

Chapter 2

The cingulate cortex and limbic systems for action, emotion, and memory

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Abstract

Different limbic structures including the hippocampal memory system and the amygdala/orbitofrontal emotion system have very different connectivity and functions, and it has been suggested that we should no longer think of a single limbic system. A framework is provided for understanding the connectivity and functions of different parts of the cingulate cortex in action, emotion, and memory, in the context of connections of different parts of the cingulate cortex with other limbic and neocortical structures. First, the anterior cingulate cortex receives information from the orbitofrontal cortex about reward and nonreward outcomes. The posterior cingulate cortex receives action-related and spatial information from parietal cortical areas. It is argued that these are inputs that allow the cingulate cortex to perform action-outcome learning, with outputs from the midcingulate motor area to premotor areas. Damage to the anterior cingulate cortex impairs action-outcome learning and emotion because of its reward-related representations. Second, the posterior cingulate cortex provides “action” and “spatial” information from the parietal cortex into the hippocampal memory system via the parahippocampal gyrus, and the anterior cingulate cortex (receiving from the orbitofrontal cortex) provides reward-related input into the hippocampal memory system via the posterior cingulate and parahippocampal gyrus. Thus posterior cingulate damage can impair hippocampal episodic memory and retrieval, especially the spatial component. These functions are related to the place of this proisocortical limbic region in brain connectivity.

INTRODUCTION

No single limbic system

A key area included by Broca in his limbic lobe (Broca, 1878) is the cingulate cortex, which hooks around the corpus callosum. The term “limbic” used by Broca referred to structures that are at the border or edge (the literal meaning of limbic) of the hemispheres (when seen in medial view), and led to the development of the concept of a limbic system (Pessoa and Hof, 2015). Other limbic structures include the hippocampus and the amygdala (which has major connections with the orbitofrontal cortex). These structures appear to have very different connections and functions. The amygdala

and orbitofrontal cortex are key structures involved in emotion and reward value with connections from ventral stream processing areas that decode “what” the stimulus is (Rolls, 2014b, 2016a, 2019a, 2019b). The hippocampus is a key structure in episodic memory with inputs from the dorsal stream cortical areas about space, action, and “where” events occur, as well as from the “what” ventral processing stream (Kesner and Rolls, 2015; Rolls, 2018b). Because of the different connectivity and functions of these limbic structures (the amygdala and orbitofrontal cortex in emotion, the hippocampus in memory, and the cingulate cortex in action), it has been suggested that the concept of a single “limbic system” is not realistic and that we should

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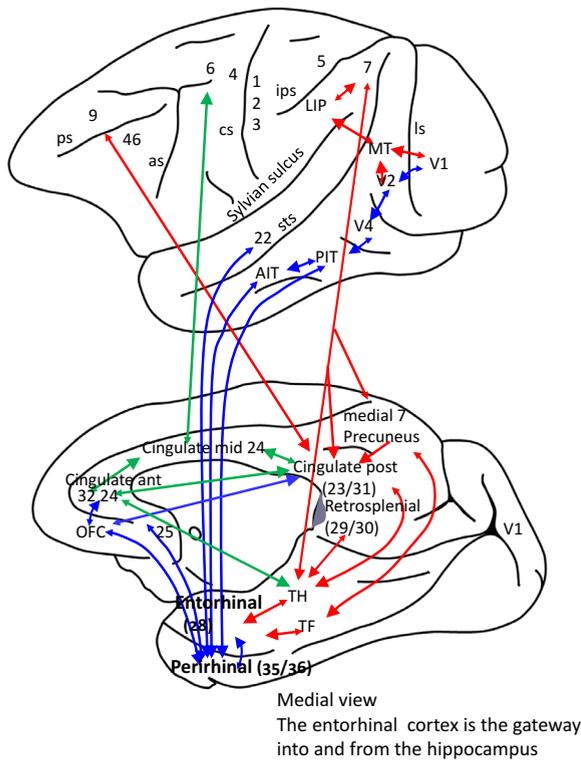


Fig. 2.1. The connections of the anterior and posterior cingulate cortex with their input areas and their outputs to the hippocampal memory system. A medial view of the macaque brain is shown below, and a lateral view is above. The *green arrows* show the convergence of reward or outcome information from the anterior cingulate cortex and of information about actions from the posterior cingulate cortex to the midcingulate motor area, which then projects to premotor areas including the premotor cortex area 6 and the supplementary motor area. This provides connectivity for action-outcome learning. The anterior cingulate cortex receives reward outcome information from the orbitofrontal cortex (OFC). The posterior cingulate cortex receives information about actions from the parietal cortex. This cingulate connectivity is compared with that of the hippocampus, which receives information from the ventral “what” processing stream (*blue*) and the dorsal “where” or “action” processing stream (*red*). The entorhinal cortex area 28 is the main entry for cortical connections to and from the hippocampus. The forward projections to the hippocampus are shown with *large arrowheads*, and the backprojections with *small arrowheads*. The main ventral stream connections to the hippocampus, which convey information about objects, faces, etc., are in blue, and the main dorsal stream connections, which convey “where” information about space and movements are in red. The ventral “what” visual pathways project from the primary visual cortex V1 to V2, then V4, then posterior inferior temporal visual cortex (PIT), then anterior inferior temporal visual cortex (AIT), then perirhinal cortex (areas 35/36), and thus to entorhinal cortex. The dorsal “where” visual pathways project from V1 to V2, then middle temporal (MT), then lateral intraparietal (LIP), then parietal area 7 (lateral) and medial (including the precuneus),

consider separately the connectivity and functions of different limbic structures in emotion, memory, and action (Rolls, 2015).

The aim of this chapter is to provide a framework for how different parts of the cingulate cortex are involved in all three of these different functions, and even systems, for emotion, memory, and action.

A conceptual framework for the cingulate cortex

The anterior cingulate cortex, itself a limbic structure, has connections with a set of other limbic and related areas including the amygdala and orbitofrontal cortex involved in emotion and reward-related processing (see Fig. 2.1) (Rolls, 2014a, 2018a). This set of limbic and related structures receiving from the ventral or “what” processing streams, and these ventral processing streams themselves, provide a major source of “what” and “reward” input into the hippocampal memory system via the perirhinal and entorhinal cortex (blue in Fig. 2.1) (Rolls, 2018b; Rolls and Wirth, 2018). The posterior cingulate cortex has connections to parietal structures such as the precuneus and lateral parietal areas and is involved in spatio-topographical and related memory functions (Kircher et al., 2002; Cavanna and Trimble, 2006; Leech and Sharp, 2014; Rolls, 2015; Rolls and Wirth, 2018). This limbic region related to the dorsal or “where” processing systems provides a second major source of input into the hippocampal memory system via the parahippocampal gyrus (areas TF and TH) and the entorhinal cortex (red in Fig. 2.1) (Rolls, 2018b; Rolls and Wirth, 2018). Because the anterior cingulate cortex and its related limbic areas and the posterior cingulate cortex and its related areas have such different

then to posterior cingulate cortex areas 23/32) including the retrosplenial cortex (areas 29/30) and thus to the parahippocampal gyrus (areas TF and TH), and then the perirhinal and entorhinal cortex. Area 22 is the superior temporal auditory association cortex. Reward information reaches the hippocampus from the OFC, anterior cingulate cortex (areas 32 and 25), and amygdala, but also via the OFC to posterior cingulate cortex connections. The lateral prefrontal cortex areas 9 and 46 involved in working memory connect via the posterior cingulate cortex. The hippocampus enables all the high-order cortical regions to converge into a single network in the hippocampal CA3 region (Rolls, 2015, 2016a). Other abbreviations: *ant*, anterior; *as*, arcuate sulcus; *cs*, central sulcus; *ips*, intraparietal sulcus; *ios*, inferior occipital sulcus; *ls*, lunate sulcus; *sts*, superior temporal sulcus; 4, 6, motor and premotor cortex. Modified from Rolls E.T., Wirth S., 2018. Spatial representations in the primate hippocampus, and their functions in memory and navigation. *Prog Neurobiol* 171: 90–113.

connections and functions, it has been argued that we should no longer think of a single limbic system, but instead of two (or more) limbic processing systems (Rolls, 2015).

However, a key concept is that the orbitofrontal/anterior cingulate/amygdala set of limbic regions related to ventral stream processing and the posterior cingulate cortex related to dorsal stream processing enable the ventral and dorsal processing streams to be brought together in the hippocampus, so that we can form memories of “what” happened “where,” which is prototypical of episodic memory (Kesner and Rolls, 2015; Rolls, 2016a; Rolls, 2018b). In an interesting twist that has been realized recently, there is in fact a connection from the orbitofrontal cortex to the posterior cingulate cortex, providing a route for reward-related information to reach the hippocampus via the dorsal route as well as the ventral route (Rolls, 2018b; Rolls and Wirth, 2018).

This conceptual framework is developed a little more next. It should be noted that this framework applies to primates including humans, with the principles of operation being considerably different in rodents due to the comparatively less developed orbitofrontal cortex, and visual and even taste cortical processing areas (Rolls, 2016a, 2018a, 2019a).

The orbitofrontal cortex is involved in representing the value of stimuli (Rolls, 2014a, 2019a, 2019b). It is in a sense an output region for all the sensory systems, including taste, olfaction, visual, auditory, and somatosensory, that represent “what” a stimulus is and uses that information to build what are frequently multimodal representations but in value space rather than in “what” or stimulus identity space. Orbitofrontal cortex neurons focus on value representations for stimuli and know little about actions.

The anterior cingulate cortex receives inputs from the orbitofrontal cortex about the value of stimuli, that is, about goals including the value of outcomes (the reward received) and the expected value. The anterior cingulate cortex, in combination with the midcingulate motor area, which contains representations of actions, interfaces actions to outcomes (rewards or punishers received) using action-outcome learning and also takes into account the cost of actions to obtain the goal when selecting actions (Rushworth et al., 2012; Kolling et al., 2016; Rolls, 2019a). The anterior and midcingulate cortical areas are thus relevant to emotion, for they implement the instrumental goal-directed actions that the instrumental reinforcers involved in emotion produce (Rolls, 2014a, 2019a, 2019b). In the context of its representations of value, damage to the anterior cingulate areas does influence emotion (Rolls, 2014a, 2019a).

The anterior cingulate cortex operates as a system that aims to obtain goals and takes into account the outcomes

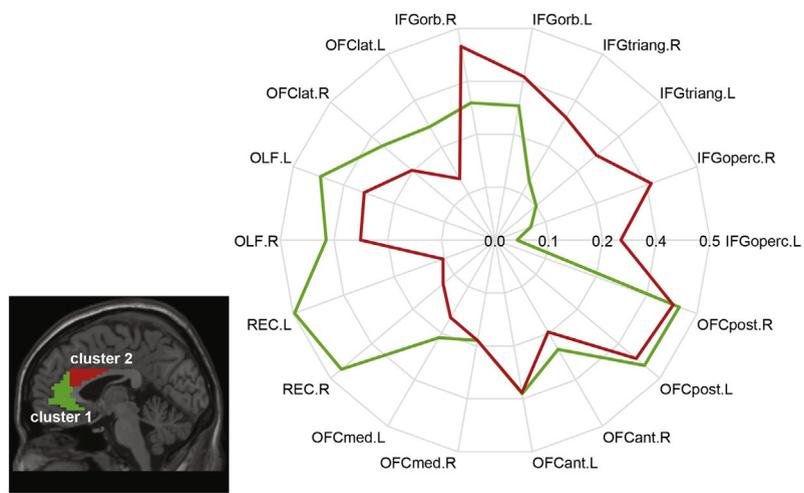
received after actions in that it is sensitive to devaluation of the goal and will not select an action if the goal has been devalued. This is in contrast to the basal ganglia, which implement a stimulus–motor response mapping, which becomes automated as a habit after much learning and is not sensitive to devaluation of the goal (Rolls, 2014a, 2019a, 2019b).

ANTERIOR CINGULATE CORTEX ANATOMY AND CONNECTIONS

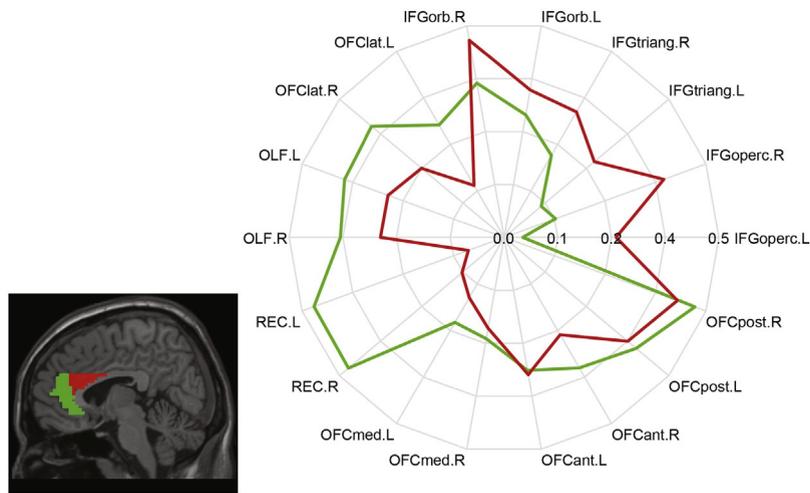
The anterior cingulate areas occupy approximately the anterior one-third of the cingulate cortex (see Fig. 2.2). They may be distinguished from a midcingulate region (i.e., caudal to the anterior cingulate region and occupying approximately the middle third of the cingulate cortex) that contains the cingulate premotor areas in the cingulate sulcus (Vogt et al., 2003; Vogt, 2009) and may be involved in action selection (Rushworth et al., 2004, 2011; Noonan et al., 2011). The anterior cingulate cortex includes area 32 the pregenual (or perigenual, meaning around the genu of the corpus callosum) cingulate cortex, area 25 the subgenual cingulate cortex, and part of area 24 (Fig. 2.2) (Öngür and Price, 2000; Öngür et al., 2003; Price, 2006a, 2006b).

As shown in Fig. 2.2, the anterior cingulate cortex receives strong inputs from the orbitofrontal cortex (Carmichael and Price, 1995; Morecraft and Tanji, 2009; Vogt, 2009). The anterior cingulate cortex is also characterized by connections with the amygdala (Carmichael and Price, 1995; Morecraft and Tanji, 2009; Vogt, 2009). The anterior cingulate cortex also receives what are probably backprojection inputs (Rolls, 2016a) from some temporal lobe areas including the parahippocampal gyrus, perirhinal cortex, and entorhinal cortex (which provide a bridge to the hippocampus) (Vogt, 2009).

A very interesting finding in relation to what follows is that the medial orbitofrontal cortex has strong functional connectivity with the pregenual cingulate cortex, in both of which rewards are represented, and that the lateral orbitofrontal cortex (and inferior frontal gyrus) has strong functional connectivity with the supracallosal, more dorsal, anterior cingulate cortex region, both of which are activated by unpleasant aversive stimuli (Rolls et al., 2019). This was shown in a resting state-fMRI investigation with 254 healthy participants (Rolls et al., 2019). Parcellation was performed based on the functional connectivity of individual anterior cingulate cortex voxels in the controls (Fig. 2.3). (The functional connectivity was measured by the correlation between the resting state-fMRI signals in pairs of brain areas.) A pregenual and subcallosal subdivision (1, green) has strong functional connectivity with the



A



B

Fig. 2.3. (A) Voxel-level parcellation of the left anterior cingulate cortex (ACC) based on its functional connectivity in healthy controls with other brain areas. Subdivision 1 is pregenual and subgenual anterior cingulate cortex. Subdivision 2 is supracallosal anterior cingulate cortex. The polar plot shows the correlations of the voxels in each subdivision of the ACC with the significantly different voxels in orbitofrontal cortex AAL2 areas. A two-way repeated measure analysis of variance (ANOVA) showed by the interaction term ($P < 0.0001$) that the two ACC subdivisions had different functional connectivity with these orbitofrontal cortex areas. (B) Voxel-level parcellation of the right ACC based on its functional connectivity in healthy controls with other brain areas. Subdivision 1 is pregenual and subgenual anterior cingulate cortex. Subdivision 2 is supracallosal anterior cingulate cortex. The polar plot shows the correlations of the voxels in each subdivision of the ACC with the significantly different voxels in orbitofrontal cortex AAL2 areas. The interaction term in the ANOVA was again significant. The AAL2 is the automated anatomic labeling atlas, which shows the abbreviations used (Rolls et al., 2015).

not be included in Price and colleagues' "orbital prefrontal network." Their "orbital prefrontal network" includes most of the areas on the posterior, central, and lateral orbital surface (agranular insular areas Ial, Iam, Iapl, and Iapm, and orbital areas 13b, 13l, 13m, 11l, 12r, 12m, and 12l; see Fig. 2.2), which are described as the orbitofrontal cortex (Rolls, 2014a, 2018a, 2019a, 2019b). The term "ventromedial prefrontal cortex" (vmPFC) is not well defined anatomically and refers generally to a medial and ventral region of the prefrontal cortex, which probably can be taken to include the ventral parts of the "medial prefrontal network" of Price et al. and also probably medial parts of the orbitofrontal cortex (Rolls, 2019a).

The outputs of the anterior cingulate cortex reach further caudal in the cingulate cortex to the midcingulate cortex, which includes the cingulate premotor areas (Vogt et al., 1996; Morecraft and Tanji, 2009; Vogt, 2009). The anterior cingulate cortex also projects forward to medial prefrontal cortex area 10 (Öngür and Price, 2000; Price, 2006b) and to temporal lobe areas including the parahippocampal gyrus, perirhinal cortex, and entorhinal cortex (Vogt, 2009). Another route for output is via the projections to the striatum/basal ganglia system. The anterior cingulate cortex, including the subgenual cingulate cortex area 25, has outputs that can influence autonomic/visceral function via the hypothalamus, midbrain periaqueductal gray, and insula, as does

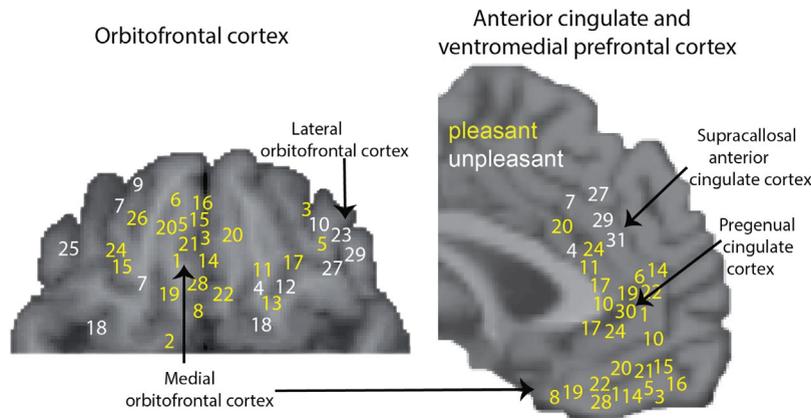


Fig. 2.4. Maps of subjective pleasure in the orbitofrontal cortex (*ventral view*) and anterior cingulate cortex (*sagittal view*). *Yellow*: sites where activations correlate with subjective pleasantness. *White*: sites where activations correlate with subjective unpleasantness. The numbers refer to effects found in specific studies. Taste: 1, 2; odor: 3–10; flavor: 11–16; oral texture: 17, 18; chocolate: 19; water: 20; wine: 21; oral temperature: 22, 23; somatosensory temperature: 24, 25; the sight of touch: 26, 27; facial attractiveness: 28, 29; erotic pictures: 30; laser-induced pain: 31. After [Grabenhorst and Rolls \(2011\)](#) who provide references to the original studies.

the orbitofrontal cortex ([Rempel-Clower and Barbas, 1998](#); [Öngür and Price, 2000](#); [Price, 2006b](#); [Critchley and Harrison, 2013](#)).

ANTERIOR CINGULATE CORTEX FUNCTIONAL NEUROIMAGING AND NEURONAL ACTIVITY

A framework

The pregenual and the adjoining dorsal anterior cingulate areas (see [Figs. 2.2](#) and [2.4](#), perhaps extending into aMCC) can be conceptualized as a relay that allows information about rewarding and punishing outcomes (respectively) to be linked, via longitudinal connections running in the cingulum fiber bundle, to information about actions represented in the midcingulate cortex. Bringing together information about specific rewards with information about actions, and the costs associated with actions, is important for associating actions with the value of their outcomes and for selecting the correct action that will lead to a desired reward ([Walton et al., 2003](#); [Rushworth et al., 2007](#); [Grabenhorst and Rolls, 2011](#); [Rushworth et al., 2011](#); [Rolls, 2014a](#); [Kolling et al., 2016](#)). Indeed, consistent with its strong connections to motor areas ([Morecraft and Tanji, 2009](#)), lesions of the anterior cingulate cortex impair reward-guided action selection ([Kennerley et al., 2006](#); [Rudebeck et al., 2008](#)), neuroimaging studies have shown that the anterior cingulate cortex is active when outcome information guides choices ([Walton et al., 2004](#)), and single neurons in the anterior cingulate cortex encode information about both actions and outcomes including reward prediction errors for actions ([Matsumoto et al., 2007](#); [Luk and Wallis, 2009](#); [Kolling et al., 2016](#)).

For example, in a task where information about three potential outcomes (three types of juice) had to be associated on a trial-by-trial basis with two different responses (two lever movements), many neurons in the anterior cingulate cortex encoded information about both specific outcomes and specific actions ([Luk and Wallis, 2009](#)).

Pregenual anterior cingulate representations of reward value and supracallosal anterior cingulate representations of punishers and nonreward

Functional magnetic resonance neuroimaging (fMRI) studies show that there are rather separate representations of positively affective, pleasant stimuli in the pregenual cingulate cortex (yellow in [Fig. 2.4](#)) and of negative, unpleasant stimuli just posterior to this above the corpus callosum in the anterior cingulate cortex (white in [Fig. 2.4](#)) ([Rolls, 2009](#); [Grabenhorst and Rolls, 2011](#)). The area activated by pain is typically 10–30 mm behind and above the most anterior (i.e., pregenual) part of the anterior cingulate cortex ([Fig. 2.4](#)) ([Vogt et al., 1996](#); [Vogt and Sikes, 2000](#); [Rolls et al., 2003b](#)). Pleasant touch is found to activate the most anterior part of the anterior cingulate cortex, just in front of the (genu or knee of the) corpus callosum (i.e., pregenual cingulate cortex) ([Fig. 2.4](#)) ([Rolls et al., 2003b](#); [McCabe et al., 2008](#)). Pleasant temperature applied to the hand also produces a linear activation related to the degree of subjective pleasantness in the pregenual cingulate cortex ([Rolls et al., 2008b](#)). Oral somatosensory stimuli such as viscosity and the pleasantness of fat texture also activate this pregenual part of the anterior cingulate cortex ([de Araujo and Rolls, 2004](#); [Grabenhorst et al., 2010b](#)).

More than just somatosensory stimuli are represented, however, in that (pleasant) sweet taste also activates the pregenual anterior cingulate cortex (de Araujo et al., 2003a; de Araujo and Rolls, 2004) where attention to pleasantness (Grabenhorst and Rolls, 2008) and cognition (Grabenhorst et al., 2008a) also enhances activations, as do pleasant odors (Rolls et al., 2003a) and cognitive inputs that influence the pleasantness of odors (de Araujo et al., 2005), and also top-down inputs that produce selective attention to odor pleasantness (Rolls et al., 2008a). Unpleasant odors activate further caudal in the supracallosal anterior cingulate cortex (the area indicated in Figs. 2.2 and 2.4) (Rolls et al., 2003a). Activations in the pregenual cingulate cortex are also produced by the taste of water when it is rewarding because of thirst (de Araujo et al., 2003b), by the flavor of food (Kringelbach et al., 2003), and by monetary reward (O'Doherty et al., 2001). Moreover, the outcome value and the expected value of monetary reward activate the pregenual cingulate cortex (Rolls et al., 2008c). The locations of some of these activations are shown in Fig. 2.4.

In these studies, the anterior cingulate activations were linearly related to the subjective pleasantness or unpleasantness of the stimuli, providing evidence that the anterior cingulate cortex provides a representation of value on a continuous scale (Fig. 2.4). Moreover, evidence was found that there is a common scale of value in the pregenual cingulate cortex, and the affective pleasantness of taste stimuli and of thermal stimuli applied to the hand produced identically scaled BOLD (Blood Oxygenation-Level Dependent) activations (Grabenhorst et al., 2010a). The implication is that the anterior cingulate cortex contains a value representation used in decision making, but that the decision itself may be made elsewhere (Rolls, 2019a). Decisions about actions that reflect the outcomes represented in the anterior cingulate cortex may be made further posterior in the midcingulate cortex. Decisions about the value of stimuli may be made in the medial prefrontal cortex area 10 (or ventromedial prefrontal cortex), which receives inputs from the orbitofrontal cortex and also from the anterior cingulate cortex (Grabenhorst et al., 2008b; Rolls and Grabenhorst, 2008; Rolls et al., 2010a, 2010b).

Value representations in the pregenual cingulate cortex are confirmed by recording studies in monkeys (Rolls, 2008; Kolling et al., 2016). For example, Gabbott, Verhagen, Kadohisa, and Rolls found neurons in the pregenual cingulate cortex that respond to taste and it was demonstrated that the representation is of reward value, for devaluation by feeding to satiety selectively decreased neuronal responses to the food with which the animal was satiated (Rolls, 2008).

The framework then is that the value representations computed in the orbitofrontal cortex, where there is little

representation of action, are transferred to the anterior cingulate cortex, where they can be used as the representation of reward vs nonreward or punishment outcome, to be associated with representations of actions as part of goal-dependent action-outcome learning. This type of learning is a key function of this limbic structure, the cingulate cortex, made possible by its inputs from limbic structures such as the amygdala and orbitofrontal cortex anteriorly and by its inputs from the parietal cortex and limbic hippocampal system posteriorly.

Anterior cingulate cortex and action-outcome representations

Some single neuron studies indicating encoding of actions and outcomes have often involved rather dorsal recordings above the pregenual cingulate cortex in the dorsal anterior cingulate cortex (in what may be d32 and 24c in the terminology of Chapter 1 (Vogt, 2019), and including the dorsal bank of the cingulate sulcus) (Matsumoto et al., 2007; Luk and Wallis, 2009; Kolling et al., 2016). In a similar area, action-outcome associations appear to be represented, 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 the anterior cingulate cortex neurons depended on the expectation of reward or nonreward (25%), the intention to move or not (25%), or a combination of movement intention and reward expectation (11%) (Matsumoto et al., 2007). Luk and Wallis (2013) described recordings in the same dorsal anterior cingulate cortex area that reflected the outcomes when monkeys made a choice of a left or right lever response to obtain a reward outcome and also described a weak dissociation for more stimulus-outcome neurons in the orbitofrontal cortex, that is, when monkeys had to choose the reward outcome based on which visual stimulus was shown. In the same dorsal anterior cingulate area, neurons were more likely to take into account the costs of the actions required to obtain rewards as well as the probability of obtaining the reward than were neurons in the orbitofrontal cortex (Kennerley and Wallis, 2009; Kennerley et al., 2011; Kolling et al., 2016). In the dorsal anterior cingulate cortex, neurons may reflect evidence about the several most recent rewards and use this to help guide choices (Kolling et al., 2016). More ventrally in the anterior cingulate cortex, neurons are more likely to reflect reward outcome rather than actions primarily (Cai and Padoa-Schioppa, 2012).

Foraging studies also implicate the anterior cingulate cortex in representing value and in taking into account costs. Hayden, Pearson, and Platt (2011) taught monkeys a simple computerized foraging task in which they could

chose to continue foraging in the same patch for diminishing returns or seek an alternative patch at the expense of paying a cost of a travel delay before foraging could resume. Single neurons in the anterior cingulate cortex that fire to reward receipt did so at an increasing rate as monkeys moved toward leaving a known patch to search for a new one. Patch moving was initiated when the anterior cingulate cortex activity reached a threshold. The threshold firing rate that had to be reached was proportional to the search costs that were to be incurred by switching away from the current foraging patch.

In a neuroimaging study that provides evidence that the anterior cingulate cortex is active when outcome information guides choices made by the individual (Walton et al., 2004), the activations were relatively caudal in the anterior cingulate cortex ($y=22$) toward the midcingulate cortex. This is consistent with the hypothesis that the reward value information in the pregenual cingulate cortex and the negative value representations just behind and dorsal to this in the anterior cingulate cortex are projected posteriorly toward the midcingulate area for interfacing to action.

ANTERIOR CINGULATE CORTEX LESION EFFECTS

Lesion studies in monkeys (Rudebeck et al., 2008) and humans (Camille et al., 2011) have demonstrated a dissociation in the role of the anterior cingulate cortex in action-outcome associations to guide behavior and of the orbitofrontal cortex in stimulus-outcome associations to update expected value (Rushworth et al., 2012). Lesions of the anterior cingulate cortex in rats impair the ability to take into account the costs of actions (Walton et al., 2002), and this is supported by a neuroimaging study in humans (Crosson et al., 2009).

An investigation more closely related to the understanding of emotion showed that patients with selective surgical lesions of the anteroventral part of the anterior cingulate cortex and/or medial BA9 were in some cases impaired on voice and face expression identification, had some change in social behavior such as inappropriateness, 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. In line with these results in humans, diminished social vocalization was found in monkeys with anterior cingulate lesions, and also emotional and social changes (Hadland et al., 2003). Consistent with the effects of the anterior cingulate lesions in humans on recognizing voice (and in some cases face) emotional expression (Hornak et al., 2003), neuroimaging studies concerned with vocal expression identification have reported orbital

and medial activation. These include a study using non-verbal sounds expressing fear, sadness, and happiness that, when compared to a neutral condition, activated BA11 (orbital cortex) bilaterally and medial BA9 on the left (Morris et al., 1996). Fear-related increases in activity were also found on the right only in BA11. In another study it was found that fearful sounds activated medial BA32 and BA24 (anterior cingulate at/below the level of the genu of the corpus callosum), again on the right side only (Phillips et al., 1998). More extensive studies of facial expression identification have been conducted, and these report activation in a number of sites within both orbital and medial regions including medial BA9 and BA32/24 (anterior cingulate) (Dolan et al., 1996; Blair et al., 1999; Nakamura et al., 1999).

There is also neuroimaging evidence that complements the effects of lesions (Hornak et al., 2003) in suggesting a role for certain medial regions in the subjective experience of emotion. In neuroimaging studies with normal human subjects, bilateral activations in medial BA9 were found as subjects viewed emotion-laden stimuli, and in both medial BA9 as well as in ventral 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., 1997a, 1997b, 1998). On the basis of a review of imaging studies that consistently emphasize the importance of anterior and ventral regions of the anterior cingulate cortex for emotion, it was argued that the anterior cingulate cortex can be divided into a ventral “affective” division (which includes the subgenual region and the part anterior to the corpus callosum) and a dorsal “cognitive” division (Bush et al., 2000), a view strengthened by the demonstration of reciprocally inhibitory interactions between these two regions.

A current working hypothesis is that the affective part of the anterior cingulate cortex 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 anterior cingulate cortex may compare these signals, take into account the cost of actions, and utilize the value representations in action-outcome learning.

SUBGENUAL CINGULATE CORTEX

The subgenual part (area 25) of the anterior cingulate cortex, via its outputs to the hypothalamus and brainstem autonomic regions, is involved in the autonomic components of emotion (Barbas and Pandya, 1989; Koski and Paus, 2000; Öngür and Price, 2000; Chiba et al., 2001; Gabbott et al., 2003; Vogt, 2009). The anterior cingulate cortex is also activated in relation to autonomic events,

and the fMRI signal has a correlation with skin conductance, a measure of autonomic activity related to sympathetic activation, in the anterior cingulate cortex and related areas (Nagai et al., 2004). The dorsal anterior and midcingulate cortical areas may be especially related to blood pressure, pupil size, heart rate, and electrodermal activity, whereas the subgenual cingulate cortex, with the ventromedial prefrontal cortex, appears anti-sympathetic (and parasympathetic) (Critchley and Harrison, 2013).

The subgenual cingulate cortex is connected with the ventromedial prefrontal cortical areas (Johansen-Berg et al., 2008) and the activations in the subgenual cingulate cortex may reflect inputs from the ventromedial prefrontal cortex. Further, neural activity in the subgenual cingulate cortex has been implicated in representing relative chosen value in an uncertain decision environment (Boorman et al., 2009). Evidence implicating the subgenual cortex and more generally the subcallosal cingulate cortex in depression is described elsewhere (Hamani et al., 2011; Laxton et al., 2013; Rolls, 2018a).

MIDCINGULATE CORTEX, CINGULATE PREMOTOR AREAS, AND ACTION-OUTCOME LEARNING

The anterior cingulate cortex is distinguished from the midcingulate cortex, the latter of which contains the two cingulate premotor areas in the cingulate sulcus (Vogt et al., 1996, 2003; Vogt, 2009; Morecraft and Tanji, 2009; Vogt, 2016). These areas are also activated by pain, but because this region is also activated in response selection tasks such as divided attention and Stroop tasks (which involve cues that cause conflict, such as the word red written in green when the task is to make a response to the green color), it is suggested that activation of the midcingulate premotor areas by noxious stimuli was related to the response selection processes initiated by painful stimuli (Vogt et al., 1996; Derbyshire et al., 1998). Both the anterior cingulate and the midcingulate areas may be 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 midcingulate region is divided into an anterior division containing the rostral cingulate premotor area (a24c') concerned with skeletomotor control, which may be required in avoidance and fear tasks, and a posterior division that contains the caudal premotor areas (p24c' and 24d), which may be involved in skeletomotor orientation of the body in space (Vogt et al., 2003).

In macaques, lesions of the anterior cingulate cortex that include the midcingulate region do not affect working memory (measured by delayed alternation) and are in

this respect different from dorsolateral prefrontal cortex lesions, but they may affect task switching (Rushworth et al., 2003, 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 (Rushworth et al., 2002).

Some anterior/midcingulate neurons respond when errors are made (Niki and Watanabe, 1979; Kolling et al., 2016; Procyk et al., 2016) or when rewards are reduced (Shima and Tanji, 1998), and activations are found in corresponding imaging studies (Bush et al., 2002; Procyk et al., 2016). 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; Kolling et al., 2016; Procyk et al., 2016).

Correspondingly, in rodents a part of the medial prefrontal/anterior cingulate cortex termed the prelimbic cortex (area 32, Vogt and Paxinos, 2014) is involved in learning relations between behavioral responses and reinforcers, that is, between actions and outcomes (Balleine and Dickinson, 1998; Cardinal et al., 2002; Killcross and Coutureau, 2003). For example, the sensitivity of instrumental behavior to whether a particular action was followed by a reward was impaired by prelimbic cortex lesions (Balleine and Dickinson, 1998). When making decisions about actions, it is important to take into account the costs as well as the benefits. There is some evidence implicating the rodent anterior cingulate cortex in this, in that rats with area 32 lesions were impaired in a task that 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., 2002, 2003).

THE POSTERIOR CINGULATE CORTEX

The posterior cingulate cortex receives major inputs from parietal cortical areas that receive from the dorsal visual stream and somatosensory areas and is involved in spatial processing, action in space, and some types of memory (Vogt and Pandya, 1987; Vogt, 2009; Vogt and Laureys, 2009; Rolls and Wirth, 2018; Rolls, 2018b). Interestingly, the posterior cingulate cortex also has connections with the orbitofrontal cortex (Vogt and Pandya, 1987; Vogt and Laureys, 2009) (Fig. 2.1). In primates the posterior cingulate cortex is a region with strong connections to the parahippocampal gyrus (areas TF and TH) and the entorhinal cortex, and thus to the hippocampal

memory system (Vogt and Laureys, 2009; Bubb et al., 2017; Rolls, 2018b; Rolls and Wirth, 2018) (Fig. 2.1). Backprojections from the hippocampal system to posterior cingulate and parietal areas are likely to be involved in memory recall (Kesner and Rolls, 2001; Rolls, 2016a; Rolls, 2018b).

The interesting concept that emerges is that orbitofrontal cortex value-related information has access to the posterior cingulate cortex and by this dorsal route into the hippocampal memory system, as well as by the ventral route via the perirhinal and (lateral) entorhinal cortex via which object-related information reaches the hippocampal memory system (Fig. 2.1) (Rolls, 2018b; Rolls and Wirth, 2018). The hippocampal memory system can then associate these three types of information, about where an object or face is present in space “out there” using spatial view cells, combining, if present, information about the reward value of the object or position in space (Rolls et al., 1997; Robertson et al., 1998; Rolls et al., 1998; Georges-François et al., 1999; Rolls and Xiang, 2005; Rolls et al., 2005; Rolls and Xiang, 2006; Kesner and Rolls, 2015; Rolls, 2016a; Rolls, 2018b; Rolls and Wirth, 2018).

Consistent with its anatomy, the posterior cingulate region (areas 23 and 31) (with the retrosplenial cortex areas 29 and 30) is consistently engaged by a range of tasks that examine episodic memory, including autobiographical memory and imagining the future, and also spatial navigation and scene processing (Auger and Maguire, 2013; Leech and Sharp, 2014). Self-reflection and self-imagery activate the ventral part of the posterior cingulate cortex (vPCC, the part with which we are mainly concerned here) (Kircher et al., 2000; Johnson et al., 2002; Kircher et al., 2002; Sugiura et al., 2005).

The posterior cingulate cortex is implicated in decision making in that some neurons there respond when risky, uncertain choices are made (McCoy and Platt, 2005), and some neurons respond more when an expected large reward is not obtained, maintaining that firing until the next trial (Hayden et al., 2008) (probably reflecting input from orbitofrontal cortex error neurons that have attractor state-like persistent firing that encodes and maintains a negative reward prediction error signal (Thorpe et al., 1983; Rolls and Grabenhorst, 2008; Rolls, 2019b)).

THE CINGULATE CORTEX AND DEPRESSION

Evidence implicating the subgenual and more generally the subcallosal cingulate cortex in depression demonstrates that neurons in this region in humans can respond to unpleasant stimuli, that the subgenual cingulate cortex may be overactive in depression, and that deep brain

stimulation may help to relieve depression in some patients (Hamani et al., 2011; Laxton et al., 2013; Rolls, 2018a).

More generally, voxels in the anterior cingulate cortex have higher functional connectivity with a number of brain areas in unmedicated depressed patients (Rolls et al., 2019). In depression, increased connectivity is found of the subcallosal anterior cingulate with the lateral orbitofrontal cortex; of the pregenual/supracallosal anterior cingulate with the medial orbitofrontal cortex; and of parts of the anterior cingulate with the inferior frontal gyrus, superior parietal lobule, and with early cortical visual areas. Parcellation of the anterior cingulate cortex showed two divisions (Fig. 2.3). A pregenual subdivision had high functional connectivity with medial orbitofrontal cortex areas, and a supracallosal subdivision had high functional connectivity with lateral orbitofrontal cortex and inferior frontal gyrus. The high functional connectivity in depression between the lateral orbitofrontal cortex and the subcallosal parts of the ACC provides a mechanism for more nonreward information transmission to the ACC, contributing to depression. The high functional connectivity between the medial orbitofrontal cortex and supracallosal ACC in depression may also contribute to depressive symptoms (Rolls et al., 2019).

In a resting state functional connectivity neuroimaging study of depression, it was found that voxels in the posterior cingulate cortex had significantly increased functional connectivity with the lateral orbitofrontal cortex, a region implicated in nonreward and which is thereby implicated in depression (Rolls, 2016b; Cheng et al., 2018; Rolls, 2018a). In patients receiving medication, the functional connectivity between the lateral orbitofrontal cortex and posterior cingulate cortex was decreased back toward that in the controls. In the 350 controls, it was shown that the PCC has high functional connectivity with the parahippocampal regions, which are involved in memory. The findings support the theory that the nonreward system in the lateral orbitofrontal cortex has increased effects on memory systems, which contribute to the rumination about sad memories and events in depression (Cheng et al., 2018).

In that the orbitofrontal cortex is the key brain region in emotion in primates including humans and in that it sends projections to the anterior cingulate cortex, which mirrors its reward- and punishment-related activations, it is suggested that the role of the orbitofrontal cortex in depression is likely to be important (Rolls, 2016b, 2019a, 2019b) and may offer potential routes to treatment.

SYNTHESIS

In this chapter, a framework is provided for understanding the connectivity of different parts of the cingulate

cortex. One set of limbic and related structures, the amygdala and orbitofrontal cortex, strongly linked with the anterior cingulate cortex, are thereby involved in emotion. Another set of limbic and related structures, the hippocampus and posterior cingulate cortex, are strongly connected and are involved in memory with spatial and action-related components received from the parietal cortex. In addition, it is argued here that the cingulate cortex, with these reward- and goal-related inputs anteriorly and action-related and spatial information posteriorly, can combine these to implement learning between actions and outcomes, with outputs directed from the premotor midcingulate cortex to premotor neocortical areas. These concepts are considered further next.

One important function of the cingulate cortex, via the midcingulate motor area with its connections to neocortical motor areas, is to associate actions with outcomes, as indicated by the connections shown in green in Fig. 2.1. My proposal is that convergence of reward or outcome information from the anterior cingulate cortex, and of information about actions from the posterior cingulate cortex, occurs in the cingulate cortex leading to outputs via the midcingulate motor area, which projects to premotor areas including the premotor cortex area 6 and the supplementary motor area (see green arrows in Fig. 2.1). This provides connectivity for action-outcome learning (Rolls, 2019a). The anterior cingulate cortex receives reward and punishment outcome information from the orbitofrontal cortex (OFC). The posterior cingulate cortex receives information about actions from the parietal cortex. Then these two types of information are brought together toward the midpart of the cingulate cortex, the cingulate motor area, which, with its connections to premotor areas, can effect the action that is most likely, given the action-outcome learning performed within this cingulate system, to obtain the goal, the desired outcome (Rolls, 2019a).

In addition, the parietal areas have projections to medial frontal areas connected with the dorsal parts of the anterior cingulate cortex (Vogt, 2009), and these projections may also provide a route for action-related information to reach the cingulate action-outcome learning system (Rolls, 2019a).

Another important function of the cingulate cortex is related to the hippocampal memory system, as shown in Fig. 2.1. This function is introduced by some anatomic considerations.

The anterior and midcingulate cortices are largely agranular, that is, they do not have a well-developed layer 4 with granule cells. The cingulate cortex is thought to be similar to the neocortex (or isocortex) in other ways, with clear layers 2 and 3, and 5 and 6. Indeed, the cingulate

cortex has a high cell density in layers 5 and 6. A term used to describe this cortex is *proisocortex* (Pandya et al., 2015). Another region of the *proisocortex* is the posterior-most part of the primate orbitofrontal cortex, which is agranular and includes the most posterior part of area 13. (The more anterior part of anterior 13 is granular.) Other regions of the *proisocortex* include the agranular anterior insula, the temporal pole, the parahippocampal cortex, and the rostral perirhinal cortex (Pandya et al., 2015). It has been hypothesized that neocortical areas develop in evolution from these *proisocortical* areas (Pandya et al., 2015).

The connections of these *proisocortical* areas include forming a connectional bridge between neocortical areas and areas such as the hippocampus (which is termed *allo-cortex*). Indeed, this is evident in Fig. 2.1, which shows how the perirhinal cortex forms a bridge from ventral stream neocortical areas (including temporal lobe cortical areas) to the hippocampus (and back) and how the posterior cingulate cortex and parahippocampal cortex form a bridge from dorsal stream neocortical areas (including the parietal cortex) to the hippocampus (and back) (via the entorhinal cortex in both cases). It is notable that the orbitofrontal cortex and anterior cingulate cortex project information, probably about rewards, via both the ventral and dorsal routes, to the hippocampal system (via the perirhinal cortex in the ventral route and the posterior cingulate cortex in the dorsal stream).

This is consistent with the framework I propose that the cingulate cortex provides a bridge linking neocortical areas with the hippocampal memory system (Rolls, 2018b; Rolls and Wirth, 2018), with spatial information reaching the hippocampal system via the posterior cingulate cortex, and reward-related information reaching the hippocampus via the anterior cingulate and orbitofrontal cortex (Rolls, 2019a).

This cingulate connectivity is further compared with that of the hippocampus, which receives information from the ventral “what” processing stream (blue) and the dorsal “where” or “action” processing stream (red) in Fig. 2.1. The entorhinal cortex area 28 is the main entry for cortical connections to and from the hippocampus. The forward projections to the hippocampus are shown with large arrowheads, and the backprojections with small arrowheads. A difference of hippocampal connectivity is that the inputs to the hippocampus from the ventral stream (blue in Fig. 2.1) are about objects and faces, etc. (from the temporal cortical visual areas), as well as reward information. This fits with the concept that the hippocampus is able to associate together “what” and reward information (blue in Fig. 2.1) with spatial information (red in Fig. 2.1) to enable the formation of episodic memories about objects and faces and where they were seen on a particular

occasion (Rolls and Kesner, 2006; Kesner and Rolls, 2015; Rolls, 2016a; Rolls, 2018b; Rolls and Wirth, 2018). In contrast, it is argued that the cingulate cortex performs the different computational function of association actions with outcomes, so it needs reward and spatial/action information, but less object information, and performs computations that may be based on several recent occasions in which outcomes resulted from actions (Rolls, 2019a).

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