly in the somatosensory cortex. The indication thus is that only certain parts of the somatosensory input, which reflect its pleasantness, are passed on (perhaps after appropriate processing) to the orbitofrontal cortex by the somatosensory cortical areas. Parts of the orbitofrontal cortex were also activated by the painful stimuli as also shown in Figure 8.2, and again this activation was greater relative to the neutral stimulus than that of the somatosensory cortex (Rolls *et al.*, 2003b). It was found in the same study that the pleasant touch activated the pACC, and that, as in earlier studies, the painful input activated posterior MCC (Fig. 8.2). The area activated by pain is typically 10-30 mm behind and above the most anterior part of ACC (see e.g. Fig 8.2 and Rolls *et al.*, 2003b; Vogt and Sikes, 2000).

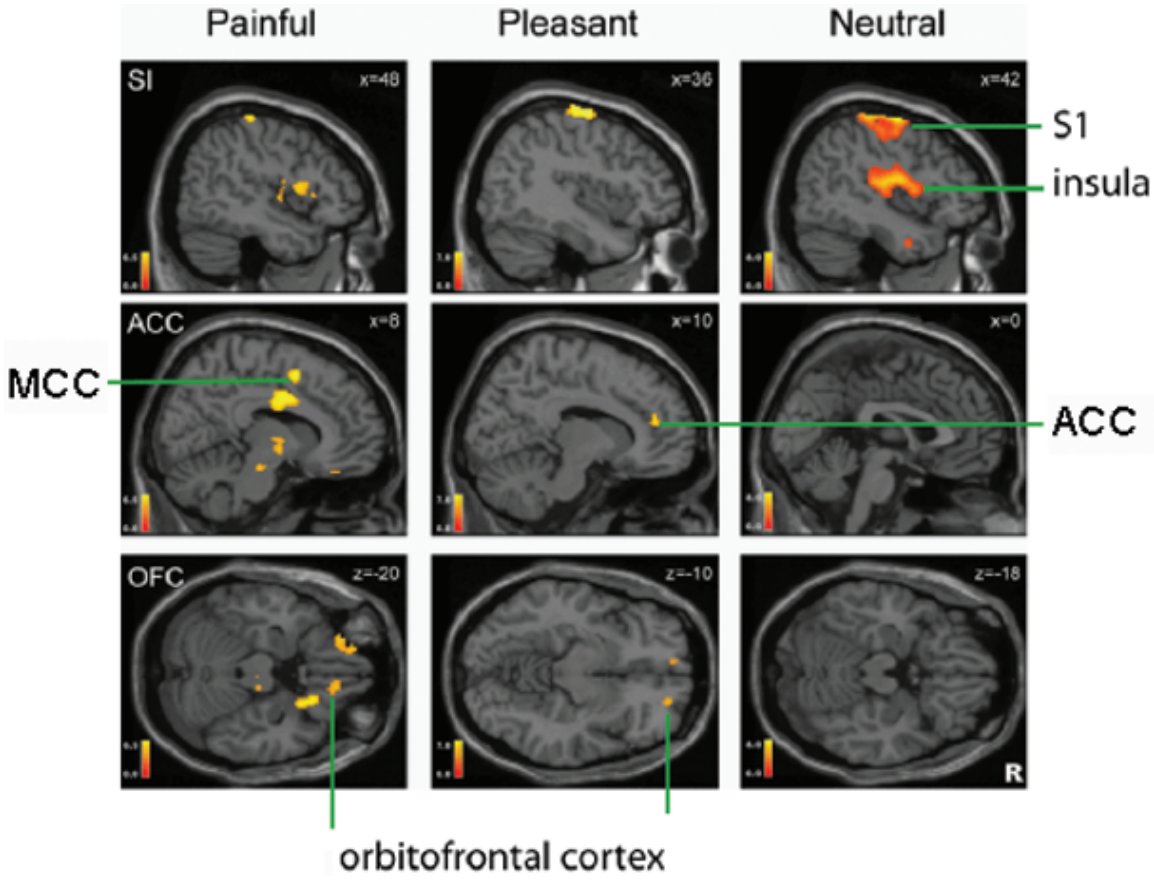

Fig. 8.2 Brain activation to painful, pleasant, and neutral touch of the human brain. The top row shows strongest activation of the somatosensory cortex S1/insula by the neutral touch on parasagittal sections. The middle row shows activation of the most anterior part of the ACC by the pleasant touch, and MCC by the painful touch, on sagittal sections. The bottom row shows activation of the orbitofrontal cortex by the pleasant and by the painful touch on axial sections (horizontal plane). The activations were thresholded at $p<0.0001$ to show the extent of the activations. (After Rolls, O'Doherty *et al.*, 2003d)

Oral somatosensory stimuli and taste

Oral somatosensory stimuli such as the texture of fat can also activate this pACC (de Araujo and Rolls, 2004). The fatty oil in this study was selected to have low olfactory and taste components, and the viscosity of the fat was controlled for by using carboxymethylcellulose (a non-fat food thickening agent) with the same viscosity. Fat texture can be pleasant, as it is a sensory cue to the presence of high-energy value of a food source. Consistent with the pregenual activation produced by fat texture being related to pleasantness, the same region was activated by the taste of sucrose (de Araujo and Rolls, 2004) as shown in Figure 8.3. There is now direct neuronal evidence that primary reinforcers represented in the macaque pACC area 32 are in a small proportion of 1.6% of neurons having taste responses, which are most tuned to sweet taste (Rolls *et al.*, 2007b).

Pleasant versus unpleasant olfactory stimuli

To investigate where the affectively pleasant vs unpleasant properties of olfactory stimuli are represented in the human brain, Rolls *et al.* (2003a) performed an fMRI study with 3 pleasant odours [linalyl acetate (floral, sweet), geranyl acetate (floral), and alpha-ionone (woody, slightly food-related)]; and three unpleasant odours (hexanoic acid, octanol, and isovaleric acid). As shown in Figure 8.4, a group conjunction analysis showed that the 3 pleasant odors produced activations in the medial orbitofrontal cortex and in MCC, whereas the 3 unpleasant odors produced activations in the lateral orbitofrontal cortex and MCC. Interestingly, a correlation analysis showed that the subjective pleasantness of the stimuli (rated during the scanning) was correlated with activations in the orbitofrontal cortex/pACC, whereas the subjective unpleasantness of the stimuli was correlated with activations in a more lateral

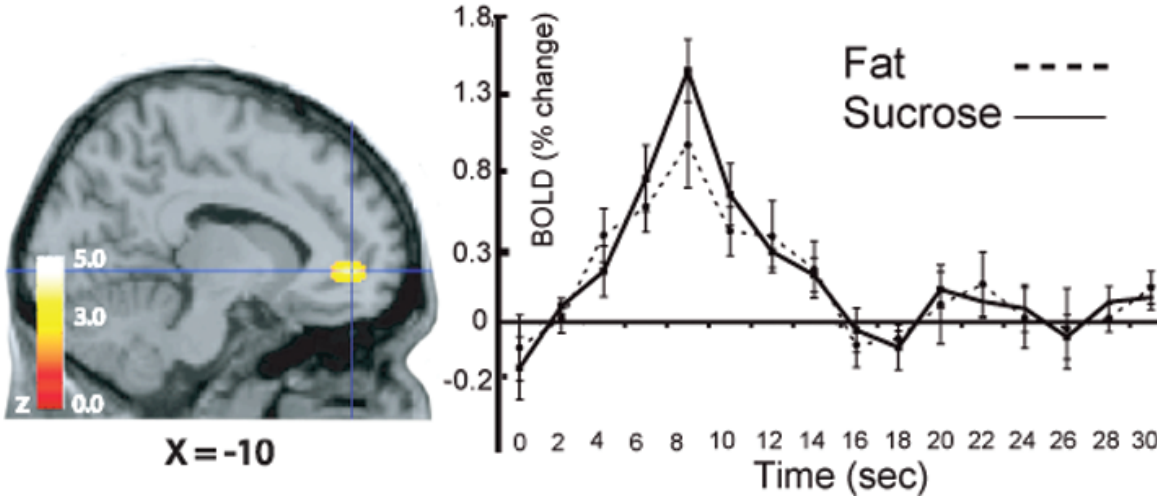

Fig. 8.3 Activation of the pACC by the texture of fat in the mouth and (in a conjunction analysis) by the taste of sucrose. The control for effects of oral viscosity was a carboxymethylcellulose solution with the same viscosity as the fatty oil. The control for somatosensory inputs produced by the sucrose taste stimulus was a tasteless solution. Right: The corresponding average time-course data across trials and subjects from the voxel marked by the cross hairs are shown. (After de Araujo and Rolls, 2004)

and posterior part of the orbitofrontal cortex (Fig. 8.5). This study thus shows a direct correlation between the subjective pleasantness of olfactory stimuli and activations in the ACC, and the results are consistent with the possibility that the origin of the affective olfactory inputs to the ACC is the orbitofrontal cortex, in which neurons in macaques are known to respond to odors based on their reward/punishment association (Critchley and Rolls, 1996; Rolls *et al.*, 1996).

The reward value of food

Activations in the ACC are produced by the flavour of food, though these activations to the flavour of food were not modulated by hunger (Kringelbach *et al.*, 2003b). In contrast, the activation in the orbitofrontal cortex to the flavour of food was correlated with the decline in the pleasantness of food after it was fed to satiety in a sensory-specific satiety paradigm (Kringelbach *et al.*, 2003b). The richness and pleasantness of the flavour of a food is also represented in the pregenual cingulate cortex, in that a glutamate taste and savory odour combination produced much greater activation of the medial orbitofrontal cortex and pregenual cingulate cortex than the sum of the activations by the taste and olfactory components presented separately. Further, activations in these brain regions were correlated with the pleasantness and fullness of the umami flavor, and with the consonance of the taste and olfactory components (McCabe and Rolls, 2007). Activations in the pACC are interestingly related to individual differences in reward, in that there are significantly larger correlations with the subjective pleasantness of the flavour of chocolate in chocolate cravers than in chocolate non-cravers (Rolls *et al.*, 2007a).

The reward value of water

Activations in the MCC are produced by the taste of water when it is rewarding because of thirst (de Araujo *et al.*, 2003). In particular, activation in two dorsal parts of the cingulate cortex was correlated with the pleasantness of the taste of water, which was decreased in thirsty subjects by allowing them to drink to satiety as shown in Figure 8.6.

Rewarding visual and auditory stimuli

Neuroimaging studies concerned with vocal expression identification have reported orbital and medial prefrontal activation. These include a study by Morris *et al.* (1996) using non-verbal sounds expressing fear, sadness, and happiness which, when compared to a neutral condition, activated area 11 (orbitofrontal cortex) bilaterally and medial area 9 on the left. Fear-related increases in activity were also found on the right only in area 11. In another study Phillips *et al.* (1998) found that fearful sounds activated medial area 32 and 24 in sACC, again on the right side only. More extensive studies of facial expression identification have been conducted, and these report activate in a number of sites within both orbital and medial regions, including medial area 9 and ACC areas 32 and 24 (Blair *et al.*, 1999; Dolan *et al.*, 1996; Nakamura *et al.*, 1999)

There is also neuroimaging evidence that complements the effects of lesions (Hornak *et al.*, 2003) in suggesting

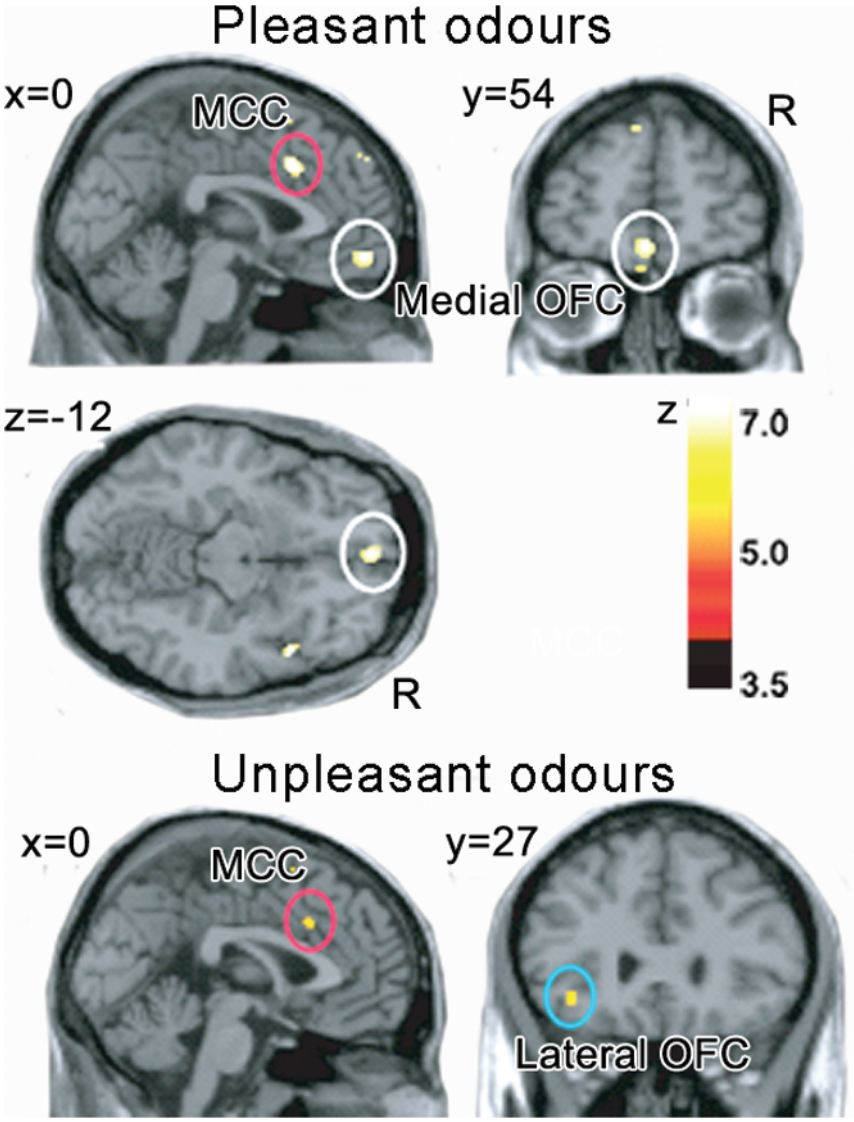

Fig. 8.4 The representation of pleasant and unpleasant odours. Above: Group conjunction results for 3 pleasant odours (see text). Sagittal, horizontal, and coronal views are shown at the levels indicated, all including the same activation in the medial orbitofrontal cortex, OFC (x,y,z = 0,54,-12; Z = 5.23). Also shown is activation for the 3 pleasant odours in the MCC (x,y,z = 2, 20, 32; Z = 5.44). These activations were significant at $p < 0.05$ fully corrected for multiple comparisons. Below: Group conjunction results for the 3 unpleasant odours. The sagittal view (left) shows an activated region of the MCC (x,y,z = 0, 18, 36; Z = 4.42; $p < 0.05$; S.V.C.). The coronal view (right) shows an activated region of the lateral orbitofrontal cortex (−36, 27, −8; Z = 4.23, $p < 0.05$ S.V.C.). All the activations were thresholded at $p < 0.00001$ to show the extent of the activations. After Rolls, Kringelbach, and De Araujo, 2003.

a role for certain medial regions in the subjective experience of emotion. In neuroimaging studies with normal human subjects, bilateral activations in medial area 9 were found as subjects viewed emotion-laden stimuli, and in both medial area 9 as well as in subgenual ACC during self-generated emotional experience (i.e., in the absence of a stimulus) as subjects recalled emotions of sadness or happiness (Lane *et al.*, 1997b; Lane *et al.*, 1998; Lane *et al.*, 1997c; Phillips, 2003; Phillips *et al.*, 2003b, a). On the basis of a review of imaging studies which consistently emphasize the importance of pACC and sACC for emotion, Bush *et al.* (2000) argue that the ACC can be divided into an "affective" division (which includes the sACC and the pACC), and a dorsal "cognitive" division, a view strengthened by the demonstration of reciprocally inhibitory interactions between these two regions.

Also consistent with this region being involved in affect produced by visual stimuli, Lane *et al.* (1997a) found increased regional blood flow in a PET study in a rostral part of ACC where it adjoins prefrontal cortex when humans paid attention to the affective aspects of pictures they were being shown which contained pleasant images (e.g. flowers) and unpleasant pictures (e.g. a mangled face and a snake).

Abstract rewards

Activations in the ACC/medial prefrontal cortex (areas 32 and 10, respectively) are also produced by monetary reward in a visual discrimination task in which money

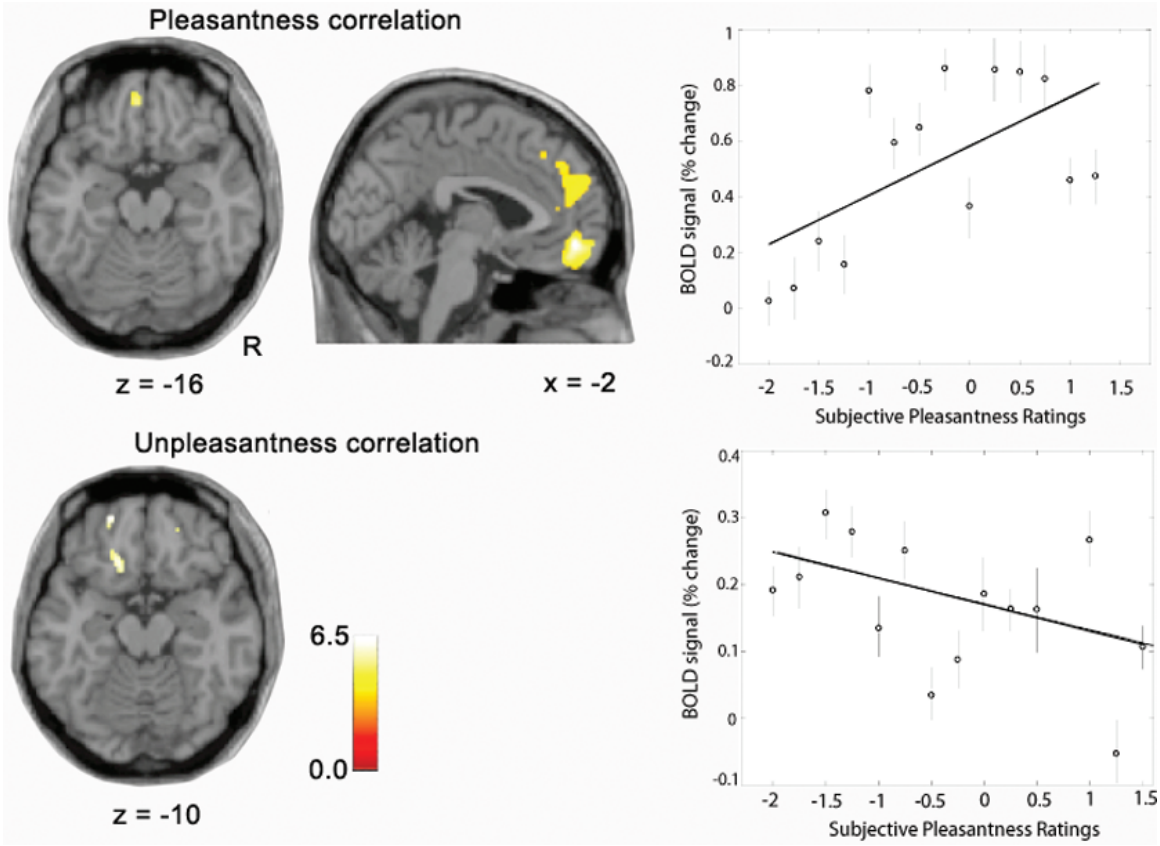

Fig. 8.5 The representation of pleasant and unpleasant odours. Random effects group analysis, correlation analysis of the BOLD signal with the subjective pleasantness ratings. On the top left is shown the region of the medio-rostral orbitofrontal (peak at [−2, 52, -10]; z = 4.28) correlating positively with pleasantness ratings, as well as the region of the anterior cingulate cortex in the top middle. On the far top right of the figure is shown the relation between the subjective pleasantness ratings and the BOLD signal from this cluster (in the medial orbitofrontal cortex at Y = 52), together with the regression line. The means±SEM across subjects are shown. At the bottom of the figure is shown the regions of left more lateral orbitofrontal cortex (peaks at [−20, 54, −14]; z = 4.26 and [−16, 28, −18]; z = 4.08) correlating negatively with pleasantness ratings. On the far bottom right of the figure is shown the relation between the subjective pleasantness ratings and the BOLD signal from the first cluster (in the lateral orbitofrontal cortex at Y = 54), together with the regression line. The means±SEM across subjects are shown. The activations were thresholded at $p < 0.0001$ for extent. (After Rolls, Kringelbach, and De Araujo, 2003)

may be won or lost depending on the visual stimulus selected (O'Doherty *et al.*, 2001).

Effects of cognitive states on reward representations in ACC

Affective states, mood, can influence cognitive processing, including perception and memory (see Rolls, 2005). But cognition can also influence emotional states. This is not only in the sense that cognitively processed events, if decoded as being rewarding or punishing, can produce emotional states (Rolls, 2005), but also in the sense described here that a cognitive input can bias emotional states in different directions. The modulation is rather like the top-down effects of attention on perception (Deco and Rolls, 2003, 2005b; Rolls and Deco, 2002), not only phenomenologically, but also probably computationally.

An example of such cognitive influences on the reward/aversive states that are elicited by stimuli was revealed in a study of olfaction described by de Araujo and Rolls (2005). In this investigation, a standard test odour, isovaleric acid with a small amount of cheddar cheese flavour added to make it more pleasant, was used as the test olfactory stimulus delivered with an olfactometer during functional neuroimaging with fMRI (de Araujo and Rolls, 2005). This odour is somewhat ambiguous, and might be interpreted as the odour emitted by a cheese-like odour (rather like brie), or might be interpreted as a rather pungent and unpleasant body odour. A word was shown during the 8 odour delivery. On some trials, the test odour was accompanied by the visually presented word "Cheddar cheese". On other trials, the test odour was

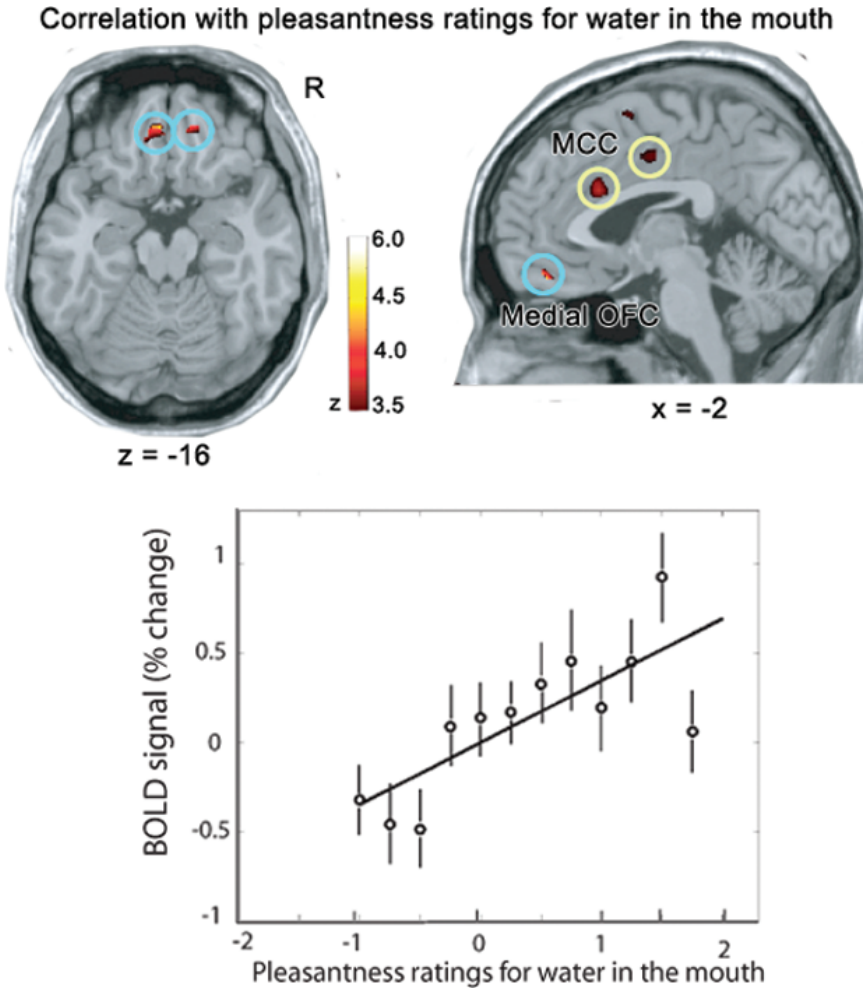

Fig. 8.6 Representation of the pleasantness of the taste of water in the human brain. Correlations with the pleasantness of the taste of water in a group random effects analysis. Top left: Regions of the medial caudal orbitofrontal where the activation was correlated with the subjective pleasantness ratings of water throughout the experiment. Bottom: A scatter plot showing the values of the BOLD signal in the medial orbitofrontal cortex (mean ± SEM across subjects), with the regression line shown. Top right: The regions of MCC where activation was correlated with the subjective pleasantness ratings of water given throughout the experiment. (After DeAraujo, Kringelbach, Rolls, and McGlone, 2003)

accompanied by the visually presented word "Body odour". A word label was used rather than a picture label to make the modulating input very abstract and cognitive. First, it was found (consistent with psychophysical results of Herz and von Clef, 2001) that the word labels influenced the pleasantness ratings of the test odour.

However, very interestingly, it was found that the word label modulated the activation to the odour in brain regions activated by odours such as the orbitofrontal cortex (secondary olfactory cortex), cingulate cortex, and amygdala. For example, in the medial orbitofrontal cortex the word label "Cheddar cheese" caused a larger activation to be produced to the test odour than when the word label "Body odour" was being presented. In these medial orbitofrontal cortex regions and the amygdala, and even possibly in some parts of the primary olfactory cortical areas, the activations were correlated with the pleasantness ratings, as shown in Figure 8.7. This is consistent with the finding that the pleasantness of odours is represented in the medial orbitofrontal cortex (Rolls *et al.*, 2003a).

The effects of the word were smaller but still present in the cingulate and medial orbitofrontal cortices when clear air was the stimulus, as shown in Figure 8.8. This indicates that the effects being imaged when the odours were present were not just effects of a word that influenced representations by a top-down recall process, but were instead cognitive top-down effects on states elicited by odours. This type of modulation is typical of a top-down modulatory process such as has been analyzed quantitatively in the case of attention (Deco and Rolls, 2005a, b), and indeed no significant effect of the word was found in the amygdala and earlier olfactory cortical areas (see Fig. 8.8). A further implication is that the activations in the human amygdala and primary olfactory cortical areas are more closely bound to the eliciting stimulus and are less influenced by cognition than are activations in the orbitofrontal and cingulate cortices.

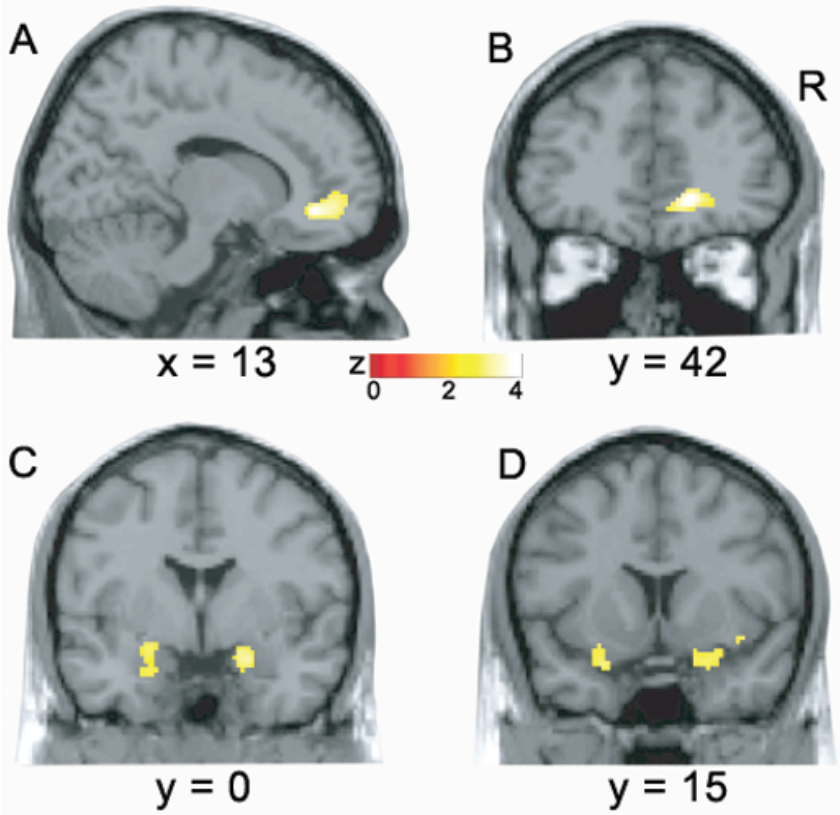

Fig. 8.7 Cognition and emotion. Group (random) effects analysis showing the brain regions where the BOLD signal was correlated with pleasantness ratings given to the test odour. The pleasantness ratings were being modulated by the word labels. A. Activations in the pACC, in the region adjoining the medial OFC, shown in a sagittal slice. B. The same activation shown coronally. C. Bilateral activations in the amygdala. D. These activations extended anteriorly to the primary olfactory cortex. The image was thresholded at $p < 0.0001$ uncorrected in order to show the extent of the activation. (After de Araujo and Rolls, 2005)

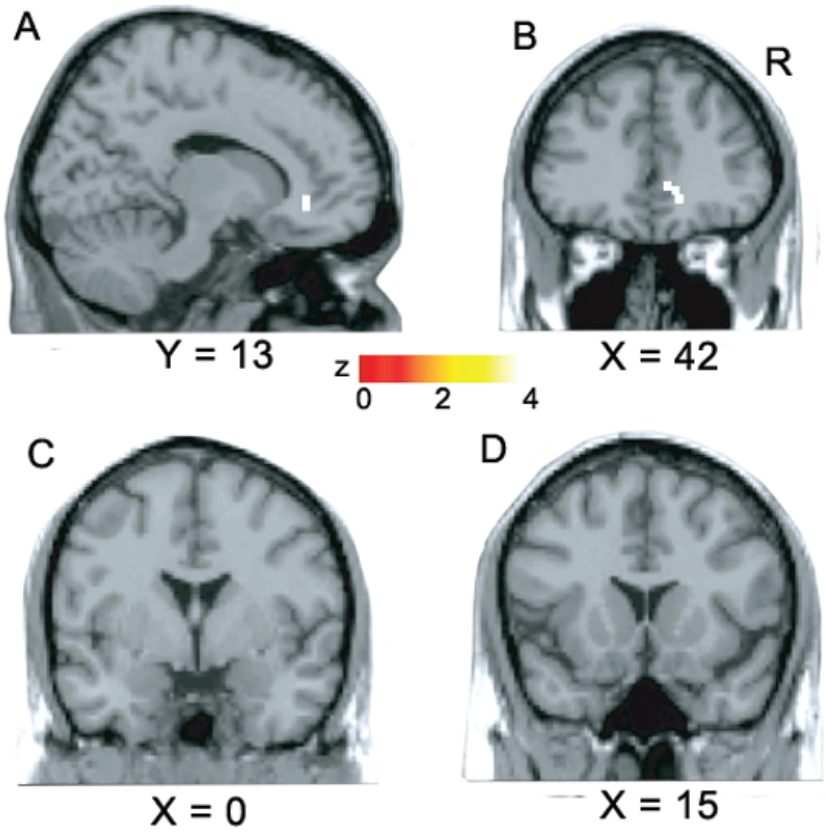

Fig. 8.8 Cognition and emotion. Group (random) effects analysis showing the brain regions where the BOLD signal was correlated with pleasantness ratings given to the clean air. The pleasantness ratings were being modulated by the word labels. A, Activations in the ACC, in the region adjoining the medial OFC, shown in a sagittal slice. B. The same activation shown coronally. No significant correlations were found with clean air in the amygdale. C. or primary olfactory cortex. D. The image was thresholded at $p < 0.0001$ uncorrected in order to show the extent of the activation. (After de Araujo *et al.,* 2005)

These findings show that cognition can influence and indeed modulate reward-related (affective) processing as far along the human olfactory system as the secondary olfactory cortex in the orbitofrontal cortex, and in the ACC and amygdala. This emphasizes the importance of cognitive influences on emotion, and shows how in situations that might range from enjoying food to a romantic evening, the cognitive top-down influences can play an important role in influencing affective representations in the brain. The mechanisms by which cognitive states have top-down effects on emotion are probably similar to the biased competition mechanisms that subserve top-down attentional effects (Deco and Rolls, 2003, 2005a, b; Rolls and Deco, 2002).

Reward reversal

As well as being able to detect when a reward has been obtained, it is also important in controlling learning and behaviour to be able to detect when an expected reward is not obtained (Rolls, 1999; Rolls, 2005). Thorpe *et al.* (1983) discovered error neurons in the macaque orbitofrontal cortex that responded when an expected reward was not obtained. Some neurons responded, for example, on reversal trials in a visual discrimination task, and others in extinction when an expected reward was no longer available. These neuronal responses encode a mismatch between the expected reward predicted by a reward-related visual stimulus, and a primary (unlearned) reward such as the taste of food.

In a neuroimaging study in humans, evidence shows that non-reward used as a signal to reverse behavioural choice is represented in the human orbitofrontal and midcingulate cortices. Kringelbach *et al.* (2003a) used the faces of two different people, and if one face was selected then that face smiled, and if the other was selected, the face showed an angry expression. After good performance was acquired, there were repeated reversals of the visual discrimination task. Kringelbach and Rolls (2003) found that activation of a lateral part of the orbitofrontal cortex in the fMRI study was produced on the error trials, that is when the human chose a face, and did not obtain the expected reward as shown in Figure 8.9. Activation was also produced on the error trials in a dorsal part of the MCC. Control tasks showed that the response was related to the error, and the mismatch between what was expected and what was obtained, in that just showing an angry face expression did not selectively activate this part of the lateral orbitofrontal cortex. An interesting aspect of this study that makes it relevant to human social behaviour is that the conditioned stimuli were faces of different individuals, and the unconditioned stimuli were face expressions. Thus the association that was being reversed in this study was between a representation of face identity and a representation of face expression. Moreover, the study reveals that the human orbitofrontal cortex and MCC are very sensitive to social feedback when it must be used to change behaviour (Kringelbach and Rolls, 2003, 2004). The non-reward signal evident in the dorsal part of the MCC shown in Figure 8.9 could reflect the inputs received from the orbitofrontal cortex, in which the same activation was found, and in which representations of stimuli associated with primary reinforcers, and the primary reinforcers themselves, are represented (Rolls, 1999, 2004, 2005, 2006).

The ACC and Reward: Effects of Lesions in Humans

Devinsky *et al.* (1995) and Cardinal *et al.* (2002) review evidence that anterior cingulate lesions in humans produce apathy, autonomic dysregulation, and emotional instability. An investigation in patients with selective surgical lesions has shown that patients with unilateral lesions of the subgenual of the ACC and/or medial areas 10 and 11 were in some cases impaired on voice and face expression identification, had some change in social behaviour [such as inappropriateness, being less likely to notice when other people were angry, not being close to his or her family, and doing things without thinking], and had significant changes in their subjective emotional state (Hornak *et al.*, 2003). Unilateral lesions were sufficient to produce these effects, and there were no strong laterality effects.

Hornak *et al.* (2003) also showed that damage restricted to the orbitofrontal cortex can produce impairments in face and voice expression identification, which may be primary reinforcers. The system is sensitive in that even patients with unilateral orbitofrontal cortex lesions may be impaired. The impairment is not a generic impairment of the ability to recognize any emotions in others, in that frequently voice but not face expression identification was impaired, and vice versa. This implies some functional specialization for visual versus auditory emotion-related processing in the human orbitofrontal cortex. The results also show that the changes in social behavior can be produced by damage restricted to the orbitofrontal cortex. The patients were particularly likely to be impaired on emotion recognition as they were less likely to notice when others were sad, happy, or disgusted. They were more impaired on emotional empathy because they were less likely to comfort those who are sad or afraid, or to feel happy for others who are happy and on interpersonal relationships because they did not care what others think, and were not close to his/her family. Finally, they were less likely to cooperate with others, were impatient and impulsive, and had difficulty making and keeping close relationships. The results also show that changes in subjective emotional state (including sadness,

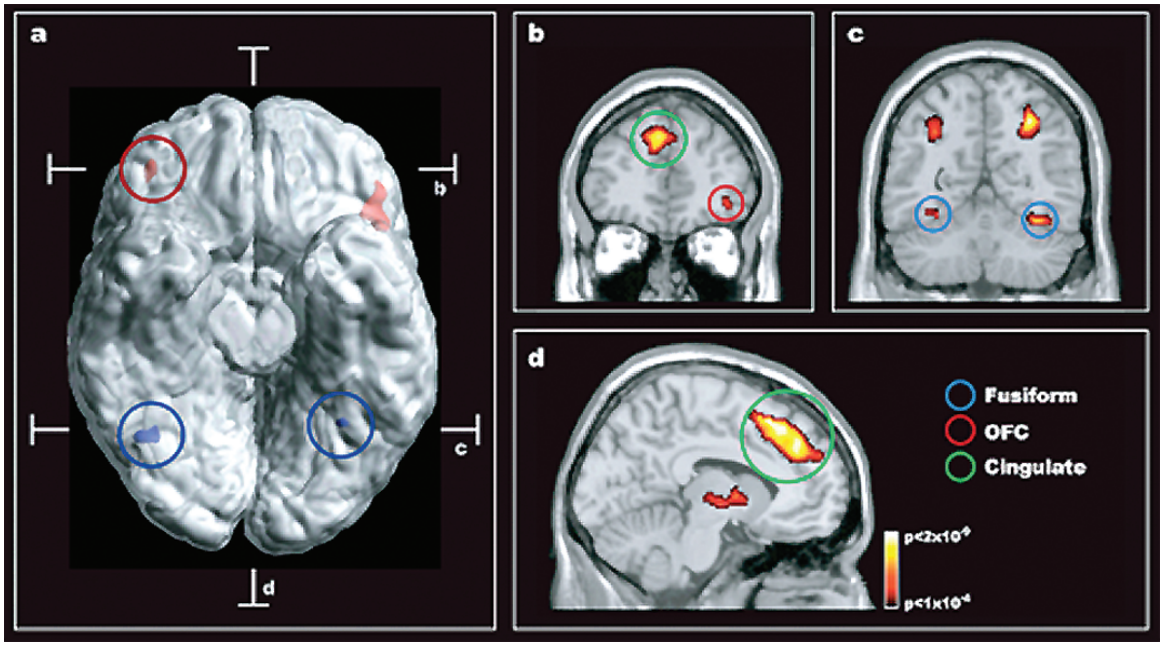

Fig. 8.9 Social reversal: Composite figure shows that changing behaviour based on face expression is correlated with increased activity in orbitofrontal and midcingulate cortices. A. Two different group statistical contrasts were superimposed on a ventral view of the brain with the cerebellum removed (activations thresholded at P=0.0001 to show their extent), and with the location of the two coronal slices (b,c) and the transverse slice (d). The red activations in the orbitofrontal cortex (OFC, maximal activation: Z = 4.94: 42,42,−8; and Z = 5.51; x,y,z = −46, 30, −8) shown on the brain surface arise from a comparison of reversal events with stable acquisition events, while the blue activations in the fusiform gyrus (Fusiform, maximal activation: Z > 8; 36,−60,−20 and Z = 7.80; −30,−56,−16) arise from the main effects of face expression. B. Coronal slice through frontal cortex shows the cluster in the right OFC across all nine subjects when comparing reversal events with stable acquisition events. Significant activity was also in much of midcingulate cortex (Cingulate, maximal activation: Z = 6.88; −8,22,52; green circle). C. Coronal slice through the posterior part of the brain shows the response to the main effects of face expression with significant activation in the fusiform gyrus and the cortex in the intraparietal sulcus (maximal activation: Z > 8; 32, −60, 46 and Z > 8: −32, −60, 44). D. The transverse slice shows the extent of the activation in midcingulate cortex when comparing reversal events with stable acquisition events. (After Kringelbach and Rolls, 2003)

anger and happiness) can be produced by damage restricted to the orbitofrontal cortex (Hornak *et al.*, 2003). In addition, the patients with bilateral orbitofrontal cortex lesions were impaired on the probabilistic reversal learning task (Hornak *et al.*, 2004).

The findings overall make clear the types of deficit found in humans with orbitofrontal cortex damage, and can be easily related to underlying fundamental processes in which the orbitofrontal cortex is involved as described by Rolls (1999, 2005), including decoding and representing primary reinforcers, being sensitive to changes in reinforcers, and rapidly readjusting behaviour to stimuli when the reinforcers make change available. The implication is that some of the inputs to the anterior and midcingulate cortices which produce similar deficits may arise in the orbitofrontal cortex. Consistent with this, unilateral lesions of the ACC and some of medial area 9 can produce voice and/or face expression identification deficits, changes in social behaviour, and marked changes in subjective emotional state (Hornak *et al.*, 2003).

Anterior Cingulate Cortex and Reward: Synthesis

The locations of some of the activations described above are shown in Figure 8.10 from which it is clear that many positively valenced affective stimuli are represented in pACC with some less positively affective or negatively valenced affective stimuli activating the anterior part of midcingulate cortex. A current working hypothesis is that the affective ACC receives inputs about expected rewards and punishers, and about the rewards and punishers received, from the orbitofrontal cortex and amygdala. There is some segregation of the areas that receive these inputs. The ACC may compare these signals, and utilize them in functions such as affective decision making and in producing

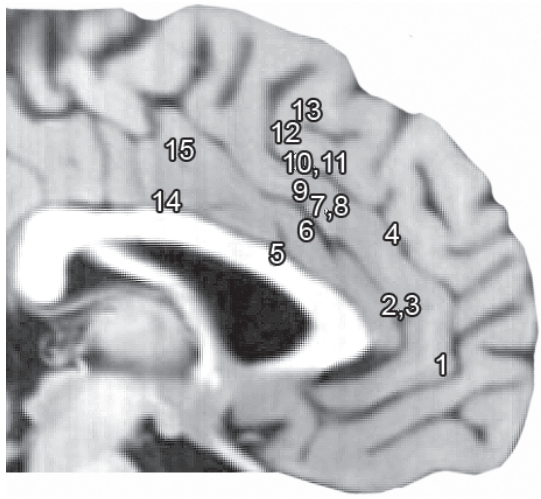

Fig. 8.10 Activations of pACC by different positively valenced, affective stimuli with less positively affective or negatively valenced, affective stimuli activating MCC. Touch: 3 pleasant [10 42 16], 14 unpleasant/pain [10 −6 34], 5 unpleasant/pain [−8 12 22] (from Rolls *et al.,* 2003d); Odour: 7 pleasant [2 20 32], 2 correlation with pleasantness ratings [4 42 12], 9 unpleasant [0 18 36] (from Rolls *et al* 2003c); 8 Monetary loss [2 25 32] (from O'Doherty *et al.,* 2001a); Water: 6 correlation with pleasantness [−2 19 28], 15 correlation with pleasantness [−2 −5 43] (from De Araujo *et al.,* 2003b); Taste: 10 glucose [9 17 42], 11 salt [15 21 42], 4 salt [−16 39 24] (from O'Doherty *et al.,* 2001b); Sucrose and fat: 1 [−10 48 −2] (from De Araujo and Rolls, 2004); Non-reward in a social reversal task did not activate cingulate cortex: 13 [−8 22 52], 12 [−6 18 48] (from Kringelbach and Rolls, 2003).

autonomic responses. As such, the pACC may act as an output system for emotional responses and actions.

The subgenual ACC (area 25) via its outputs to the hypothalamus and brainstem autonomic regions, is involved in the autonomic component of emotion (Barbas and Pandya, 1989; Gabbott *et al.*, 2003; Koski and Paus, 2000; Ongur and Price, 2000; Chapter 10). The ACC is also activated in relation to autonomic events and Nagai *et al.* (2004) have shown that there is a correlation with skin conductance, a measure of autonomic activity related to sympathetic activation in the ACC and related areas.

Midcingulate Cortex, the Cingulate Motor Area, and Action-Outcome Learning

The ACC has been distinguished from MCC anatomically as discussed above. The MCC is activated by noxious stimulation during pain perception but, because this area is also activated in response-selection tasks such as divided attention and Stroop tasks which involve cues which cause conflict such as the word red written in green when the task is to make a response to the green colour, it is suggested that activation of this MCC by painful stimuli was related to the response-selection processes initiated by painful stimuli (Derbyshire *et al.*, 1998; Vogt *et al.*, 1996). Both the ACC and MCC regions have been activated in functional neuroimaging studies not only by physical pain, but also by social pain, for example being excluded from a social group (Eisenberger and Lieberman, 2004).

The MCC may be further subdivided into an anterior part that includes the rostral cingulate motor area (area a24c′) concerned with skeletomotor control during avoidance and fear tasks, and a posterior MCC part that includes the caudal cingulate motor area (area p24c′ and 24d) which may be more engaged in skeletomotor orientation (Vogt *et al.*, 2003; Chapter 5).

In macaques, lesions that include parts of the ACC/MCC do not affect working memory (measured by delayed alternation), and are in this respect different from dorsolateral prefrontal cortex lesions, but may affect task switching (Rushworth *et al.*, 2003; Rushworth *et al.*, 2004). In human imaging studies it has been found that the anterior/midcingulate cortex is activated when there is a change in response set or when there is conflict between possible responses, but it is not activated when only stimulus selection is at issue cite (Rushworth *et al.*, 2002; van Veen and Carter, 2002).

Some anterior/midcingulate neurons respond when errors are made (Niki and Watanabe, 1979; Amiez *et al*, 2006), or when rewards are reduced (Shima and Tanji, 1998; Chapter 5) and in similar imaging studies (Bush *et al.*, 2002). In humans, an event-related potential (ERP), called the error-related negativity (ERN), may originate in the area 24c′ (Ullsperger and von Cramon, 2001), and many studies provide evidence that errors made in many tasks activate the anterior/midcingulate cortex, whereas tasks with response conflict activate the superior frontal gyrus (Rushworth *et al.*, 2004).

Anterior cingulate neurons in macaques may also respond to rewards (Ito *et al.*, 2003), and indeed action-outcome associations appear to be represented in the ACC, in that in tasks in which there were different relations between actions and rewards, it was found that even before a response was made, while the monkey was looking at a visual cue, the activity of ACC neurons depended on the expectation of reward or non-reward (25%), the intention to move or not (25%), or a combination of movement intention and reward expectation (11%) (Matsumoto *et al.*, 2003). There is now neuronal evidence that primary reinforcers are represented in the primate pregenual cingulate cortex, in that a small proportion, 1.6% of neurons have taste responses, with most tuned to sweet taste (Rolls *et al.*, 2007b). In rodents a part of the medial prefrontal/ACC is involved in learning relations between behavioural responses and

reinforcers, that is between actions and outcomes (Balleine and Dickinson, 1998; Cardinal *et al.*, 2002; Killcross and Coutureau, 2003). Balleine and Dickinson (1998) showed that the sensitivity of instrumental behaviour to whether a particular action was followed by a reward was impaired by ACC lesions in area 32.

To perform action-outcome learning, the anterior/midcingulate cortical regions must contain a representation of the behavioural action just performed, and receive information about rewards and punishers being obtained. The reward-related information may come from structures such as the orbitofrontal cortex and amygdala. In addition, the cortical area involved in action-outcome learning must be able to hold the representation of the action just performed in a type of working memory until the reward or punishment is received (or more probably receive delay-related information from the prefrontal cortex, see Rushworth *et al.*, 2004), as there may be a delay between the action and the outcome.

When making decisions about actions, it is important to take into account the costs as well as the benefits (rewards). There is some evidence implicating the rodent subgenual ACC in this, that rats with lesions in this area were impaired in a task which required decisions about an action with a large reward but a high barrier to climb versus an action with a lower reward but no barrier (Walton *et al.*, 2003; Walton *et al.*, 2002). An output region from the ACC for action-outcome learning may be the nucleus accumbens, for neurons in the macaque nucleus accumbens as well as the ACC appear to encode the position of the monkey in a sequence of actions required to obtain a reward (Shidara and Richmond, 2002). It should be noted that stimulus-response or habit learning, although instrumental, is separate, in that it involves different associations (between stimuli and responses, not between actions and outcomes), and is implemented in different brain regions such as the basal ganglia.

Although understanding of the brain mechanisms of action-outcome learning is still at an early stage, it may well involve the ACC. It is not yet clear whether the ACC and MCC regions are involved together in action-outcome learning, but this does appear to be a possibility. There may be strong representations of rewards and punishers (see above), and the elicitation of autonomic responses (Nagai *et al.*, 2004), in the ACC, accounting for its designation as an affective region. This reward and punisher-related information may then reach the MCC, where it can be associated with skeletomotor response representations, producing neurons that respond to different combinations of actions and outcomes. Although such neurons may well be a crucial part of the implementation of action-outcome learning, it is not yet clear at the computational level how costs are taken into account and the correct action is selected. This will be a topic of future interest.

In any case, it is useful to place action-outcome learning in the wider context of emotion. When stimuli are presented, they are decoded to determine whether they are primary rewards or punishers by structures such as the orbitofrontal cortex and amygdala. If the stimulus presented has been associated with a primary reward or punisher, this stimulus-stimulus association is also decoded in the orbitofrontal cortex and amygdala. Affective states and autonomic responses, can be produced by these processes, subjective states are influenced, and choices of stimuli to select are determined. Indeed, a whole host of behavioural changes occur, including behaviours which are different in that they are not influenced normally by expected punishers. When reinforcer contingencies change, the orbitofrontal cortex is important in reversing the stimulus-stimulus association, and contains appropriate error neurons. It thus seems to be able to implement stimulus selection. The orbitofrontal cortex is involved in this way in decision making and executive function (Rolls, 2005). On the other hand, if more complex contingencies are operating so that actions that give rise to particular outcomes must be selected, then this clearly requires a representation of actions, and it may be for these situations that the anterior cingulate cortex is especially important. Much affective computation, including the elicitation of affective states, may thus not computationally require the anterior cingulate cortex; but if to obtain the goal particular responses must be selected, then in those affective situations the anterior cingulate cortex may be especially computationally important (Rolls, 2005).

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