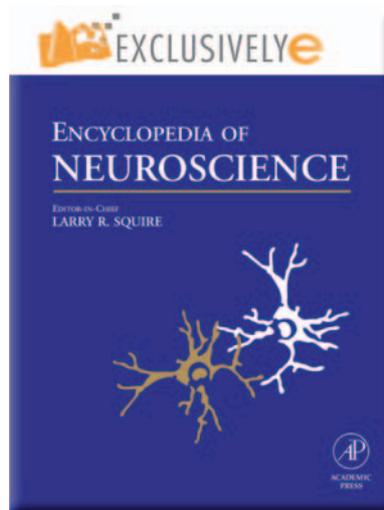


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Cingulate Cortex

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Anatomy of Cingulate Cortex

Subdivisions

The mammalian cingulate cortex occupies a vast territory stretching rostrocaudally along the cingulate sulcus on the medial surface of the cerebral hemispheres (**Figure 1(a)**). In both human and nonhuman primates, the cingulate cortex consists of the cingulate gyrus as well as the cortex lining the superior and inferior banks of the cingulate sulcus. The name ‘cingulate,’ derived from the Latin word for belt, reflects the fact that the cingulate cortex encircles the corpus callosum. The cingulate cortex can be divided into the more rostral anterior cingulate cortex (ACC) and the more caudal posterior cingulate cortex (PCC). In primates, the ACC consists of Brodmann’s areas 24, 25, 32, and 33, while the PCC consists of Brodmann’s areas 23, 29, 30, and 31. The clearest distinction between the ACCs and PCCs is that ACC has a thin agranular layer 4, whereas PCC has a pronounced granular layer 4.

The ACC and PCC can be further subdivided. The ACC consists of at least three distinguishable areas – the perigenual anterior cingulate cortex (pACC), the dorsal anterior cingulate cortex (dACC; sometimes referred to as midcingulate cortex, MCC), and the rostral and caudal cingulate motor areas (CMAs). The PCC comprises at least two distinct areas, the more rostral posterior cingulate cortex proper and the more caudal retrosplenial cortex, which constitutes the entire PCC in rodents.

Although there is a great deal of functional overlap between regions of the cingulate cortex, each of the anatomically defined subdivisions serves discrete functions. The pACC and dACC are thought to process emotional and cognitive information, respectively, while the CMAs process motor information. Although response properties of neurons in the CMAs are similar, electrical stimulation in the more caudal areas CMAd/v has a stronger and more consistent effect on movement than stimulation in CMAr. This difference is consistent with the stronger connections to the motor cortex and spinal cord made by neurons in CMAd/v. Response properties of single neurons within the CMAs are similar to those in supplementary motor cortex (SMA), but SMA neurons respond earlier and

more phasically than neurons in the CMAs. These findings suggest that SMA initiates movements while the CMAs contribute to their execution. The PCC differs from ACC by virtue of having a closer linkage to processing spatial information and a less direct role in the generation of voluntary action. Within the PCC, the retrosplenial cortex has been implicated in episodic memory formation and consolidation.

Connections

The cingulate cortex has been described as a neural interface between emotion, sensation, and action. This idea is strongly supported by the presence of anatomical connections linking the cingulate cortex with brain areas closely associated with each of these functions. The centrality of motivational and emotional processing to cingulate function is highlighted by its strong reciprocal connections to the reward centers of the brain, including the orbitofrontal cortex (OFC), the basal ganglia, and, in the case of the ACC, the insula (**Figure 1(b)**). The ACC is a major target of midbrain dopamine neurons, which respond to a variety of reward-related parameters. In addition, the ACC is reciprocally connected with the amygdala, a collection of nuclei that participates in assigning both positive and negative valence to events. Motivational and emotional inputs to ACC may be directly communicated to the PCC via massive reciprocal connections between these two regions.

Both the ACC and PCC are reciprocally connected with the lateral prefrontal cortex (LPFC), a region implicated in executive control, working memory, and rule learning and expression. The strong connections between the cingulate cortex and the LPFC suggest that the cingulate cortex serves as a gateway for incorporating reward-related information into sensorimotor mappings subserved by the LPFC. Furthermore, the ACC sends strong projections to the locus coeruleus (LC), a brain stem nucleus providing widespread noradrenergic inputs to the rest of the brain. Inputs from the LC to the prefrontal cortex may shift the organism between ‘exploit’ and ‘explore’ modes of behavior.

The cingulate cortex also shares strong reciprocal connections with motor structures. These include the primary and supplementary motor cortices and the main cortical regions controlling eye movements, the frontal and supplementary eye fields. The PCC is reciprocally connected with several parietal premotor areas, including 7a, 7m (also connected with ACC), and 7/PG. Both PCC and the caudal CMAs send direct projections to the spinal cord, likely pathways

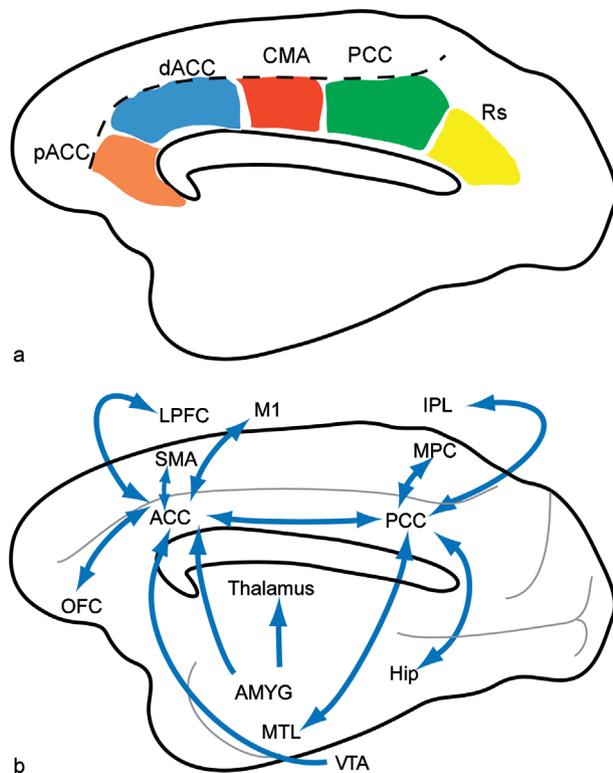


Figure 1 Anatomical subdivisions of the cingulate cortex and adjacent areas of the cortex. (a) The cingulate cortex anterior to the central sulcus is traditionally known as the anterior cingulate cortex (ACC), while the cingulate cortex posterior to the central sulcus is traditionally known as the posterior cingulate cortex (PCC). The ACC is divided into a rostral perigenual ACC (pACC), a central dorsal ACC (dACC), and the caudal motor regions within the sulcus called the cingulate motor areas (CMAs). The posterior cingulate cortex is generally divided into the more rostral posterior cingulate proper (PCC) and more caudal retrosplenial cortex (Rs). (b) Some, but not all, of the major connections between the anterior and posterior cingulate cortices and other areas in the macaque brain. ACC, anterior cingulate cortex; AMYG, amygdala; Hip, hippocampus; IPL, inferior parietal lobule; LPFC, lateral prefrontal cortex; M1, primary motor cortex; MPC, medial parietal cortex; MTL, medial temporal lobe; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; SMA, supplementary motor area; VTA, ventral tegmental area.

by which the cingulate cortex most directly controls behavior.

The strong connections between PCC and the parietal cortex suggest that it may play a central role in orienting attention. In fact, the parietal, cingulate, and frontal cortices are often thought to comprise a network specialized for attentional control. Indeed, damage to these areas leads to neglect, a selective deficit in orienting attention. Recent neuroimaging work has suggested that the PCC may participate in selecting locations for enhanced attention while ACC plays a more general, nonspatial role in controlling

attention. This idea is supported by the finding that blood flow to PCC increases when spatial attention is shifted contralaterally, whereas blood flow to ACC increases in a nonselective fashion. Cingulate cortex is unique among attentional control areas by virtue of its strong connections to limbic regions, which are thought to be important for reward processing. These connections may serve as a gateway by which reward-related information is integrated with executive processes controlling the allocation of attention.

A final set of important connections is that linking cingulate cortex to structures that form long-term memories. The PCC makes strong reciprocal connections with the hippocampus and the medial wall of the temporal lobe, both of which are associated with consolidation of long-term memories. The ACC shares strong connections with the amygdala, which processes information about emotionally relevant stimuli. Both sets of connections provide a potential mechanism for enhancing long-term memories of motivationally significant events.

Each region of the cingulate cortex is most strongly connected, both anatomically and functionally, to adjacent regions of the cerebral cortex. Thus, pACC, involved in emotional aspects of cognition, is located adjacent to the OFC, which is thought to be the primary cortical site for emotional and motivational information processing. The dACC, concerned with more abstract cognitive processes, is located adjacent to the LPFC and pre-SMA, which are thought to participate in rule representations, working memory, and other abstract cognitive processes. The cingulate motor areas, the most directly motor of the cingulate areas, are adjacent to the primary and supplementary motor areas of the frontal lobe. Finally, the posterior cingulate and retrosplenial cortex, which link rewards with locations in space, are adjacent to the parietal and parahippocampal regions, the chief cortical sites for storing and manipulating spatial representations.

Role of Cingulate Cortex in Behavior

Early Ideas of Cingulate Function

As with many other areas of the brain, early hypotheses of cingulate cortex function were based on the anatomy of the region and its connections. Neuroanatomists in the late nineteenth century identified strong connections from the olfactory bulb to the cingulate cortex, suggesting a prominent role for this area in olfaction. The contrast between the large size of the cingulate cortex and the relative unimportance of olfaction in primates, however, weakened this idea. In 1937, the neuroanatomist James Papez

proposed an emotional role for the cingulate cortex, clearly linked to the widespread importance of olfaction to emotional processing in mammals as well as the strong connections to the cingulate cortex from the hypothalamus, which was then thought to be the source of emotions. Initial support for Papez' model came from Wilder Penfield's studies demonstrating that intracranial electrical stimulation of the hippocampal regions adjacent to the cingulate cortex evoked strong emotional reactions in awake human surgical patients. Additional support for the Papez model came from the results of bilateral cingulotomies on humans with severe depression, schizophrenia, and obsessive-compulsive disorder. Although this procedure, in which the entire cingulate cortex was removed, sometimes alleviated unwanted symptoms, it also resulted in blunted emotions and flat affect.

Early electrophysiological studies of the cingulate cortex used methods that had proven successful in elucidating the functions of primary sensory cortical areas, particularly visual cortex. These early studies, however, showed that cingulate neurons in anesthetized monkeys failed to respond to simple stimuli, such as bars and points of light, which strongly activate neurons in visual cortex. Subsequent studies in awake monkeys have shown that cingulate neurons do respond to large textured patches and other behaviorally salient stimuli, probably because such stimuli attract attention. Although most studies have probed cingulate function using visual stimuli, it is not an exclusively visual structure; neuroimaging studies have revealed PCC activation in response to emotionally relevant (threat-related) auditory stimuli, and these responses depend on the locus of auditory attention. Furthermore, when human subjects are hypnotized, pain-related responses in ACC, but not in somatosensory cortex, are reduced. Collectively, these results suggest that the cingulate cortex is not exclusively a sensory or emotional structure, but instead contributes to cognitive processing of motivationally relevant stimuli and for guiding action.

Role of Cingulate Cortex in Reward-Guided Behavior

Early evidence for the role of cingulate cortex in processing motivational and reward-related information came from studies of intracranial self-stimulation (ICSS) in rats. In the ICSS paradigm, a rat can press a lever to receive direct electrical stimulation from an electrode placed in its brain. The extent to which the rat presses the lever serves as an index of the reinforcing effects of activating this region. The strongest ICSS is evoked by stimulation of the medial forebrain bundle (MFB) or the ventral tegmental area (VTA) in the midbrain. ICSS can also be elicited by stimulation

in the ACC and the retrosplenial cortex, as well as in areas connected to the cingulate cortex, including the hippocampus, the orbitofrontal cortex, and entorhinal cortex. While MFB and VTA stimulation causes rats to forsake food to the point of starvation, stimulation in cingulate cortex and related structures has much weaker effects on behavior. Notably, the rate of ICSS elicited by cingulate stimulation does not depend on electrical current or pulse frequency, as it does in the MFB or VTA. Also, unlike VTA and MFB, rates of ICSS elicited by cingulate activation gradually increase over time. One possible explanation for the gradually increasing rates of ICSS in cingulate cortex is that the stimulation slowly potentiates the formation of memories linking the animal's behavioral response with the stimulation. These results suggest that cingulate cortex does not simply generate a reward signal, but rather guides the formation of associations between rewards and sensory-guided actions.

Role of Cingulate Cortex in Selecting Action

Electrophysiological and pharmacological studies strongly implicate cingulate cortex in motor planning, possibly by binding reward-related information to action. One important example of the motor functions of cingulate cortex comes from a study of rhesus monkeys performing a task in which the links between sensory cues, rewards, and motor responses were systematically altered. Monkeys were presented with one of two cues that instructed one of two motor responses (either saccade or maintain fixation), and each motor response either was or was not associated with a reward. All combinations of parameters (sensory cue, motor response, mapping rule, and reward) were tested. In this task, ACC neurons represented both the motor plan and the reward contingency but almost never represent the pure sensory attributes of the cues.

One important question about the motor role of the cingulate cortex is the degree to which motor signals within cingulate cortex are abstract versus specific to a particular action. One study of a human patient with an ACC lesion supports the idea that motor coding in cingulate cortex is specific to a particular type of movement. This patient performed poorly on a Stroop task when manual responses were required, but was not affected when the task required verbal responses. This finding is also consistent with reports that electrical stimulation of cingulate cortex during surgical procedures can elicit uncontrolled hand movements. Together, these results demonstrate that motor representations within the cingulate motor areas are effector specific.

One important aspect of motor selection subserved by the cingulate cortex is the correct sequential ordering of responses. When monkeys perform a series of actions to obtain a single reward, many neurons in the

ACC fire selectively before only one of the actions but do not fire when rewards are given randomly. These results imply that one role of the ACC may be to control the order or timing of behavioral sequences.

Role of Cingulate Cortex in Monitoring Behavioral Outcomes

A substantial body of research has investigated the role of the cingulate cortex in monitoring errors and in evaluating and resolving conflict. These studies follow from the observation that negative electrical potentials are generated within the ACC when subjects make errors in many psychological tasks. This error-related negativity, or ERN, appears around 100 ms after the initiation of an incorrect motor response. A second ERN occurs about 250 ms after the subject is told she has made an error. Because the ERN arises after the behavioral response, it must reflect the consequences of an action rather than its planning or initiation. Moreover, since the ERN is generated independently of the modality of the motor response, it likely reflects abstract cognitive processing rather than movement-specific computations.

Subsequent studies have shown that an ERN is also generated on trials in which there is a high probability of error, but no error actually occurs. These trials are characterized as having high conflict, defined as the tension between two or more incompatible competing motor responses. For example, in a Stroop task, subjects must mediate between the habitual tendency to read the word and the instructed task of naming the color in which the word is printed (Figure 2(a)). When the word and the color are incongruent, these two responses conflict with each other. Conflict signals may trigger an executive control function that initiates increased effort to improve performance on subsequent trials. In support of this idea, behavioral studies have shown that trials with larger ERNs are more likely to be subsequently corrected and that subjects performing high-conflict tasks show the greatest increases in reaction time following trials with the greatest ERN.

These observations are supported by several functional magnetic resonance imaging (fMRI) studies showing hemodynamic responses believed to reflect the same processes that generate the ERN. However, two electrophysiological studies have failed to find any evidence for explicit conflict signals in the activity of single ACC neurons. Together, these observations raise the possibility that the cingulate cortex does not explicitly encode response conflict, but instead encodes all possible motor actions and their likelihood of yielding reward. Because high-conflict conditions may be associated with multiple motor plans, which would recruit multiple overlapping groups of

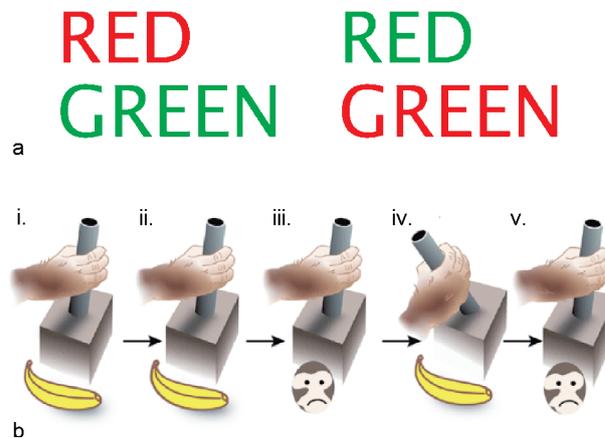


Figure 2 Behavioral monitoring in ACC. (a) Examples showing the low- and high-conflict conditions of the Stroop task. The Stroop task requires subjects to name the color while ignoring the word. The high-conflict condition (right, incongruent word/color) evokes an increased BOLD response in the dorsal ACC. (b) Cartoon indicating the trial structure of the task used by Shima and Tanji. Subjects can perform one of two actions (turn or push a handle). One action is consistently rewarded (i and ii). At some point, the rewarded action is switched (iii). A normal subject will alter the strategy at this point to begin receiving rewards again (iv). Monkeys with reversible ACC lesions fail to reliably adopt the new strategy. Recent work has shown that monkeys with permanent ACC lesions can adopt the new strategy for a few trials, but soon revert to the former strategy (v).

neurons, this might lead to what appears to be a conflict-related BOLD signal. Nonetheless, the precise role of cingulate cortex in conflict monitoring remains unclear.

Both electrophysiological and neuroimaging studies consistently report that cingulate cortex seems to be more active when subjects actively search for the optimal strategy to solve a task than when they simply follow arbitrary rules. Enhanced activity is seen in ACC in tasks that require unspecified responses (e.g., word-generation tasks) or in monkeys when movements are triggered internally rather than in response to explicit external cues. Moreover, neurons in ACC are more active when monkeys endeavor to learn the order in which they must press three squares on a computer screen than after they have learned the sequence. Similarly, BOLD activity in ACC is much stronger when human subjects monitor the monetary payoffs associated with pressing buttons and try to maximize their yield than when they merely follow explicit instructions.

Role of Cingulate Cortex in Assigning Motivational Significance to Potential Actions

One model of cingulate cortex function that may account for most of the foregoing observations purports that the general function of cingulate

circuitry is to link reward information to potential sensory-guided actions. This model is supported by the findings (described above) that cingulate cortex participates in both sensory and motor processing and, moreover, appears to integrate reward information into the context of ongoing sensorimotor transformations. According to this view, cingulate cortex provides a functional linkage between limbic areas and cortical sensory and motor areas.

One landmark study supporting this model demonstrated that cingulate cortex participates specifically in reward-based guidance of action. In this study, monkeys grasped a joystick that they could either lift or turn on each trial (Figure 2(b)). One of these actions was rewarded and the other was not. The only way the monkey could identify which action was rewarded was to monitor the consequences of their actions. When reward value associated with one action declined, the monkey could switch to the other action to receive a larger reward. Reward-related switches in behavior elicited high firing from neurons in CMAs. Moreover, temporary lesions in this area

abolished the animal's ability to modify its behavior based on changing rewards. Later work has shown that permanent lesions to the ACC do not specifically impair the ability to modify behavior in response to changing outcomes, but instead disrupt the ability to sustain new behavioral strategies following the reward-guided switch. These results suggest that the ACC specifically participates in the reward-based consolidation of new behavioral strategies.

Further support for a role for cingulate cortex in integrating reward outcomes into ongoing sensorimotor transformations comes from the finding that ACC does not represent abstract stimulus–reward mappings when they have no influence on the selection of motor responses. In one study, monkeys were trained to perform two different tasks. One task was a variant of the reward-based switching task, as described above, in which monkeys performed one of two actions (lift or turn a handle) in response to a reward. The other task was a visual discrimination task in which monkeys learned to associate one of two stimuli with a reward and then select the

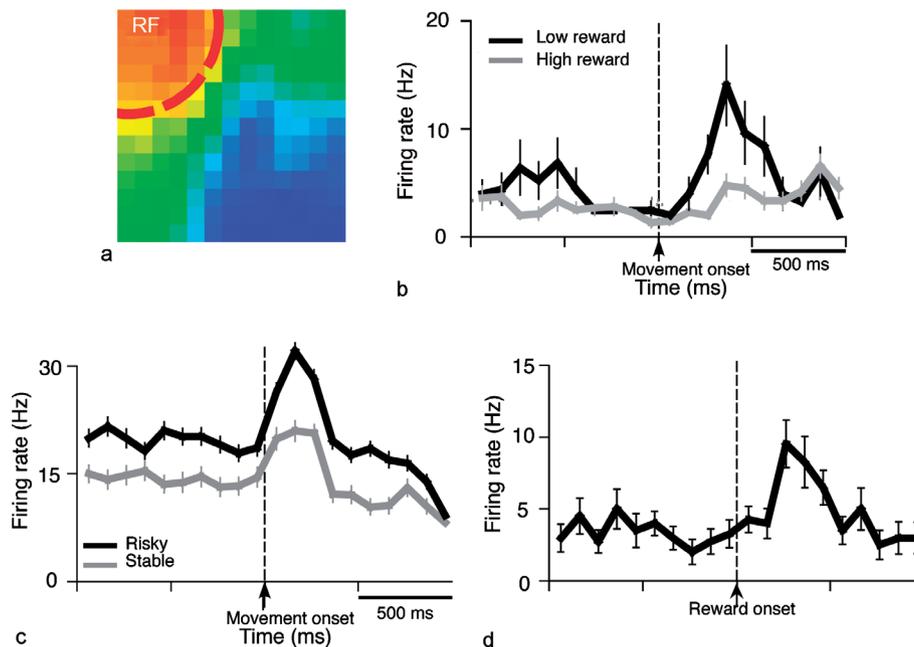


Figure 3 Visuospatial information encoded by neurons in PCC is modulated by reward variables. (a) Neurons in PCC have large contralateral response fields. Color map showing average response of a single neuron following saccades to points in a grid of locations, size 40×40 degrees. Responses are greater when saccades are directed to the upper-left quadrant (response field, RF). (b) PCC neurons encode reward size associated with saccades into their RF. Peri-stimulus time histograms (PSTHs) showing the temporal evolution of the average response of a single PCC neuron in a free choice task. Responses are significantly greater on high reward trials (black line) than on low reward trials (gray line). This modulation affects both the decision period and the postsaccade period of the trial. (c) PCC neurons encode reward uncertainty, or risk, even when average expected payoff is identical. PSTHs showing the average response of a single PCC neuron in a free choice task. Responses are greater when subject chooses to shift gaze to the risky target (black line). (d) PCC neurons respond following unexpected rewards. PSTH showing average response of a single PCC neuron when an unexpected reward is delivered. From McCoy AN and Platt ML (2005) Risk-sensitive neurons in macaque posterior cingulate cortex. *Nature Neuroscience* 8: 1220–1227. Figures reproduced with permission from McCoy et al.

rewarded stimulus. ACC-lesioned monkeys were specifically impaired in their ability to perform the reward-based switching task but their performance was unaffected in the visual discrimination task.

Reward-related computations within cingulate cortex are not limited to the ACC. Neurons in the PCC, for example, represent the subjective value of rewards associated with orienting toward particular locations in space (Figure 3). PCC neurons respond after the illumination of targets, saccade onset, and following reward delivery. Because PCC neurons respond in proportion to the size and probability of rewards, as well as subjective preference for uncertain rewards associated with orienting to a visual target, it has been hypothesized that firing rate in PCC is proportional to the subjective utility of a location in space. The responses of PCC neurons to events within a trial may reflect continuous updating of the subjective utility of the preferred location. Collectively, these results suggest that PCC, like ACC, participates in connecting information about rewards to ongoing sensorimotor transformations.

Conclusion

The cingulate cortex has long been viewed as a large and mysterious terra incognita. Nonetheless, a great deal of knowledge has been gained in recent years. This knowledge, derived from single-unit electrophysiology, lesion studies, fMRI, and event-related potential (ERP) studies, implicates the cingulate cortex in the use of reward information to optimize the process of selecting actions based on sensory information.

See also: Attentional Networks; Attentional Networks in the Parietal Cortex; Decision-Making and Vision; Parietal Cortex and Spatial Attention; Representation of Reward; Reward Systems: Human; Reward Decision-Making; Reward Neurophysiology and Primate Cerebral Cortex; Visual System: Multiple Visual Areas in Monkeys.

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