Functional Heterogeneity in Cingulate Cortex: The Anterior Executive and Posterior Evaluative Regions

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The cingulate gyrus is a major part of the "anatomical limbic system" and, according to classic accounts, is involved in emotion. This view is oversimplified in light of recent clinical and experimental findings that cingulate cortex participates not only in emotion but also in sensory, motor, and cognitive processes. Anterior cingulate cortex, consisting of areas 25 and 24, has been implicated in visceromotor, skeletomotor, and endocrine outflow. These processes include responses to painful stimuli, maternal behavior, vocalization, and attention to action. Since all of these activities have an affective component, it is likely that connections with the amygdala are critical for them. In contrast, posterior cingulate cortex, consisting of areas 29, 30, 23, and 31, contains neurons that monitor eye movements and respond to sensory stimuli. Ablation studies suggest that this region is involved in spatial orientation and memory. It is likely that connections between posterior cingulate and parahippocampal cortices contribute to these processes. We conclude that there is a fundamental dichotomy between the functions of anterior and posterior cingulate cortices. The anterior cortex subserves primarily executive functions related to the emotional control of visceral, skeletal, and endocrine outflow. The posterior cortex subserves evaluative functions such as monitoring sensory events and the organism's own behavior in the service of spatial orientation and memory.

Cingulate cortex forms a ring or cingulum around much of the corpus callosum. Its defining anatomical traits are a prominent deep layer of large pyramidal neurons and input from the anteromedial thalamic nucleus. Cingulate cortex is traditionally viewed as one of the principal limbic structures because it is a major component of Broca's "grand limbic lobe " It also has a prominent place in Papez's conception of circuitry critical for emotional experiences, and it is pivotal to MacLean's view of the limbic system and its contributions to family and social interactions (for reviews, see MacLean, 1989, 1993). These views emphasize the undifferentiated structure of limbic cortex, and its connections with the hippocampus and amygdala in the "anatomical limbic system."

The anatomical limbic system, however, consists of diverse components that contribute not only to emotional but also to nonemotional behaviors. The hippocampus, for example, which has a relatively simple cytoarchitectural organization and is an integral part of the anatomical limbic system, subserves primarily mnemonic and spatial rather than affective functions. Zola-Morgan et al. (1986) described a patient with postischemic damage to the CA1 sector of the hippocampus. Although this patient exhibited a marked anterograde amnesia, there was little or no cognitive impairment beyond the amnesia, and personality and affective behaviors such as appropriate responses to family members were intact. In contrast, the amygdala is preferentially involved in emotional functions. Zola-Morgan et al. (1991) in a combined study of emotion and memory found that lesions of the hippocampus altered memory as assessed in the delayed nonmatching-to-sample task, whereas lesions of the amygdala altered emotional behavior, including responses to objects with affective significance. Thus, the hippocampus is likely involved in information processing associated with cognitive rather than emotional activities, while the amygdala is more closely linked to affective than memory functions.

It has long been known that cingulate cortex is cytoarchitecturally heterogeneous, as summarized in Figure 1*A*, that anterior and posterior cingulate cortices have differing thalamic and cortical connections, and that anterior cingulate cortex is reciprocally connected with the amygdala whereas posterior cingulate cortex is not. These observations led several authors (Vogt et al., 1979; Baleydier and Mauguiere, 1980) to

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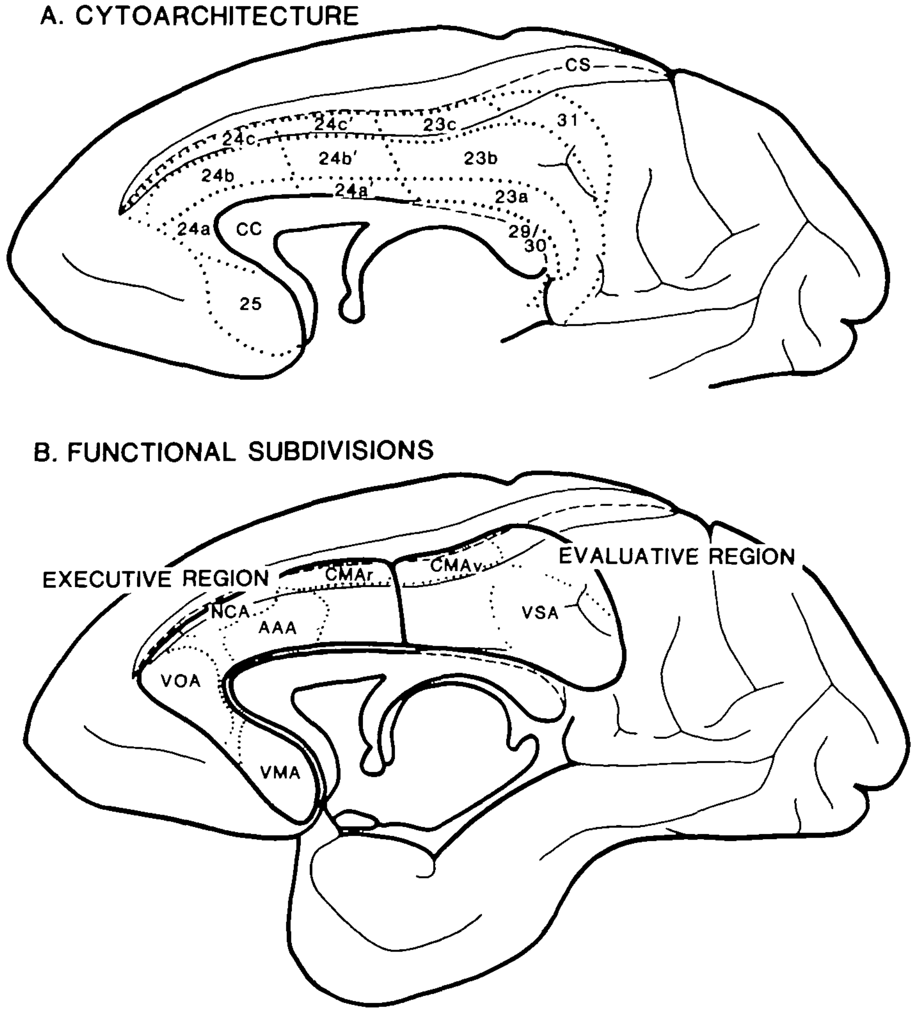

Figure 1. Two perspectives on the regional organization of the cingulate gyrus. Each view represents the medial surface of the rhesus monkey brain. *A*, Cytoarchitectural areas are delineated with *dotted lines*. The depths of the cingulate sulcus (*CS*) and callosal sulcus are identified with *dashed lines*. The corpus callosum is indicated (*CC*). This map is based on a recent review and refinement of primate cytoarchitecture (Vogt, 1993). *B*, The two major functional divisions of cingulate cortex are the executive and evaluative regions (both outlined with *thick lines*). The executive region has further subdivisions including the visceromotor (*VMA*), vocalization (*VOA*), nociceptive (*NCA*), rostral cingulate motor (*CMAr*), and attention to action (*AAA*) areas. The evaluative region includes the ventral cingulate motor (*CMAv*) and visuospatial (*VSA*) areas.

propose a functional dichotomy between anterior and posterior cingulate cortices. There was little information available at that time, however, about where in cingulate cortex these functions might be organized. Furthermore, recent studies of posterior cingulate cortex suggest that it is involved in functions that are not usually considered characteristic of limbic structures. It is time to reanalyze the functions of cingulate cortex, considering both the possibility that they extend beyond emotional and instinctual behaviors and the possibility that cingulate cortex, like the limbic system as a whole, is characterized by its own internal functional heterogeneity.

Anterior Cingulate Cortex: The Executive Region

Studies based on a variety of approaches, including lesions, electrical stimulation, microelectrode recording, and positron emission tomography, have implicated the anterior cingulate cortex in numerous functions: emotion, pain, maternal behavior, visceromotor and skeletomotor control, and attention. At first sight, these functions appear to be highly diverse. There is, however, a uniform theme to nearly all functional observations that have been made of anterior cingulate cortex. This region is involved primarily in effector or executive functions, in controlling output, whether to visceromotor, endocrine, or skeletomotor systems. The classic view that anterior cingulate cortex is involved in emotional processes is entirely compatible with this generalization. Emotional states are closely related to effector processes insofar as every emotion achieves expression through autonomic, endocrine, and skeletomotor outflow and insofar as most emotions involve a tendency to act. It is reasonable that an area contributing to a multiplicity of effector processes should function in part as a staging area for emotional processes. The representation of emotion, however, in anterior cingulate cortex is not uniform.

Emotion

Observations following natural and neurosurgical ablations, and in cases of cingulate epilepsy, have implicated anterior cingulate cortex in affective behaviors. Infarction of the anterior cerebral artery is usually associated with large lesions of anterior cingulate cortex and adjacent frontal cortex. These large lesions produce akinetic mutism (Amyes and Nielsen, 1953; Barris and Schuman, 1953), which includes minimal movement and spontaneous speech, apathy, lack of responses to noxious stimuli, and inattention. Laplane et al. (1981) reported a case with a more restricted infarct in which there were no motor deficits, but there was indifference, docility, inappropriate urination, and a severe lack of attention. Angelini et al. (1980) reported that a tumor in the right anterior cingulate cortex of a boy resulted in serious behavioral abnormalities including a lack of social restraint, heightened sexuality, bulimia, and aggressiveness, but no changes in intelligence or memory. The behavioral deficits were alleviated following tumor removal in a restricted part of anterior cingulate cortex. In adult cases, tumors in anterior cingulate cortex have been associated with tension, ambivalence, hostility, and assaultiveness (Malamud, 1967). Thus, although infarct of the anterior cerebral artery involves adjacent frontal cortex as well as cingulate cortex, lesions restricted to cingulate cortex also implicate the anterior region in emotional expressions such as aggressivity and social interactions.

Whitty et al. (1952) employed anterior cingulectomy for the treatment of mental illnesses. This procedure involved removal of much of anterior area 24 and the underlying white matter, that is, parts of the cingulum bundle. A survey of these cases suggested that there was marked improvement in obsessive behaviors, anxiety, and aggression without gross personality or intellectual changes (Lewin, 1961). There was also a reduced drive behind obsessional thoughts in these cases. Long et al. (1978) made similar observations following anterior cingulotomy. In these cases, intellectual and memory functions were intact, while the effect on personality was impressive, involving a substantial relief of anxiety with some improvement in cases of depression. Finally, Ballantine et al. (1987) reviewed a series of 198 psychiatrically disabled patients who were treated with small ablations in the cingulum bundle. They found that patients with major affective and anxiety disorders were usually returned to normal functioning, and there was a general reduction in violent behaviors. Brown and Lighthill (1968) state "when affective components were the dominant feature of the illness the result of cingulotomy was most rewarding."

Epileptic discharges in anterior cingulate cortex substantiate its role in affective behavior (for review, see Devinsky and Luciano, 1993). Mazars (1970) reported that seizures confirmed to originate in cingulate cortex were frequently precipitated by emotion. These seizures were associated with head movements including nodding or turning, and in some instances there was blushing. Regaining of consciousness was associated with an outburst of temper. The associated temper tantrums occurred on a background of permanent psychotic behavior with unsociability and hostility. Anterior cingulotomy usually alleviated both the epileptic activity and psychotic behavior.

Lesions and electrical stimulation in experimental animals confirm that anterior cingulate cortex is involved in affective behaviors. Smith (1945) and Ward (1948) observed that anterior cingulate lesions in monkeys reduced aggressivity and fear of humans, increased curiosity, and produced inappropriate intraspecies behaviors such as walking over other monkeys as though they were inanimate objects. The cingulectomized animals would also take food from their cage mates and were surprised when rebuffed. These interactions did not lead to fighting, however, because the cingulectomized animals were docile and quickly lost interest A direct role of anterior but not posterior cingulate cortex in aggression is also indicated by electrical stimulation studies. Stimulation of anterior cortex in cats increases latencies to hypothalamically evoked attack, while stimulation of posterior cingulate cortex is without effect (Siegel and Chàbora, 1971) It should be noted, however, that the behavioral consequences of cingulectomy in animals are not uniform. Mirsky et al. (1957) observed only transient alterations in the social behavior of female monkeys following cingulectomy. There is a need for more thoroughly controlled experimental studies in order to resolve the specific contributions of cingulate cortex to affective behaviors.

Pain

There is a nociceptive region in anterior cingulate cortex, and it may be involved in affective responses to noxious stimuli. In human this has been demonstrated by elevated blood flow during noxious heat stimulation (Jones et al., 1991; Talbot et al., 1991), while single-cell studies in the rabbit have shown that neurons in a similar region respond to noxious mechanical and heat stimuli over large parts of the body (Sikes and Vogt, 1992). Both approaches suggest that cortex responsive to noxious stimuli is located at a dorsal level of area 24, as shown in Figure 1*B* (NCA, nociceptive area).

Ablations of the rostral cingulum bundle reduce responsivity to noxious stimuli and abolish pain in chronically ill patients (Foltz and White, 1968; Ballantine et al., 1975). Patients with lesions of the cingulum bundle frequently report that they can still localize the source of a noxious stimulus but that they no longer mind it. Although this outcome is often interpreted in terms of interruption of connections between frontal and parahippocampal cortices, another interpretation is that this lesion disrupts connections of rostral cingulate cortex that are pivotal for pain sensation and/or responses to noxious stimuli.

The contribution of cingulate cortex to avoidance learning is well known from ablation studies in experimental animals (Peretz, 1960; Lubar and Perachio, 1965; Gabriel et al., 1991). These studies suggest that cingulate cortex is involved in the animal's ability to predict and/or avoid noxious stimuli, since the unconditional stimulus is aversive footshock. Although skeletomotor responses in these tasks may not require emotion per se, particularly in late stages of training, it is likely that the animal's ability to simulate the affective consequences of receiving noxious stimuli initiates the premotor activity that leads to avoidance behaviors. Furthermore, enhanced neuronal discharges to the positive versus the negative conditional stimulus occur early in training in anterior cingulate cortex (Gabriel et al., 1980), when affective responses to the noxious stimulus are presumably greatest. During late stages of training when performance of the avoidance task involves "less emotion," increased neuronal activity to the positive versus the negative conditional stimulus develops in posterior cingulate cortex.

Maternal Behavior

Maternal behavior involves complex instinctual behavior patterns and numerous affective responses There have been a number of lesion studies that suggest that cingulate cortex may be critical for this behavior. Ablations of rat cingulate cortex disrupt nest building, pup retrieval, and nursing, while lesions in adjacent neocortex are without such effects (Stamm, 1955; Slotnick, 1967). Electrical stimulation of a rostral part of area 24 evokes oxytocin release (Beyer et al., 1961). Furthermore, lesions of rostral area 24, but not area 25, interfere with the separation cry of infant monkeys (MacLean and Newman, 1988). Thus, interactions between mother and offspring may depend critically on anterior cingulate cortex.

Visceromotor Control

As a general rule, emotional activity is associated with autonomic outflow. Alterations in autonomic state serve a social function in communicating emotion and prepare the organism for skeletomotor activity associated with fighting, flight, consummatory, and sexual behaviors. Therefore, visceromotor outflow is one way to specify the contribution of a cortical area to affective behaviors. Areas 25 and 24 are both involved in visceromotor activity as reviewed by Neafsey et al (1993).

Electrical stimulation of area 25 and rostral area 24 alters blood pressure and respiration rates, evokes piloerection, pupillary dilation, and other autonomic signs (e.g , Smith, 1945; Kaada, 1951, Burns and Wyss, 1985), and elevates plasma corticosterone levels (Dunn, 1990). Lesions in rat area 25 virtually abolish respiratory and vocalization responses to noxious footshock in a classical conditioning paradigm (Frysztak and Neafsey, 1991). Since this latter training paradigm is interpreted as an animal model of conditioned emotion, area 25 is crucial for emotional responses. Furthermore, lesions in dorsal parts of rabbit anterior cingulate cortex attenuate classically conditioned bradycardia (Buchanan and Powell, 1982), and neurons in area 24b respond in specific patterns during classically conditioned changes in heart rate (Gibbs and Powell, 1991). Thus, both areas 25 and 24 are involved in autonomic adjustments associated with classical conditioning.

The structural basis for involvement of area 25 in visceromotor activity is well known. Area 25 projects directly to the parasympathetic nucleus of the solitary tract (Terreberry and Neafsey, 1983) and dorsal motor nucleus of the vagus (Hurley et al., 1991). Similar connections have been demonstrated in the cat (Room et al., 1985; Willett et al., 1986). Area 25 also projects to the sympathetic thoracic intermediolateral cell column (Hurley et al , 1991). In contrast, rostral area 24 does not have direct projections to brainstem autonomic centers. It does, however, have limited connections with area 25 (Vogt and Pandya, 1987) and a number of other structures associated with visceromotor activity including the amygdala. In light of the more direct involvement of area 25 in visceromotor activity, we have delineated the visceromotor area (VMA) in Figure 1*B* as coextensive with area 25

Cinguloamygdala Interactions in Relation to Emotion and Visceral Control

The amygdala plays a role in the evaluation of the motivational significance of sensory stimuli. In particular, it contributes to conditioned fear, that is, classical conditioning that employs an aversive unconditional stimulus, as recently reviewed by LeDoux (1991). Many of the observations and arguments raised in connection with anterior cingulate cortex have been made for the amygdala. For example, the central nucleus projects to the dorsal motor nucleus of the vagus, the nucleus of the solitary tract, and the periaqueductal gray (Price and Amaral, 1981); it contains neurons that code for the significance of sensory stimuli (Nishijo et al., 1988); lesions of the central nucleus disrupt cardiovascular function (Kapp et al., 1979); and electrical stimulation of the central nucleus in awake animals evokes cardiovascular responses that are similar to those associated with conditioned emotional responses (Iwata et al., 1987). In light of these observations, connections of the amygdala may be useful for characterizing those parts of the CNS that are involved in affective behaviors.

Rostral parts of cingulate cortex in the cat and monkey receive inputs from the accessory basal and laterobasal nuclei of the amygdala (Porrino et al., 1981; Vogt and Pandya, 1987; Musil and Olson, 1988), while posterior area 24' and areas 23, 30, and 29 do not receive this input Thus, the amygdala-recipient cortex is approximately coextensive with the cingulate executive region. It is likely that the amygdala and anterior cingulate cortex operate in tandem to produce affective behaviors. In particular, signals arising in the amygdala may contribute to the motivational drive underlying processes carried out by the executive region.

Skeletomotor Functions

It has long been known that electrical stimulation of anterior cingulate cortex evokes skeletomotor responses (e.g., Smith, 1945; Kaada, 1951), that skeletomotor activity occurs during cingulate epilepsies (Mazars, 1970), and that lesions of cingulate cortex disrupt motor function (Amyes and Nielsen, 1953; Barris and Schuman, 1953). The evidence for cingulate involvement in skeletomotor processes is particularly strong in the case of vocalization. Vocalization is usually evoked in monkeys with stimulation around the rostrum of the corpus callosum and may be part of coordinated movements including opening the eyes and pupillary dilation (Smith, 1945; Kaada, 1951). The sounds that are evoked are natural ones that may be associated with the expression of internal states including shrieking and cooing. Lesions in rostral cingulate cortex disrupt spontaneous and discriminatively conditioned vocalizations (Aitken, 1981). The relevance of these vocalizations to emotional expression is emphasized by the finding that the separation cry in infant monkeys is impaired by lesions in rostral area 24 (MacLean and Newman, 1988). The region from which electrical stimulation is most likely to evoke vocalization is outlined in Figure 1*B* (VOA, vocalization area).

Projections to the periaqueductal gray are probably critical to the vocalization functions of anterior cingulate cortex. "Defensive-rage" responses have been evoked from the cat periaqueductal gray with electrical and glutamate stimulation (Skultety, 1963; Bandler, 1982). These responses include ear flattening, back arching, tail and back piloerection, pupillary dilation, and hissing and/or growling. Area 25 and rostral area 24 project to the periaqueductal gray (Mantyh, 1982; Wyss and Sripanidkulchai, 1984), which in turn projects to the laryngeal motor neurons in nucleus ambiguus. The importance of the periaqueductal gray for the vocalization functions of anterior cingulate cortex is indicated by the fact that vocalization elicited by cingulate electrical stimulation is abolished following lesions rostral to the periaqueductal gray (Jürgens and Pratt, 1979). It is also possible that the cingulo-periaqueductal gray connection modulates responses to noxious stimuli because the periaqueductal gray itself influences these responses (Mayer and Liebeskind, 1974; Yaksh, 1979)

In addition to vocalization, stimulation of gyral area 24 evokes complex coordinated movements involving large parts of the body. Talairach et al. (1973) analyzed responses to electrical stimulation of cortex on the surface of the cingulate gyrus in awake epileptic patients. They observed touching, leaning, sucking, and other complex movements. These movements were frequently adapted to environmental constraints and were associated with mood changes, most often euphoria, and autonomic responses including mydriasis, tachycardia, and increased respiration. Electrical stimulation in the depths of the cingulate sulcus gives rise to lower-threshold and less complex movements (Mitz and Wise, 1987; for review, see Dum and Strick, 1993).

Single-neuron recording has provided additional support for the notion that anterior cingulate cortex is involved in voluntary movements. Neurons in area 24c′ exhibit task-related activity during both self-paced and sensory-triggered hand movements (Shima et al., 1991). Many neurons begin firing long before the hand movements, and so clearly carry signals related to the intention to move rather than related to sensory feedback. The dorsal sector of area 24 in which task-related firing has been observed is identified as the rostral cingulate motor area (CMAr) in Figure 1*B*.

Cingulate cortex projects to the caudate and pontine nuclei like many other cortical regions. A number of additional projections, however, provide it with a unique place among limbic cortices. The anterior cingulate motor area projects directly to the spinal cord (Dum and Strick, 1991; for review, see Dum and Strick, 1993) and to the red nucleus, motor thalamus, and premotor cortical areas (for reviews, see Dum and Strick, 1993; Van Hoesen et al., 1993). The cingulate motor areas and area 24b also project to the medial reticular formation (Keizer and Kuypers, 1989).

Attention to Action

In studies that employ positron emission tomography, it has been demonstrated that anterior cingulate cortex exhibits differentially high metabolic activity in subjects performing cognitively demanding stimulus–response tasks. Conditions under which this cortex is active include responding to a noun by producing an associated verb versus simply repeating the noun (Petersen et al., 1988), detecting a change in a visual stimulus when the change might affect shape, color, or speed versus when the change will affect only one known dimension (Corbetta et al., 1991), and naming the color of the letters composing a word when the letters spell the name of a different color versus when they spell the name of the same color (Pardo et al., 1990). The contribution of cingulate cortex to attentional processes is further suggested by the observation that neglect can follow from anterior cingulate injury (Watson et al., 1973) Posner et al (1988) conceptualize this area as being involved in attention to action. The locus of activity in these studies was on the gyral surface of area 24. Accordingly, an "attention to action" area (AAA) is projected onto the gyral surface of the monkey brain in Figure 1*B*.

Cognitive processes such as attention may occur without concurrent motor activities and are clearly separable from emotion. If cognitive processes are to be converted into behavior, however, it is difficult to conceive of them as independent of motivation. For example, there is a strong motivational component in any activity involving highly focused attention or difficult discriminations. Anterior cingulate cortex may provide a meeting place for interactions between cognitive and motivational processes, particularly in relation to the generation of motor output.

In conclusion, there is extensive evidence indicating that executive functions of the cerebral hemisphere, functions that have to do with the control of behavior and of visceral and neuroendocrine outflow, depend on anterior cingulate cortex. Anterior cingulate cortex is involved in a variety of such functions and exhibits regional functional differentiation. The cingulate motor area, located dorsally in the depths of the cingulate sulcus, has connections and functions similar to those of adjacent premotor areas and is least involved in affective behaviors. Area 25, located ventrally, has robust visceromotor projections and is directly involved in visceral control and emotional expression. At an intermediate level, areas 24a and 24b contribute to complex emotional processes; these include vocalization and attention.

Posterior Cingulate Cortex: The Evaluative Region

Lesion, electrical stimulation, behavioral, and connectional studies have failed to implicate posterior cingulate cortex in emotional, visceromotor control, and other functions ascribed to anterior cingulate cortex. Instead, most of the evidence bearing on the functions of posterior cingulate cortex suggests that it is involved in assessing the environment and in memory rather than in the initiation of action. To stress the probable role of this cortex in assessing and assigning mnemonic associations to sensory input, we refer to it as an evaluative region (Fig. 1*B*).

Eye Movements

The electrical activity of posterior cingulate cortex is modulated during eye movements in several species (Sikes et al., 1988; Musil and Olson, 1993; Olson et al., 1993). The zone in which neurons carrying oculomotor signals have been encountered in monkey is coincident with the "visuospatial area" (VSA) as delineated in Figure 1*B*. Many neurons in this area undergo shifts of firing frequency at or after the time of the corresponding eye movement. This strongly suggests that the posterior cingulate cortex is involved in monitoring rather than in controlling eye movements. There is variability across neurons in the nature of the oculomotor parameters that are encoded. The firing of some neurons is determined by the size and direction of the saccadic eye movement. Other neurons carry orbital position signals, firing tonically throughout each period of fixation at a level determined by the angle of the eye in the orbit. Systematic analysis in the monkey has revealed that the two classes are not discrete insofar as many neurons are influenced both by the parameters of the saccade and by the orbital angle of the eye. It is appealing to speculate that posterior cingulate neurons monitor eye movements in connection with neural computations underlying visuospatial awareness This is plausible because the parameters of each saccadic eye movement convey information about the spatial relation between the current and previous objects of fixation, while the angle of the eye in the orbit must be known in order to determine the location of any visible object relative to the body.

Vision

Posterior cingulate neurons responsive to visual stimulation have been encountered in all species where visual testing has been conducted (Sikes et al., 1988; Musil and Olson, 1993; Olson et al , 1993). Systematic testing in the monkey has revealed that the physical characteristics of the stimulus are a crucial determinant of response level. Small spots presented on a screen in front of the monkey do not elicit neuronal responses even if the animal is attending to and making motoric responses to them. In contrast, large, bright, textured stimuli elicit responses even if they are totally irrelevant to tasks the animal is performing and are not subject to voluntary attention. A possible interpretation of these findings is that posterior cingulate neurons respond to visual stimuli to the degree to which they are physically salient. It is also possible that the preference for large stimuli reflects an involvement in scene recognition.

Somatic Function

A division of posterior cingulate cortex in the depths of the cingulate sulcus (area 23c) contains neurons that project to the spinal cord and that are active in conjunction with hand movements (Shima et al., 1991) This "ventral" cingulate motor area (CMAv) is identified in Figure 1*B* as a subdivision of the posterior cingulate evaluative region. We imply by this classification that CMAv is involved in assessing the state of the skeletomotor system, in contrast to CMAr, a division of anterior cingulate cortex, which is involved in motor control. This functional distinction is compatible with several facts. First, electrical stimulation of cingulate cortex at moderate current levels fails to evoke movement (Shima et al., 1991). Second, neurons that begin firing only after the onset of electromyographic activity are more numerous in CMAv than in CMAr (Shima et al., 1991). Third, the "sensory" cytoarchitecture of area 23c is fundamentally different from the "motor" architecture of area 24c'. Area 23c has larger layer IIIc pyramids, a well developed layer IV, and smaller pyramids in layer Va (Vogt, 1993). The fact that many neurons in CMAv begin firing before hand movements does not rule out its contributing primarily to evaluative processes. This is indicated by the observation that premovement firing also occurs in area 5, which is generally considered to be more involved in sensory than in motor processes (Burbaud et al., 1985).

Spatial Orientation

Several observations have suggested that posterior cingulate cortex contributes to orientation of the animal in the environment and to spatial working memory. Lesions of posterior but not anterior cingulate cortex disrupt a rat's ability to swim to a hidden platform (Sutherland et al., 1988; for review, see Sutherland and Hoesing, 1993), and cingulate ablations impair spatial delayed nonmatching-to-sample in a T maze (Markowska et al., 1989). Lesions of monkey cingulate cortex also disrupt spatial learning (Murray et al , 1989). Single-neuron electrophysiological studies support a role for posterior cingulate cortex in spatial orientation, neurons in rat posterior cingulate cortex are sensitive to the angle of the body relative to the environment and to displacements of the body (Chen et al., 1991).

If posterior cingulate cortex makes a contribution to spatial orientation, then the nature of its contribution may rest on its anatomical interposition between parietal area 7 and the parahippocampal gyrus. McNaughton et al. (1991) have proposed that cingulate neurons utilize displacement signals arising in parietal cortex to update position signals encoded at the level of the parahippocampal gyrus. Alternatively, cingulate neurons might participate in the transformation from a parietal representation of space based on a body-centered frame of reference to a parahippocampal representation based on a world-centered frame of reference Another possibility is that representation of allocentric space becomes progressively more refined in the sequence of areas leading from posterior cingulate cortex through parahippocampal cortex to the hippocampus. In support of this view, it has been shown that layer II entorhinal neurons exhibit spatially selective firing (Barnes et al., 1990; Quirk et al., 1992), but that their spatial selectivity is coarser than that of hippocampal neurons.

Memory and Cingulohippocampal Interactions

There are indications that posterior cingulate cortex is involved in memory functions beyond those underlying spatial orientation. Valenstein et al. (1987) reported a case in which there was profound impairment of anterograde and retrograde memory following a hemorrhage from an arteriovenous malformation near the splenium of the corpus callosum. The lesion in this case was restricted to retrosplenial cortex, part of area 23a, and part of the corpus callosum. This individual had intact pain sensation, fluent speech, and intact visuospatial and intellectual abilities. Further evidence for the involvement of cingulate cortex in memory has come from studies of long-term potentiation. Long-term potentiation has been demonstrated in cingulate cortex following electrical stimulation of glutamatergic (Jay et al., 1991) hippocampal formation efferents (Laroche et al., 1990).

Connections with parahippocampal cortex probably play a major role in memory-related functions of cingulate cortex. Subicular afferents terminate in the rostral and caudal parts of cingulate cortex including areas 25 and 29/30, respectively (Rosene and Van Hoesen, 1977). Projections to entorhinal cortex originate from a similar region of cingulate cortex, but also include a rostral part of area 24a and area 23a (Insausti et al., 1987). Finally, the projections of areas TH and TF are widely distributed in cingulate cortex (Vogt and Pandya, 1987). Rostral parts of these areas terminate in mid levels of cingulate cortex, while posterior levels of these parahippocampal areas terminate in rostral area 24 and caudal areas 23 and 30.

Functional Heterogeneity of Cingulate Cortex

The above observations taken together imply that posterior cingulate cortex is involved in orientation within and interpretation of the environment. The functions of posterior cingulate cortex include monitoring of visual events and eye movements, spatial orientation, and memory. This region appears to be devoid of functions related to motivation and affect. In contrast, anterior cingulate cortex is involved in a variety of effector functions, many of which posses an emotional dimension. Functions served by anterior cingulate cortex include visceromotor and skeletomotor control, responses to noxious stimuli, and attention.

In spite of the functional dissociation of the cingulate executive and evaluative regions, these entities are certainly are not independent. Many studies have documented the strong connections between anterior and posterior cingulate cortices, as well as within them in the ventrodorsal plane. These connections have been described in the rat (Vogt and Miller, 1983; Finch et al., 1984), cat (Musil and Olson, 1988), and monkey (Baleydier and Mauguiere, 1980; Vogt and Pandya, 1987). It is quite likely, therefore, that the functions of these divisions are coordinated. In particular, output functions of the anterior executive region may be directed by activity in the posterior evaluative region. This pattern of connectivity has been referred to as a feedforward system by Van Hoesen et al. (1993).

The position of cingulate cortex in the limbic system is far more complex than envisioned in classical schemes. At least two functionally distinct limbic subsystems interact with cingulate cortex. On one hand, the amygdala, a structure crucial for emotion and motivation, is linked strongly to the anterior cingulate area. Anterior cingulate cortex and the amygdala probably operate in tandem in the production of motivated behavior and emotional expression. On the other hand, the parahippocampal cortex communicates with both divisions of cingulate cortex, and likely contributes to the role of posterior cingulate cortex in memory and spatial orientation. It is ironic that links between the cingulate gyrus and the hippocampal formation led Papez to propose that cingulate cortex mediates emotional experience, since these connections probably subserve cognitive functions rather than emotion.

Notes

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