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REVIEW ARTICLE

Contributions of anterior cingulate cortex to behaviour

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Summary

Assessments of anterior cingulate cortex in experimental animals and humans have led to unifying theories of its structural organization and contributions to mammalian behaviour. The anterior cingulate cortex forms a large region around the rostrum of the corpus callosum that is termed the anterior executive region. This region has numerous projections into motor systems, however, since these projections originate from different parts of anterior cingulate cortex and because functional studies have shown that it does not have a uniform contribution to brain functions, the anterior executive region is further subdivided into 'affect' and 'cognition' components. The affect division includes areas 25, 33 and rostral area 24, and has extensive connections with the amygdala and periaqueductal grey, and parts of it project to autonomic brainstem motor nuclei. In addition to regulating autonomic and endocrine functions, it is involved in conditioned emotional learning, vocalizations associated with expressing internal states, assessments of motivational content and assigning emotional valence to internal and external stimuli, and maternal–infant interactions. The cognition division includes caudal areas 24' and 32', the cingulate motor areas in the cingulate sulcus and nociceptive cortex. The cingulate motor areas project to the spinal cord and red nucleus and have premotor functions, while the nociceptive area is engaged in both response selection and cognitively demanding information processing. The cingulate epilepsy syndrome provides important support of experimental animal and human functional imaging studies for the role of anterior cingulate cortex in movement, affect and social behaviours. Excessive cingulate activity in cases with seizures confirmed in anterior cingulate cortex with subdural electrode recordings, can impair consciousness, alter affective state and expression, and influence skeletomotor and autonomic activity. Interictally, patients with anterior cingulate cortex epilepsy often display psychopathic or sociopathic behaviours. In other clinical examples of elevated anterior cingulate cortex activity it may contribute to tics, obsessive–compulsive behaviours, and aberrent social behaviour. Conversely, reduced cingulate activity following infarcts or surgery can contribute to behavioural disorders including akinetic mutism, diminished self-awareness and depression, motor neglect and impaired motor initiation, reduced responses to pain, and aberrent social behaviour. The role of anterior cingulate cortex in pain responsiveness is suggested by cingulumotomy results and functional imaging studies during noxious somatic stimulation. The affect division of anterior cingulate cortex modulates autonomic activity and internal emotional responses, while the cognition division is engaged in response selection associated with skeletomotor activity and responses to noxious stimuli. Overall, anterior cingulate cortex appears to play a crucial role in initiation, motivation, and goal-directed behaviours. The anterior cingulate cortex is part of a larger matrix of structures that are engaged in similar functions. These structures form the rostral limbic system and include the amygdala, periaqueductal grey, ventral striatum, orbitofrontal and anterior insular cortices. The system formed by these interconnected areas assesses the motivational content of internal and external stimuli and regulates context-dependent behaviours.

Keywords: limbic system; premotor function; epilepsy; visceromotor control; affect; cognition; nociception; akinetic mutism; schizophrenia

Introduction

Cingulate cortex is one of the largest parts of the limbic lobe (Broca, 1878) and the limbic system (MacLean, 1990). Early theories viewed the entire cingulate gyrus as being involved in emotion. Recent experiments, however, have shown that the anterior part of the cingulate gyrus plays a role in emotion and motor functions, and that the posterior region is involved in visuospatial and memory functions with little or no involvement in affect. Although anterior cingulate cortex has prominent projections to motor systems, its contributions to human behaviour have been elusive because isolated cingulate lesions are rare and surgical interventions in the inter-hemispheric space are infrequent. Spontaneous lesions of anterior cingulate cortex, such as tumours and strokes, almost always involve adjacent areas, such as mesial frontal cortex, white matter and the septum. Stroke and epilepsy rarely provide examples of isolated cingulate dysfunction.

The mixed involvement of cingulate and adjacent cortices in stroke is due to the distribution of the anterior cerebral artery. The anterior cerebral artery has eight branches which, in addition to supplying cingulate cortex, distribute to the medial portions of the orbital gyri, the entire medial aspect of the anterior two-thirds of the cerebral hemispheres including the supplementary motor area, and through the recurrent artery of Huebner, the head of the caudate nucleus, anterior putamen, and the anterior limb of the internal capsule (Marino, 1976; Perlmutter and Rhoton, 1978). Thus, a selective occlusion of one of the cortical branches does not usually give rise to an isolated cingulate infarct. Further, the cingulate gyri are deep in the interhemispheric fissure and selective disruption during a seizure cannot be confirmed without invasive electrodes. In light of its complicated vascularization and anatomical inaccessibility, PET studies and selective cortical ablations are the most useful approaches to characterizing functions subserved by human anterior cingulate cortex.

This review considers the 'executive functions' of anterior cingulate cortex including its interactions with motor systems, its role in response selection and cognitive processing, and behaviours which involve affect. First, we briefly review the organization and functions of anterior cingulate cortex in experimental animals because they are relevant to interpreting human findings and because so much is known about anterior cingulate cortex connections in non-human primates. The human anterior cingulate cortex surface features and cytoarchitecture is then discussed. Information about its function in human brain is derived from lesions, electrical stimulation, and PET studies. Pre- and post-operative observations of patients with epilepsy provide particularly strong support for the contributions of anterior cingulate cortex to motor function and affective behaviours. Therefore, in addition to a review of previously reported cases, two new epilepsy cases are presented with invasive electrode confirmation of cingulate seizure foci. Other movement disorders that may result from a significant disruption of cingulate function are assessed and include akinetic mutism and Gilles de la Tourette syndrome. The wealth of structural and functional information available for anterior cingulate cortex and its numerous links with motor systems makes this cortical region a rich site for behavioural neurological studies.

Anterior cingulate structure and function in experimental animals

Organization and projections to motor systems

The anterior cingulate cortex lies ventral, rostral and dorsal to the corpus callosum, and it has particularly large layer V pyramidal neurons that project into motor systems. Although parts of anterior cingulate cortex play a role in motor function which is similar to premotor and supplementary motor area cortices, anterior cingulate cortex also modulates autonomic activity associated with affective behaviours and response selection (*see* below). One of the unique features of anterior cingulate cortex circuity is its diverse thalamic afferents and consequent ability to sample inputs from more thalamic nuclei than any other cortical region. The ability to sample from a wide range of thalamic inputs may be crucial for its contributions to motor response selection functions.

These thalamocortical projections have recently been summarized in the broader context of thalamic connections of the cingulate gyrus by Bentivoglio *et al.* (1993). The thalamic nuclei which project to anterior cingulate cortex include projections from the anteromedial, paraventricular, parataenial, paracentral, central and centrolateral, reuniens, parafascicular, limitans, mediodorsal, and ventral anterior nuclei. Although the roles of each of these nuclei in brain functions are not known, it is possible, for example, that the midline and intralaminar thalamic nuclei transmit information relating to nociception (Casey, 1966; Dong *et al.*, 1978; Sikes and Vogt, 1992) and eye movements (Schlag-Rey and Schlag, 1984). Such thalamic activity could drive responses in human anterior cingulate cortex associated with nociceptive stimuli (Jones *et al.*, 1991*a*) and eye movement activity (Petit *et al.*, 1993). Thus, when considering the unique contributions of anterior cingulate cortex to motor function, it may also be productive to consider thalamocortical projections that are engaged during premotor activity in addition to the direct projections of anterior cingulate cortex to motor systems.

The anterior cingulate cortex mediates skeletomotor and autonomic activity as discussed below, and unilateral cingulate lesions in monkey produce contralateral motor neglect (Watson *et al.*, 1978). Figure 1 is a schematic view of the medial surface of the rhesus monkey brain onto which have been placed functional divisions of the anterior executive region. The concept of an executive region was originally proposed to account for the involvement of anterior cingulate cortex in many motor functions (Vogt *et al.*, 1992*a*). This region may be further divided in order to account for two different contributions to behaviour. A primary division

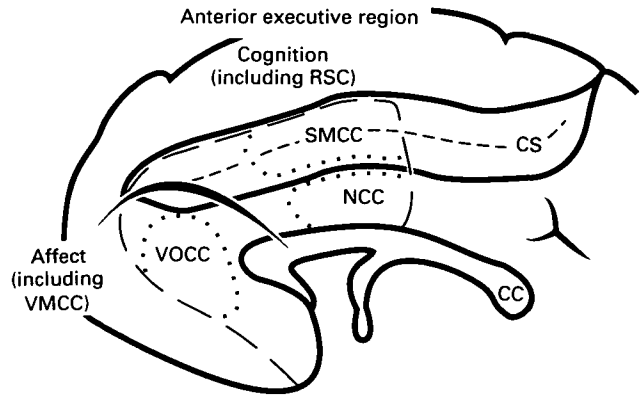

Fig. 1 Distribution of the two components of the anterior executive region for affect and cognition (approximate border of each denoted with a swish). The affect region includes visceromotor control cortex (VMCC) and a subregion of vocalization control cortex (VOCC). The cognition region includes a subset of cortex engaged in response selection, nociceptive cortex (NCC), and skeletomotor control cortex (SMCC). CC = corpus callosum; CS = cingulate sulcus.

within the anterior executive region is made here on the basis of contributions to affect and cognition. The affect division encompasses areas 25, 24 and 32 (Vogt, 1993; *see* Fig. 4). These areas are a projection site of the amygdala (Vogt *et al.*, 1987; Van Hoesen *et al.*, 1993), and the pivotal involvement of the amygdala in affect is well documented (e.g. LeDoux, 1991; Aggleton, 1992). Since electrical stimulation in any part of this cortical region can modulate autonomic functions (*see* below), one of the common features of its constituent areas is their involvement in visceromotor control. Another common feature of areas in the affect division are the pronounced projections to the periaqueductal grey (Müller-Preuss and Jürgens, 1976; Hardy and Leichnetz, 1981). The periaqueductal grey has been implicated in mediating affective defence and other emotional behaviours associated with flight and immobility (Siegel and Brutus, 1990; Bandler *et al.*, 1991; Holstege, 1992). Thus, areas comprising the affect division of the anterior executive region have common features both in their inputs and outputs.

The cognition division has not been implicated in emotional behaviours, modulation of autonomic function, nor does it have substantial connections with the amygdala or periaqueductal grey. The cognitive division of the anterior executive region is characterized by its contributions to skeletomotor control as documented in monkey, while its involvement in nociception has been demonstrated in the human. The dissociation between affective and cognitive regions is also supported by connection studies. There are few connections between rostral area 24 and area 24′. In addition, there are reciprocal connections between rostral area 24 and area 23 with little interconnection between the mid-levels of cingulate cortex and these two former areas (Vogt and Pandya, 1987).

Layer V contains many of the neurons that project to motor systems, and it is primarily responsible for the role of anterior cingulate cortex in executive functions. Human neurological syndromes associated with disruption of anterior cingulate cortex all involve disruption of some aspect of motor control or cognitive processes associated with motor or premotor events. The topographical specialization of motor function in anterior cingulate cortex is best demonstrated by its projections to the striatum. This region has projections to all major components of the striatum: the caudate nucleus, ventral striatum including the nucleus accumbens, and the putamen (Müller-Preuss and Jürgens, 1976; Yeterian and Van Hoesen, 1978; Baleydier and Mauguière, 1980).

Kunishio and Haber (1994) demonstrated important topographies in striatal projections that confirm cyto-architectural delineations in anterior cingulate cortex and distinctions in motor function for different parts of the anterior executive region. Figure 2 presents three cases from their study and a sample coronal section from each with neurons retrogradely radio-labelled to emphasize differences in the topography of this projection. In the first case the retrograde tracer injection was into the shell region of the nucleus accumbens, in the second it was into the lateral division of the ventral striatum, and in the third it was in the dorsolateral part of the caudate nucleus. The distribution of labelled neurons differs in anterior cingulate cortex in the following ways. The nucleus accumbens injection labelled neurons mainly in areas 25 and ventral parts of area 24 including areas 24a and 24b. The ventral striatum injection labelled neurons in dorsal parts of area 24b and medial parts of area 24c. The third injection into the dorsolateral caudate nucleus labelled neurons in the depths of the cingulate sulcus in area 24c and to a lesser extent in area 24c′.

The differential projections of parts of anterior cingulate cortex to the striatum suggests that these cortical projection zones are engaged in different aspects of motor function. Thus, the dorsolateral striatum receives large projections from sensorimotor cortex and, as discussed below, area 24c′ modulates skeletomotor activity and projects to the dorsolateral striatum. Neurons in this part of the striatum can acquire long-term changes in excitability during classical conditioning (Aosaki *et al.*, 1994) and these response plasticities may be initiated or maintained by anterior cingulate cortex inputs. In contrast, rostral area 24 and area 25 project to the nucleus accumbens; a division of the ventral striatum which receives many inputs from other limbic structures including the amygdala and parahippocampal cortex (Russchen *et al.*, 1985). Neurons in the ventral striatum discharge in relation to the reward properties of unconditional stimuli and may be involved in the motivational aspects of behaviour (Schultz *et al.*, 1992). Although the stimulus significance of rewarding stimuli are probably determined by amygdala inputs to the ventral striatum, changes in neuronal responsivity to new environmental cues may be guided by anterior cingulate cortex.

In addition to differential projections to one motor structure like the striatum, heterogeneities in the contributions of anterior cingulate cortex to motor functions also are likely

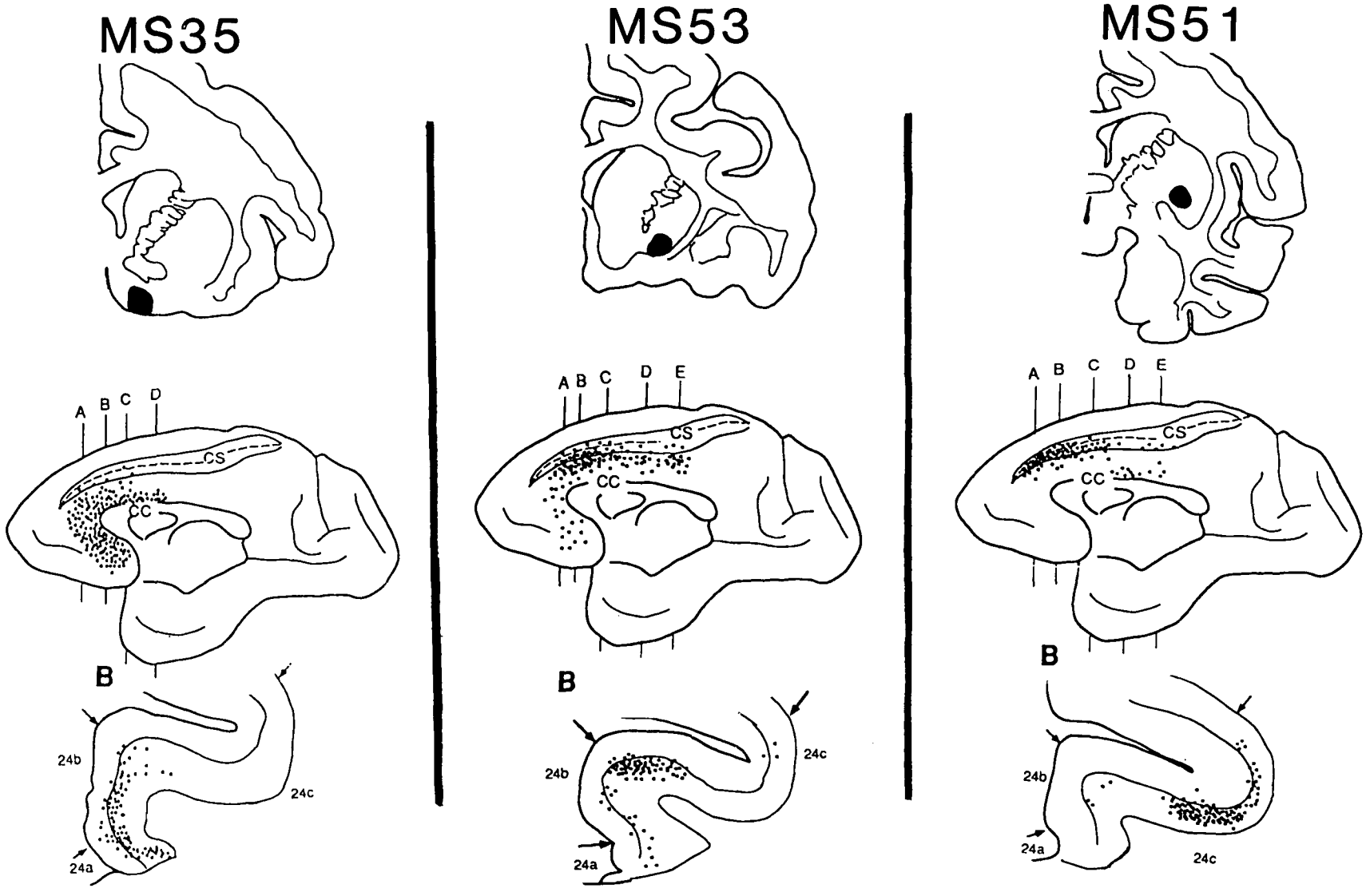

Fig. 2 Distribution of retrogradely radio-labelled neurons in anterior cingulate cortex (dots) following injections into three parts of the striatum (solid areas in first of each series of sections). A single transverse section (B) was selected as an example of the topography of labelled neurons in the cingulate gyrus. These three cases show the differential topography of striatal projection neurons in anterior cingulate cortex. Modified with permission from Kunishio and Haber (1994).

from, anterior cingulate cortex projections to many components of the skeletomotor and autonomic nervous systems. Parts of anterior cingulate cortex can directly influence the following motor systems: (i) the autonomic nervous system via projections to the nucleus of the solitary tract and dorsal motor nucleus of the vagus; (ii) dorsolateral and ventromedial components of the skeletomotor system via projections to the spinal cord, red nucleus, and pontine nuclei; (iii) nuclei in the reticular formation that regulate integrated motor responses; and (iv) parts of the limbic system that are engaged in initiating behaviours related to the motivational significance of sensory stimuli such as the amygdala and periaqueductal grey. The remainder of this section summarizes the specific experimental anatomical and functional observations that support views of the role of anterior cingulate cortex in executive motor functions.

Visceromotor control cortex

Area 25 has several projection sites that may mediate visceromotor activity. In the rat and cat, area 25 projects directly to the parasympathetic nucleus of the solitary tract (Terreberry and Neafsey, 1983; Willett *et al.*, 1986) and dorsal motor nucleus of the vagus (Room *et al.*, 1985; Hurley *et al.*, 1991). Area 25 also projects to the sympathetic thoracic intermediolateral cell column (Hurley *et al.*, 1991). Although area 24 does not have similar connections, the projections of area 24 that mediate visceromotor function may include interactions with area 25 (Vogt and Pandya, 1987), orbitofrontal cortex (Morecraft *et al.*, 1992) and projections to the peiaquaductal grey noted above. The rostral portion of area 24 and area 25 are part of the affect division (Fig. 1), which includes both direct visceromotor control from area 25 and indirect regulation by rostral area 24. The prominent connections between the amygdala and the visceromotor control region (Vogt and Pandya, 1987) may partly account for the important contributions of anterior cingulate cortex to affective behaviours.

Early anterior cingulate cortex electrical stimulation studies in cats, dogs and monkeys revealed prominent autonomic changes, including increases and decreases in blood pressure, heart and respiratory rates, and pyloric antral contractions (Smith, 1945; Kaada *et al.*, 1949; Kaada, 1951). Subsequent studies confirmed the effects of anterior cingulate cortex stimulation on virtually all autonomic and many endocrine functions. These include the cardiovascular, respiratory, digestive, thermoregulatory systems; increases in skin conductance; gonadal and adrenal cortical hormone secretion; drinking; penile erection; and aggression (Dua and MacLean, 1964; Setekleiv, 1964; Robinson and Mishkin, 1968; Lubar *et al.*, 1973; Cacerees and Taleisnnik, 1980; Hurley-Gius and Neafsey, 1986; Dunn, 1990; Neafsey, 1990; Buchanan and Powell, 1993).

In an animal model of emotional stress, the conditioned emotional response, anterior cingulate cortex modulates sympathetic nervous system responses, vocalization and respiratory responses (Neafsey *et al.*, 1993). In the conditioned emotional response, an animal is presented a neutral conditioning stimulus (e.g. tone) followed by an emotionally aversive unconditional stimulus (e.g. footshock) (Smith and Nathan, 1967). In this model, autonomic and other physiological changes following the conditioning stimulus reflect anticipatory emotional responses. Lesions of anterior cingulate cortex in the rat significantly reduce heart rate changes (both tachycardia and bradycardia), respiratory inhibition and vocalization during the conditioning stimulus phase of the conditioned emotional response (Frysztak and Neafsey, 1991). In addition, lesions in dorsal parts of rabbit anterior cingulate cortex including area 24b attenuate classically conditioned bradycardia (Buchanan and Powell, 1982) and neurons in this area respond in specific patterns during classically conditioned changes in heart rate (Gibbs and Powell, 1991). Thus, areas 25 and 24 are involved in autonomic adjustments associated with classical conditioning.

Vocalization control cortex

Cingulate cortex has been directly implicated in vocalization in monkeys, cats and rats. Vocalization modulated by anterior cingulate cortex is considered in conjunction with visceromotor control because vocalization evoked from anterior cingulate cortex in non-human primates has affective content and appears to express primarily internal emotional states. Also, lesions of area 25 in rats abolish conditioned emotional, respiratory and vocalization responses to noxious footshock (Frysztak and Neafsey, 1991). Thus, in Fig. 1 the affect region includes functions associated with both visceromotor control cortex and vocalization control cortex.

Cingulate-modulated vocalizations are different from other skeletomotor activities because there are a limited number of vocalization patterns, while other skeletomotor responses frequently require generation of new patterns of muscle activity. Electrical stimulation of anterior cingulate cortex in monkeys evokes growling and cackling calls (Jürgens and Ploog, 1970) or arrests vocalization (Elliot, 1969). Removal of anterior cingulate cortex in cats and monkeys may lead to a transient increase or decrease in spontaneous and conditioned vocalizations (Smith, 1944; Kennard, 1955; Gomez and Mettler, 1962; Aitken, 1981) and learning of prolonged vocalization (Sutton *et al.*, 1974; Aitken, 1981). Even when spontaneous vocalization is reduced, however, animals can screech and scream normally in response to threats or attacks (Sutton *et al.*, 1974).

Cingulate-evoked vocalizations may be mediated by the periaqueductal grey because electrical stimulation there also evokes vocalizations, and ablation of the pathway connecting anterior cingulate cortex and the periaqueductal grey abolishes cingulate stimulation-evoked vocalizations (Jürgens and Pratt, 1979). Finally, the cingulate vocalization area appears distinct from the anterior cingulate motor areas (CMAs) and the region involved in nociception (Fig. 1). The vocalization region includes areas 32 and 24 and a rostral part of area 25

(Vogt and Barbas, 1988), while the CMAs lie in the depths of the cingulate sulcus, and the nociceptive region appears to include areas 24a′ and 24b′ on the cingulate gyral surface.

Skeletomotor control cortex

The dorsolateral skeletomotor system regulates distal musculature via the corticospinal and rubrospinal projections, while the ventromedial skeletomotor system regulates the axial musculature via the reticulospinal and vestibulospinal projections (for review, *see* Cheney *et al.*, 1991). Cortex in the depths of the cingulate sulcus contains corticospinal projection neurons (Biber *et al.*, 1978) and Dum and Strick (1993) defined three CMAs in the depths of cingulate sulcus; a rostral division (CMAr) in area 24c′, a ventral division (CMAv) in posterior cingulate area 23c, and a dorsal division (CMAd) in area 6c. These areas have connections that are similar to premotor areas in prefrontal cortex including direct projections to the spinal cord (Dum and Strick, 1991) and reciprocal connections with primary motor cortex and the supplementary motor area (Moorecraft and Van Hoesen, 1992; Bates and Goldman-Rakic, 1993).

Electrophysiological studies confirm that anterior cingulate cortex regulates movement and may be engaged in premotor functions. Electrical stimulation of cortex in the ventral bank of the monkey cingulate sulcus evokes simple and complex movements from a somatotopically organized motor field (Luppino *et al.*, 1991) which appears to lie in area 24c′. Furthermore, neurons in the CMAs may prepare for movement. Single-unit neuronal discharges in these areas were evaluated in monkeys during sensory-triggered and self-paced forelimb movements (Shima *et al.*, 1991). Neuronal responses in CMAr preceeded self-paced movements with long-lead times of 0.5–2.0 s, while responses in CMAv were related to sensory stimuli.

Nociceptive cortex and avoidance learning and memory

Schäffer and associates reported decreased pain sensitivity after cingulate lesions in monkeys (Brown and Schäfer, 1888; Horsley and Schäfer, 1888). Experimental studies in rats suggest that impaired conduction through the cingulum bundle disrupts the affective component of tonic pain (Vaccarino and Melzack, 1989). Although functional imaging studies of nociceptive responses are not available in non-human primates, anterior cingulate cortex involvement in human nociception is based on extensive neurosurgical and blood flow studies. Thus, part of caudal anterior cingulate cortex is outlined in Fig. 1 to approximate nociceptive cortex reported for human brain (Jones *et al.*, 1991*a*).

Individual neurons in a dorsal and anterior part of rabbit area 24 respond to noxious heat or mechanical stimuli (Sikes and Vogt, 1992). These responses have almost no stimulus localization information, since noxious stimuli anywhere on the body surface can activate most nociceptive neurons. The source of nociceptive inputs to anterior cingulate cortex may be the medial thalamic nuclei. The anterior cingulate cortex receives significant inputs from the midline thalamic nuclei which themselves contain nociceptive neurons in the monkey (Vogt *et al.*, 1979) and rabbit (Vogt *et al.*, 1992*b*). In addition, reduced activity in these nuclei with lidocaine blocks nociceptive activity in anterior cingulate cortex (Sikes and Vogt, 1992). Thus, anterior cingulate cortex receives nociceptive afferents, and is involved in some aspect(s) of assessing painful stimuli.

The anterior cingulate cortex may be involved in the following aspects of pain sensation: (i) specifying the affective content of noxious stimuli; (ii) motor response selection for noxious stimuli; (iii) learning associated with the prediction and avoidance of noxious stimuli. Controlled testing paradigms demonstrate subtle deficits following bilateral cingulectomy. These included increased errors and impaired precision in learning and impaired acquisition and maintenance of avoidance responses (Pribram and Kruger, 1954; Pechtel *et al.*, 1958; Peretz, 1960; McCleary, 1961). In discriminative avoidance learning, animals learn to avoid an aversive unconditional stimulus by discriminating between a positive conditioning stimulus (e.g. a tone that reliably predicts footshock) and a negative conditioning stimulus (e.g. a tone that does not predict footshock). Lesions of anterior cingulate cortex in rabbits retard acquisition of discriminative avoidance learning (Gabriel *et al.*, 1989, 1991), while multi-unit recordings in anterior cingulate cortex during avoidance learning suggest that this area is involved in task acquisition or processes involving early training-induced neuronal activity (Gabriel *et al.*, 1991). Gabriel (1993) suggests that the principal brain modification underlying discriminative avoidance learning is the 'construction of cingulate cortical command volleys and the plasticity that makes these volleys contingent on the external presence of the learning context and the positive conditioning stimulus'.

Studies in electrical self-stimulation, a model of reinforcement, initially focused on the medial forebrain bundle and lateral hypothalamus (Olds and Milner, 1954; Olds and Olds, 1963). However, self-stimulation behaviour occurs in anterior cingulate cortex, although the characteristics differ from medial forebrain bundle sites (Porrino, 1993). In contrast to medial forebrain bundle self-stimulation behaviour, anterior cingulate cortex and other limbic sites require longer acquisition times, have lower rates of responding, require higher current levels to obtain responses and are not facilitated by food deprivation or amphetamines (Goodall and Carey, 1975; Robertson *et al.*, 1981, 1982; Corbett *et al.*, 1982). Also, unlike the medial forebrain bundle, anterior cingulate cortex self-stimulation does not plateau but is strengthened over time (Douglin and Glassman, 1979). The initial lack of reinforcement and progressive enhancement of self-stimulation have been attributed to synaptic plasticity (Corbett *et al.*, 1982) and likened to kindling (Corbett and Stellar, 1983). Interestingly, short inter-stimulus intervals retard both

kindling and anterior cingulate cortex self-stimulation (Goddard *et al.*, 1969; Corbett *et al.*, 1982) and anticonvulsant drugs retard the development of cingulate self-stimulation (Robertson *et al.*, 1982).

Social interactions

Traditional systems analysis in neurobiology focuses on sensorimotor activity and these approaches have proven useful in assessing anterior cingulate cortex function. However, complex social interactions such as maternal–infant interactions involve a level of brain organization beyond that subserved by simple sensorimotor reflex arcs. Several of these interactions may involve affect and executive functions subserved by anterior cingulate cortex and long-term memories possibly stored in posterior cingulate cortex. The analysis of sensorimotor reflexes will not explain such complex functions of anterior cingulate cortex. Lesion studies provide the bulk of information that hints at the role of anterior cingulate cortex in social interactions.

The most commonly reported persistent behavioural changes following anterior cingulate cortex lesions included the following: reduced and, occasionally, increased aggressivity, diminished shyness and fear of man, emotional blunting, decreased motivation, disruption of mating behaviour, impaired maternal–infant interactions, impatience, lowered threshold for fear or startle responses, and inappropriate intraspecies social behaviour (Smith, 1944; Ward, 1948*a*, *b*; Glees *et al.*, 1950; Kennard, 1955; Pechtel *et al.*, 1958; Larsson, 1962). Area 24 lesions in infant monkeys impair the separation cry when the infant is removed from the mother and disrupt the mother's ability to attend to the infant (MacLean and Newman, 1988).

Although there have been some reports that bilateral cingulectomy fails to produce significant changes in social behaviour in monkeys (Pribram and Fulton, 1954; Gomez and Mettler, 1962; Meyers, 1975), there are a number of possible explanations for the different observations. Behavioural changes after cingulectomy may reflect species differences as well as differences in lesion sites and in the testing context. For example, caged rhesus monkeys are more aggressive towards humans than are free-ranging monkeys. Furthermore, results may vary according to the methods for studying and quantifying behaviour. Most consistent findings have followed structured behavioural evaluations (e.g. impaired learning, avoidance responses, contralateral motor neglect).

Although the specific contributions of anterior cingulate cortex to social behaviours is not known, these experimental lesion studies have served an important role for interpreting the consequences of stroke in humans. In addition, the finding of docile behaviour after bilateral cingulectomy (Smith, 1944; Ward, 1948*a*; Kennard, 1955) led several neurosurgical groups to perform this procedure in humans for disorders of aggression, agitation, psychosis, and compulsive behaviour (Whitty, 1952; LeBeau, 1954; Ballantine *et al.*, 1987). These efforts further suggested a potential use of cingulate lesions for the relief of pain (Foltz and White, 1962; Ballantine *et al.*, 1967).

Anterior cingulate cortex in the rostral limbic system

Before addressing the role of anterior cingulate cortex in human brain function, one further theoretical issue should be considered. Some investigators hesitate to use the limbic system concept because this system is difficult to define, extremely heterogeneous in terms of its structure and functions, and there is little evidence that it operates as a single entity (Brodal, 1981). MacLean (1990, 1993) has made a case for this conceptualization from an evolutionary perspective, and it has particular value for assessing structures involved in social interactions. A modified viewpoint, however, is suggested from studies of cingulate cortex that may be more readily reconciled with recent experimental observations. A dichotomy in the cingulate gyrus has been proposed (Vogt *et al.*, 1992*a*) because anterior and posterior cingulate cortices are characterized by very different cytoarchitecture, connections and functions. In contrast to the anterior cingulate cortex, the posterior region has the following characteristics: (i) a prominent layer IV; (ii) thalamic inputs from the anterodorsal, anteroventral, laterodorsal and medial pulvinar nuclei; (iii) involvement in visuospatial and memory functions; (iv) limited access to motor systems via projections to the striatum, premotor projections of area 23c, and projections to the pontine nuclei.

In view of the striking dichotomy in cingulate cortex structure and function, the cingulate cortex may be conceptualized as participating in two distinct parts of the limbic system. A rostral part engaged in executive functions including those associated with affect and a caudal part involved in visuospatial and memory functions; in other words, rostral and caudal limbic systems, respectively. In this context the rostral limbic system includes the amygdala and septum, and orbitofrontal, anterior insula, and anterior cingulate cortices, the ventral striatum including the accumbens nucleus, and several brainstem motor nuclei including the periaquaductal grey. The caudal limbic system includes the hippocampus, and posterior parietal, posterior parahippocampal, and posterior cingulate cortices, and the dorsal striatum. Area 24′ would be a transitional region in this conceptualization of two limbic systems.

All components of the rostral limbic system are not uniformly engaged during any particular behavioural function. Similarly, sensory and motor cortices are not uniformly engaged during sensory stimulation or movement, respectively. The concept of the rostral limbic system does suggest that there are structures with common connections that potentially operate in unison to produce a particular functional output. One interesting perspective on the rostral limbic system is provided in recent studies by Ketter *et al.*

(1994) in which blood flow was evaluated in individuals following intravenous administration of procaine. These injections produce emotional and psychosensory experiences that are associated with activation of anterior cingulate cortex (including areas 24 and 24′), the amygdala, orbitofrontal and anterior insular cortices. Although the mechanism of procaine's actions are not known, it is impressive that such a system can be activated simultaneously without coactivation of any parts of the caudal limbic system.

In conclusion, anterior cingulate cortex is an agranular cortical region that has extensive projections into motor systems and is involved in many executive functions including those that are associated with affect. The consequences of strokes on the medial surface and primary epileptic foci therein should be considered in the context of these connections and electrical stimulation findings. In addition, anterior cingulate cortex is part of the rostral limbic system which includes the amygdala, ventral striatum, periaquaductal grey, orbitofrontal and dorsolateral prefrontal cortices, and the anterior insula. Subdivisions of each of these areas form matrices that implement motor functions relevant to particular external events.

Structure of human anterior cingulate cortex

Surface features

Although non-human primates have a single, constant, and non-segmented cingulate sulcus, medial surface features in the human brain are extremely variable. Figure 3 shows two examples of medial surfaces and some of the variations in cingulate gyrus and sulcus morphology. The first is an example of a single cingulate sulcus that is not segmented. In this case the splenial sulcus anastomoses with the cingulate sulcus and the parascentral sulcus, which is usually a vertical branch of the cingulate sulcus, is detatched therefrom and bifurcates. In the anterior cingulate gyrus there are two horizontal dimples or shallow depressions. In the second case there is a double parallel pattern of cingulate sulci (Ono *et al.*, 1990). The cingulate sulcus is segmented into two parts, while the superior cingulate sulcus is non-segmented and anastomoses with the cingulate sulcus ventral to the genu of the corpus callosum. This pattern of sulci produces two cingulate gyri with the superior cingulate gyrus lying dorsal and rostral to the cingulate sulcus.

Distribution of areas

The cytoarchitecture and distribution of areas in human anterior cingulate cortex have been described (Vogt *et al.*, 1995). The following comments provide a summary of this work to guide the analysis of anterior cingulate cortex function and includes a cytoarchitectural map in Fig. 4 which is a schematic generalization from a number of cases. This modification of Brodmann's (1909) original work was necessitated by the high level of cytoarchitectonic and

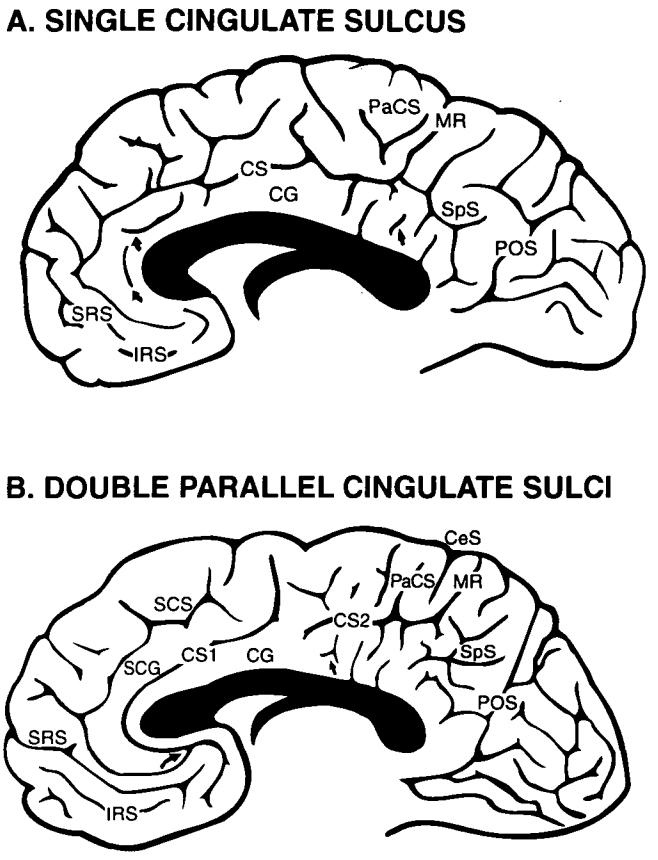

Fig. 3 Features of the medial surfaces for two human cases with different sulcal patterns. In the first case (*top*) there is a single cingulate sulcus (CS) and cingulate gyrus (CG) with horizontal cortical dimples in anterior cingulate cortex (curved arrows) and a vertical dimple in posterior cingulate cortex (straight arrow). The second case (*bottom*) with a double parallel pattern of sulci has a segmented cingulate sulcus (CS1, CS2), a superior cingulate sulcus (SCS) and a superior cingulate gyrus (SCG) between the two sulci. The CS1 anastomoses with the SCS at the curved arrow below the genu of the corpus callosum (solid black). CeS = central sulcus; IRS = inferior rostral sulcus; MR = marginal ramus of the cingulate sulcus; PaCS = paracentral sulcus; POS = parietooccipital sulcus; SpS = splenial sulcus; SRS = superior rostral sulcus.

connection details available for non-human primates. Furthermore, the numerous functional imaging studies now available identify different parts of anterior cingulate cortex as critically engaged in many human behaviours. Localization of cortical activation sites must be guided by current views of the morphology of the medial cortex. Also, investigators need a common language for functional observations.

One of the outstanding features of anterior cingulate cortex cytoarchitecture is its prominant layer V neurons; differences in layer V morphology usually characterize each area in anterior cingulate cortex. The distribution of these areas is shown in Fig. 4 where anterior cingulate cortex is outlined by the dashed line. Areas 32 and 32′ form a dorsal rim around area 24 and are included in anterior cingulate cortex, although they are referred to as cingulofrontal transition areas. They are transitional because they share features of both

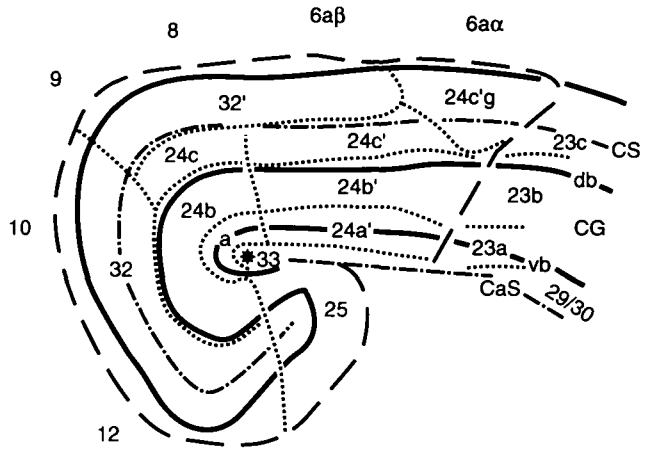

Fig. 4 Schematic overview of the distribution of areas on the human anterior cingulate cortex. The asterisk is the rostral tip of the corpus callosum which itself forms the depths of the callosal sulcus (CaS, dot–dash line). The dorsal and ventral borders of the cingulate gyrus are labelled (db and vb for CG, respectively) and the depths of the cingulate sulcus is indicated (CS, dot–dash line).

cingulate and frontal cortices. Thus, they have a prominent cingulate layer V, while also having a thin layer IV and large layer IIIc pyramidal neurons which is characteristic of some prefrontal areas. Areas 25 and 33 are the least differentiated in anterior cingulate cortex with only external and internal pyramidal layers and a hint of large neurons in layer Va. The a, b and c divisions of areas 24 and 24′ are progressive differentiations not originally reported by Brodmann. As a rule, cortex adjacent to the corpus callosum is poorly differentiated, although a layer Va is clear as is the distinction between layers II and III. Dorsal areas have a more prominent layer II/III border. Area 24b includes the magnocellular anterogenual field of Braak (1979). This area has the broadest and most dense layer V in the cingulate gyrus. Differences between rostral area 24 and caudal area 24′ include one of neuron density in that area 24 has a generally higher neuron density than does area 24′. In addition, layers III and Va are thinner in area 24′ than in area 24. Finally, cortex in the depths of the cingulate sulcus undergoes a rostrocaudal differentiation: (i) area 24c has the thickest layer Va; (ii) area 24c′ has a sparse layer III and layer Vb has many medium-sized neurons; (iii) area 24c′g has many medium-sized pyramidal neurons in layer Va and the largest pyramids in the cingulate gyrus in layer Vb. Area 24c′g is simlar to Braak's (1976) primitive gigantopyramidal field, it abuts area 32′ at its rostral border, and it likely has spinal projection neurons.

Although the resolution of most PET scanners is 7–10 mm, it is possible, in some instances, to relate activation sites to the cingulate gyral surface and the depths of the cingulate sulcus. This distinction is extremely important because it is in the depths of the cingulate sulcus where the cingulate motor areas with their spinal projection neurons are located. In addition, the dichotomy within anterior cingulate cortex of cognitive and affective regions is probably best made with a line drawn just caudal to the border of area 32 and including most of area 24, area 25 and much of area 33. While area 24′ may be related to some affective processes, most evidence suggests that its role in affect is secondary to its role in cognitive processes, such as response selection, that do not require affect.

Contributions to human behaviour

Executive functions

Neglect follows anterior cingulate cortex lesions in primates and this is one reason that anterior cingulate cortex is considered part of a matrix of cortical areas involved in attention. Thus, unilateral motor neglect followed unilateral anterior cingulate cortex lesions in monkeys (Watson *et al.*, 1973), and hypokinesia and hypometria arose contralateral to a right anterior cingulate cortex and supplementary motor area lesion in one patient (Meador *et al.*, 1986). Hypokinesia improved when the affected left upper extremity was placed into the right hemispace suggesting hemispatial motor neglect. Sensory neglect also occurs after anterior cingulate cortex lesions. A woman with a right anterior cingulate cavitary lesion developed depression, anosognosia for a left hemiparesis, visual and somatesthetic neglect, and contralateral hemibody neglect (Heilman and Valenstein, 1972). In another case, a severe attentional deficit arose with bilateral anterior cerebral artery infarcts in the anterior cingulate gyri, the fornices and small areas of adjacent prefrontal cortex (Laplane *et al.*, 1981). Although these case studies suggest a role for anterior cingulate cortex in attention, functional imaging with PET has shown that anterior cingulate cortex is not engaged in all attentional processes. For example, although the left dorsolateral prefrontal cortex is activated when reading words and during semantic processing, anterior cingulate cortex is silent (Petersen *et al.*, 1990). Thus, specific roles for anterior cingulate cortex beyond that of general attention must be considered.

The anterior cingulate cortex has a role in premotor function and some cognitively demanding processes and is often engaged in responses associated with affect. The anterior cingulate cortex is involved in direct control of skeletal and visceromotor systems, response selection, cognitively demanding processing not necessarily requiring movement, and possibly retrieval from short-term memory. The common features of each of these anterior cingulate cortex functions is that they occur well before a movement occurs. Although anterior cingulate cortex in the depths of the cingulate sulcus has the architecture, connections, and neuronal discharge patterns characteristic of premotor areas (Dum and Strick, 1993), there are events which must precede motor activity beyond determining the pattern of muscle contractions to attain a goal. Cognitive processes to determine whether or not a movement is needed and the correct response pattern probably involve early premotor processing and this is one of the primary contributions of anterior cingulate cortex to

human behaviour. The following discussion is organized according to the topography of functional regions in anterior cingulate cortex beginning with visceromotor control and affect.

Visceromotor control and vocalization

Autonomic activity is a frequent correlate of affective behaviour, and visceromotor changes are the most consistent responses evoked by electrical stimulation of rostral area 24 and area 25. Both increases and decreases in respiratory and cardiac rate and blood pressure, mydriasis, piloerection, and facial flushing can occur (Pool and Ransohoff, 1949; Pool, 1954; Escobedo *et al.*, 1973; Talairach *et al.*, 1973). Visceral responses include nausea, vomiting, epigastric sensation, salivation, or bowel or bladder evacuation (Pool and Ransohoff, 1949; Lewin and Whitty, 1960; Meyer *et al.*, 1973). Respiratory arrest occurs with cingulate stimulation, although patients can breath to command (Penfield and Jasper, 1954; Escobedo *et al.*, 1973; Meyer *et al.*, 1973). This contrasts with the non-volitional inhibition of motor responses evoked by primary motor cortex stimulation, and supports the role of anterior cingulate cortex in motor acts that can be modulated volitionally through other neural systems.

The anterior cingulate cortex in the perigenual region of non-human primates is involved in vocalizations associated with the expression of internal states and in some conditioning paradigms (*see* above). Although mutism can result from large lesions in human anterior cingulate cortex and adjacent areas, as discussed below, human vocalization is rarely altered by anterior cingulate cortex electrical stimulation. Involuntary vocalization or speech arrest is rarely if ever produced in humans with electrical stimulation, but it is more common with cingulate seizures (Whitty *et al.*, 1952; Pool, 1954; Talairach *et al.*, 1973; Van Buren and Fedio, 1976). Momentary arrest of speech or respiration also occurs in isolated stimulation cases (Lewin and Whitty, 1960). In contrast to other studies, Meyer and colleagues (1973) commonly observed alterations in speech with cingulate stimulation: dysphasia, perseveration, and change in rate or volume. It still is not known whether anterior cingulate cortex is engaged during highly emotional expressions such as 'AAAH' or 'EEEK' that are very short-latency, non-linguistic expressions of fright or other emotional states.

Cingulate dysfunction in stuttering supports a contribution of anterior cingulate cortex to verbal expression. Pool *et al.* (1991) studied xenon-133 single photon emission computed tomography (SPECT) in 20 children with stuttering and in age-matched control cases. They found reduced blood flow in the left perigenual part of anterior cingulate cortex and in the superior and middle temporal gyri in the stutterers. With only one exception, all severe stutterers had decreased blood flow in the anterior cingulate cortex. Furthermore, although blood flow in anterior cingulate cortex is elevated during processing of words (Petersen *et al.*, 1988; Grossman *et al.*, 1992) suggesting a role in word and sentence selection, this is part of a general role of anterior cingulate cortex in response selection (*see* below), not a specific language function nor necessarily a contribution to the interpretation of the emotional significance of words *per se*. Each of these observations on human anterior cingulate cortex and its contributions to language suggest that area 24′ is engaged in word and sentence selection as part of a broader response selection function and that perigenual cortex is involved in vocalization, although the evidence that it is engaged in the expression of emotionally charged vocalizations in humans, as in non-human primates, is not yet available.

Affect

Emotion is mediated, at least in part, by anterior cingulate cortex as indicated by electrical stimulation and spontaneous seizures in humans and in some individuals with either spontaneous or neurosurgically induced cingulate lesions. Emotional responses may follow electrical stimulation of anterior cingulate cortex including fear, pleasure and agitation (Meyer *et al.*, 1973). Electrical stimulation of different parts of anterior cingulate cortex evokes different types of emotions (Bancaud and Talairach, 1992). Stimulation of part of area 24′ in an epilepsy patient evoked the report, 'I felt something, as though I were going to leave,' while stimulation of perigenual area 24 produced this response, 'I was afraid and my heart started to beat.' This supports the very important dissociation between the role of area 24′ in avoidance behaviours and that of area 24 in affect.

Euphoria and a sense of well-being have been reported (Laitinen and Vilkki, 1973; Talairach *et al.*, 1973), while some investigators could not elicit emotional responses with electrical stimulation (Lewin and Whitty, 1960; Escobedo *et al.*, 1973; Van Buren and Fedio, 1976). Affective responses during stimulation of other brain regions also are uncommon. For example, only 1% of mesial temporal lobe stimuli elicit affective responses (Halgren *et al.*, 1978). Among patients with cingulate seizure foci (*see* below), emotional changes are common during ictal (e.g. laughing, crying) and interictal (e.g. irritability, sexual deviancy, emotional lability) periods.

Cingulate tumors and other lesions in humans can cause a variety of affective changes, including apathy, disinhibition, placidity, depression, aggressiveness, lack of social restraint, anxiety, obsessive–compulsive behaviours, heightened sexuality, and bulimia (Ironside and Guttmacher, 1929; Frazier, 1936; Jarvie, 1954; Malamud, 1967; Faris, 1969; Poeck, 1969; Gautier-Smith, 1970; Angelini *et al.*, 1981; Levin and Duchowny, 1991). Further, cingulectomy and cingulumotomy can successfully treat patients with psychosis and pathological aggression, obsessive–compulsive behaviours, and depression (Whitty *et al.*, 1952; Lewin, 1961; Ballantine *et al.*, 1967; Brown and Lighthill, 1968; Ledesma and Paniagua, 1969; Mazars, 1970). Ballantine *et al.* (1967) found that cingulumotomy improved behaviour in the majority of a combined series of 150 patients with various

neuropsychiatric disorders in which 'disordered affect' was a dominant feature.

A PET study of healthy women showed that transient sadness or happiness are associated with elevated blood flow in anterior cingulate cortex (George *et al.*, 1994*b*). The most active site appears to be a region including area 25. Furthermore, activity in the cingulate during happiness is inversely related with blood flow in the amygdala, while sadness is proportionately related to elevated blood flow in the amygdala. Evidence for the involvement of area 24 in recognizing the emotional content in facial expressions derives from a PET study by George and colleagues (1993) and emphasizes its role in emotion. In this study blood flow in area 24 was elevated with photographs of facial expressions with emotional content. Thus, electrical stimulation and PET studies confirm the involvement of areas 24 and 25 in affect, while area 24′ has little direct involvement in such functions. In addition, reciprocal connections between areas 24/25 and the amygdala are probably engaged during internal states associated with emotion.

Movement execution

Cortex in the depths of the cingulate sulcus regulates skeletomotor activity and shares many features classically associated with premotor areas. Electrical stimulation studies of human anterior cingulate cortex provide other important clues to its motor functions. Stimulation has been undertaken before cingulectomy for psychiatric and, less often, seizure disorders. Methodological differences in terms of electrode placement and stimulus intensity and waveform characteristics probably account for most of the variability in the reported series. Electrical stimulation of anterior cingulate cortex elicits a spectrum of behavioural changes including autonomic and affective, involuntary vocalization, speech arrest and automatic behaviours. Primitive gestures include touching, kneading, rubbing, or pressing fingers or hands together, and lip puckering or sucking (Escobedo *et al.*, 1973; Meyer *et al.*, 1973; Talairach *et al.*, 1973). These movements are often adapted to the environment; they can be modified with sensory stimuli and, at times, resisted. Hand movements can be bilateral or contralateral to the stimulated side. Other studies have reported restlessness, complex movements mainly of the contralateral leg (Escobedo *et al.*, 1973), pedalling movements (Bancaud *et al.*, 1976), rubbing of the face, lip-smacking, and picking at bedclothes (Meyer *et al.*, 1973). These latter automatisms are common with temporal lobe (Theodore *et al.*, 1983) and orbitofrontal (Swartz, 1994) complex partial seizures, and, interestingly, as post-cingulectomy 'tics' (Whitty *et al.*, 1952).

Since the supplementary motor area mediates the preparation and initiation of movement (Deecke and Kornhuber, 1978; Orgogozo and Larsen, 1979; Roland *et al.*, 1980; Verfaellie and Heilman, 1987), it may operate in conjunction with or even be activated by the CMAs (Goldberg, 1985). Schlaug *et al.* (1994) used PET to show that during sequential thumb–finger apposition movements two divisions of the supplementary motor area were activated as well as part of anterior cingulate cortex. It is possible in this latter study that there was activation of one of the CMAs. Thus, the connections between anterior cingulate cortex and supplementary motor area may be particularly important including those between area 24c′ in the depths of the cingulate sulcus and the supplementary motor area (Morecraft and Van Hoesen, 1992; Bates and Goldman-Rakic, 1993). Interruption of connections between these areas by medial frontal lesions may contribute to motor neglect and other impairments of sensorimotor and early premotor processing.

Response selection and cognition

The anterior cingulate cortex is engaged in early premotor events that require cognitive information processing and response selection where a movement may be needed. Blood flow in anterior cingulate cortex increases during semantic processing of single words or letters (Petersen *et al.*, 1988; Frith *et al.*, 1991*a*; Grossman *et al.*, 1992), target detection tasks (Posner *et al.*, 1988; Posner and Peterson, 1990), and the Stroop interference task (Pardo *et al.*, 1990). The contribution of anterior cingulate cortex to this latter task is particularly important, since behavioural performance is related to blood flow in anterior cingulate cortex (George *et al.*, 1994*a*). Frith *et al.* (1991*b*) compared blood flow during routine and willed acts. Routine acts included repeating words or responding with the previously rehearsed opposite word (e.g. hot–cold). Willed acts required an open-ended response and thus a deliberate choice. Willed acts in two response modes (verbal and lifting a finger) were associated with increased blood flow in the dorsolateral prefrontal cortex and, less prominently, in the anterior cingulate cortex. The Stroop test responses are entirely determined by the stimulus, as opposed to willed responses. Since anterior cingulate cortex but not dorsolateral prefrontal cortex cerebral blood flow is increased during the Stroop, Frith *et al.* (1991*b*) argue that dorsolateral prefrontal cortex is essential for willed acts. However, the significant increase in anterior cingulate cortex blood flow with willed acts suggests that anterior cingulate cortex also contributes to willed actions.

The contributions of anterior cingulate cortex to response selection has been refined in a number of recent PET studies. Raichle *et al.* (1994) showed that the region activated in left anterior cingulate cortex by a verb generation to a novel list of nouns was mainly in area 32′. When the list of nouns was re-used a number of times, the response habituated, while the anterior cingulate cortex response returned with a novel list of nouns. In addition, the left dorsolateral prefrontal and cerebellar cortices were activated, while the anterior insula had reduced blood flow. Petit *et al.* (1993) showed that cortex in the depths of the cingulate sulcus and the midcingulate gyral surface (i.e. area 24′) is involved in response selections associated with saccadic eye movements. Subjects performing self-paced voluntary horizontal saccadic eye movements at

maximal amplitude activated this region. The elevation of anterior cingulate cortex blood flow included areas 24c′ and 23c and was higher than any other cortical area including the supplementary motor area. The anterior cingulate cortex is not engaged directly in eye movement generation *per se* because it does not have brainstem projections like the frontal eye fields and cingulate neuronal responses associated with saccadic and quick-phase eye movements occur after not before the movement (Sikes *et al.*, 1988; Olson *et al.*, 1993). Also, the frontal eye fields do not project to cingulate cortex (Stanton *et al.*, 1993). This common misconception is fostered by anatomical studies in which authors do not carefully identify the rostral limits of the frontal eye fields. Thus, anterior cingulate cortex is involved in response selection when any of a wide range of novel choices are required, but not during practiced responses.

The contributions of anterior cingulate cortex to response selection and attention to action is supported by a study of patients with primary depression (Bench *et al.*, 1992). In these patients, blood flow was decreased in anterior cingulate cortex. This altered blood flow pattern was not associated with depression-related cognitive impairment, but, rather, depressed mood. Therefore, functional disruption of anterior cingulate cortex in depression may contribute to impaired initiation and organization of behaviour.

The response selection functions discussed so far may be part of a broader contribution of anterior cingulate cortex to cognitively demanding information processing. In visual discrimination tasks requiring divided attention for two features of a stimulus (Corbetta *et al.*, 1991), maximal activation occurs near the gyral surface of anterior cingulate cortex (i.e. areas 24a′ and 24b′). Blood flow in a region that appears to be in area 24b was not significantly altered in the same divided attention task. In less challenging auditory discriminations involving little decision making and simple movements, there was a reduction of blood flow in anterior cingulate cortex (Cohen *et al.*, 1988). Thus, when suspending movement while waiting for low probability signals, reduced activity in anterior cingulate cortex may enhance detection of an external signal (Posner and Petersen, 1990).

When considering the topography of activation sites in PET studies, it is difficult to assess the extent to which areas 24′ and 32′ contribute to similar or different functions. Tasks requiring target assessment and attention for linguistic and other features of the sensory environment may engage area 32′, while cognitively demanding tasks that may or may not require a movement may engage area 24′.

Responses to pain

Foltz and White (1962) found that anxious patients who 'augmented' their pain were most likely to benefit from cingulumotomy. Patients with chronic pain disorders treated successfully with cingulumotomy report that they may continue to 'feel the pain' but it does not bother them or trigger any adverse emotional reaction. 'The perception of pain as such does not appear to be modified, but the patient's total reaction to pain and the threat to existence that it represents is modified markedly. Most of the patients stated that they continued to have pain but it was 'not particularly bothersome,' 'doesn't worry me . . .' (Foltz and White, 1962). Following cingulumotomy, patients with chronic pain could often be withdrawn from narcotic analgesics with minimal or no signs of withdrawal (Foltz and White, 1962).

Extensive neuropsychological and psychiatric evaluations have been performed on patients before and after cingulumotomy. Overall, IQ usually increases slightly or shows no change (Meyer *et al.*, 1973; US Department of Health, Education and Welfare, 1977; Corkin *et al.*, 1979; Ballantine *et al.*, 1987). The mechanism for increased IQ scores post-cingulumotomy is unknown, but most likely results from diminished anxiety, depression and obsessive thoughts, which leads to improved motivation and concentration. Also, cognitive performance may improve when medications are lowered after surgery. Wilson and Chang (1974) observed neurological sequelae that quickly resolved, including bladder and bowel incontinence, confusion, uninhibited facetious speech, diminished attention span, hallucinations and automatisms. Flattened affect was common (57%) and often persisted at the time of hospital discharge.

There has long been a question as to whether post-cingulumotomy observations of altered responses to noxious stimuli were due to disruption of cingulate cortex itself or to disruption of axons of passage underlying cingulate cortex. A direct role of anterior cingulate cortex in processing nociceptive information has been provided by three PET studies. These studies show that anterior cingulate cortex is activated during the application of acute, noxious-heat stimuli to the body surface (Jones *et al.*, 1991*a*; Talbot *et al.*, 1991; Casey *et al.*, 1994).

Functional imaging studies suggest that cingulate and prefrontal cortices may respond together during responses to noxious stimuli in chronic pain syndromes. Administration of morphine to an individual suffering from chronic pain following removal of a squamous carcinoma in the left jaw elevated blood flow in anterior cingulate cortex as well as in prefrontal and insular cortices (Jones *et al.*, 1991*b*). The joint activation of these cortices may be the product of shared expression of opioid receptors or reflect reorganization of common inputs from brainstem nociceptive nuclei such as the midline thalamic nuclei. Cingulate cortex may interact directly with prefrontal cortex as suggested in cases of atypical facial pain. When noxious thermal stimuli are applied to the skin of these patients, blood flow is elevated in anterior cingulate cortex and reduced in prefrontal cortex (Derbyshire *et al.*, 1994). There are strong and reciprocal connections between dorsal, middle and inferior prefrontal cortices and anterior cingulate cortex (Pandya *et al.*, 1981; Vogt and Pandya, 1987; Barbas and Pandya, 1989). Although there are several possibilities to account for the differential regulation of responses to noxious stimuli in these areas, a

likely one is that anterior cingulate cortex inhibits activity in prefrontal cortex during noxious stimulation.

The specific role of anterior cingulate cortex in pain is not yet known. The options include generating an affective component, organizing motor responses, or memory associated with predicting and avoiding such stimuli without actually allowing them to be presented to the body surface. The general lack of evidence for emotional activity and memory associated with area 24′ function may indicate that the role of anterior cingulate cortex in pain is response selection processes. Nonetheless, after 100 years of clinical and experimental observations, it appears that the first conclusions of Horsely and Schäfer (1888) were correct. Lesions of anterior cingulate cortex reduce pain sensitivity and are not the result of collateral damage to other structures. Strategies for relieving pain, whether surgical or pharmacological, can now legitimately focus on anterior cingulate cortex as one of the likely areas that organizes responses to noxious stimuli and may be involved in chronic pain syndromes.

Short-term declarative memory

Animal studies of Gabriel and his colleagues (Gabriel, 1993) suggest that anterior cingulate cortex is involved in the early stages of discriminative avoidance learning, while posterior cingulate cortex is involved in long-term performance of acquired tasks. A human case with a small infarct in posterior cingulate cortex (Valenstein *et al.*, 1987) had a profound disruption of both anterograde and retrograde memory. Limited information using functional imaging supports the contributions of anterior cingulate cortex to learning and memory. Raichle *et al.* (1994) showed that verb selection in response to repeated presentations of a list of nouns reduced anterior cingulate cortex blood flow (i.e. over time the response habituates). For well-learned lists the response disappears and use of a novel list of nouns increases blood flow in anterior cingulate cortex. Grasby *et al.* (1993) showed that perigenual parts of anterior cingulate cortex have elevated blood flow during auditory–verbal memory by subtracting blood flow during a subspan memory task from that for a supraspan memory task. Interestingly, a part of posterior cingulate cortex including areas 31, 23, 29 and 30 were also activated in the supraspan task. In a [^{5}F]fluorodeoxyglucose PET (FDG-PET) study of 11 amnestic patients, Fazio *et al.* (1992) found bilateral metabolic reductions in the hippocampal formation, thalamus, cingulate gyri and frontal basal cortex. This supports a role of anterior cingulate cortex in a memory network.

Events related to early processing of stimuli and preparation for motor responses appear to be registered in anterior cingulate cortex, however, they are not retained for long periods of time. During short-term verbal memory tasks there is joint activation of perigenual and perisplenial cingulate cortices (Grasby *et al.*, 1993). Since these regions are reciprocally connected (Vogt and Pandya, 1987; Van Hoesen *et al.*, 1993), it is possible that, when long-term memories are needed, they are stored in posterior cingulate cortex and are accessed in anterior cingulate cortex via these reciprocal connections. Notice also that the midlevels of cingulate cortex, including areas 24′ and rostral parts of area 23, are not connected directly to the perigenual and perisplenial cortices (Vogt and Pandya, 1987); thus there may be an uncoupling of response selection processes from this part of the medial memory circuits.

Social interactions

Structural or functional changes in anterior cingulate cortex can cause prominent changes in social behaviour. Patients with cingulate lesions or epilepsy can develop blunted affect, apathy, impulsivity, disinhibition, aggressive behaviour with minimal or no provocation, psychosis, sexually deviant behaviour, disabling obsessions and compulsions, and impaired social judgement (Ironside and Guttmacher, 1929; Vonderahe, 1943; Ward, 1948*b*; Jarvie, 1954; Ledesma and Paniagua, 1969; Mazars, 1970; Damasio and Van Hoesen, 1983; Levin and Duchowny, 1991). These behaviours can seriously impair social success. In some cases, patients have been diagnosed with 'sociopathic personality disorder,' been institutionalized or prosecuted for criminal actions (Mazars, 1970; Bancaud and Talairach, 1992). Following elective bilateral cingulectomy for psychiatric disorders, there may be impaired personal and social judgment (Tow and Whitty, 1953).

Following bilateral anterior cingulate cortex and orbitofrontal damage after tumour resection, a previously successful accountant was unable to maintain his job, marriage and finances despite preserved 'intelligence and memory' (Eslinger and Damasio, 1985). His problems appeared largely due to a lack of judgement and common sense. Thus, the social consequences of combined anterior cingulate cortex and orbitofrontal cortex damage can be devastating. This man, despite normal intelligence and memory, failed 'in real life'. His ability to interpret social cues and adapt to social situations was severely impaired. Although he could recall normal patterns of social behaviour when questioned about them in a hypothetical setting, he could not execute correct actions in real life situations. Many of his disastrous actions were labelled as 'sociopathic'. When his skin conductance was measured during exposure to emotional visual images of mutilation, nudity and social disaster, there was virtually no response (Damasio *et al.*, 1990). Thus, there was a disconnection between the intellectual understanding of the images and the autonomic expression with anterior cingulate cortex and orbitofrontal lesions. The lack of physiological emotional cues may contribute to this patient's failure to appreciate the emotional significance of stimuli. Notably, sociopathic individuals often had blunted autonomic responses to emotional stimuli (Hare, 1978). The frontal lesion might lead to failure to develop the emotion that leads to the autonomic changes, or the frontal lesion may prevent

the autonomic changes that signal emotion to other central sites. In either case, the cingulate and orbitofrontal cortex are important in linking emotional stimuli and autonomic changes to emotional stimuli, and the behavioural changes that follow such stimuli.

The difficulties quantifying and categorizing social behavioural changes in humans after cingulate lesions are apparent from the subtle behavioural changes observed by Tow and Whitty (1953). Two patients who read extensively in good literature before surgery subsequently read only sporadically and only 'poorer light magazines' and 'much less worth-while books.' One patient gave up carpentry, gardening and reading entirely. Both he and another patient lost all interest in sports and stopped attending soccer matches. Although difficult to measure, these are significant behavioural changes that relate to individual and social situations.

Anterior cingulate syndromes

Cingulate cortex seizures

Studies of anterior cingulate cortex seizures provide one of the most convincing bodies of evidence for the role of anterior cingulate cortex in motor function and affective behaviour. Cingulate cortex seizures can alter the level of attention or consciousness, voluntary and involuntary skeletomotor activity, affective expression, and autonomic activity. Cingulate seizures pose a challenge for epileptology, since surface recordings with scalp electrodes cannot detect ictal onsets in anterior cingulate cortex and invasive depth or subdural electrodes provide limited sampling (Quesney, 1986, 1992). Further, surface or invasive electrode recordings may reflect rapid contralateral or ipsilateral spread of seizure activity and fail to identify the true ictal onset (Saint-Hilaire, 1988; Quesney *et al.*, 1992). Cingulate seizures may be misdiagnosed as a generalized seizure when the EEG reveals a generalized spike-and-slow wave discharge accompanied by staring with impaired responsiveness (absence seizure), head nod (atonic seizure) or convulsive movements (tonic-clonic seizure) (Tükel and Jasper, 1952; Ralston, 1961; Mazars, 1970; Talairach *et al.*, 1973; Levin and Duchwony, 1991). Despite the limitations and confusion associated with cingulate epilepsy, the pleomorphic features of anterior cingulate cortex seizures have been defined and can be used to characterize a cingulate epilepsy syndrome.

Clinical features

Seizures can begin at any age, but usually occur between the ages of 3 and 30 years (Mazars, 1970; Stoffels *et al.*, 1981; Levin and Duchowny, 1991). Available data suggest that manifestations of cingulate seizures may partly reflect the patient's age. Young children are more likely to stare and have mild atonia (e.g. head nod), while older children and adults are more likely to have complex behavioural features (e.g. vocalizations and automatisms). Cingulate seizures tend to be frequent, brief, stereotyped, nocturnal, and lack a significant preictal or postictal phase. The clinical features of cingulate seizures may be divided as follows:

(i) Aura. Auras are often absent or are reported as nonspecific or autonomic symptoms. Dizziness, warmth, abdominal sensation, pallor, tachycardia, mydriasis, fear, feeling of suffocation, urge to void, forced urination, or apnea which can be voluntarily overcome have been reported (Penfield and Jasper, 1954; Talairach *et al.*, 1973; Geier *et al.*, 1975, 1977; Bancaud and Talairach, 1992).

(ii) Altered level of attention and consciousness. There may be an arrest of motor and verbal activity, staring which can mimic absence seizures but may be associated with a very brief postictal period (in contrast to absence seizures) and diminished or absent responsiveness (Mazars, 1970; Talairach *et al.*, 1973; Stoffels *et al.*, 1980, 1981; Levin and Duchowny, 1991). Although consciousness may be altered, patients may maintain contact with the environment and integrate stimuli into motor automatisms (*see* below, Bancaud and Talairach, 1992).

(iii) Tonic or clonic movements. Contralateral or bilateral tonic or clonic movements can occur in the extremities. Head deviation is usually contralateral to the ictal focus and may be accompanied by elevation of the contralateral arm suggesting spread to the ipsilateral cingulate motor areas and supplementary motor area (Mazars, 1970; Talairach *et al.*, 1973; Geier *et al.*, 1975, 1977; Bancaud *et al.*, 1976).

(iv) Sudden loss of muscle tone. Sudden loss of muscle tone has been reported, e.g. head nods (Mazars, 1970; Levin and Duchowny, 1991).

(v) Automatisms. Automatisms are often more complex and occur earlier than those during temporal lobe seizures. They may involve muscular activity of the following types: oral-alimentary (lipsmacking), facial (expression of fear, grimace, contortion, 'haggard eyes'), appendicular (touching hair or cloths, waving or hitting movements), truncal (turning the body, assuming the foetal position) or vocal (e.g. humming, unintelligible sounds, onomatopoieas, screaming, curses, brief phrases such as 'Oh my God,' laughing, crying, or moaning), or tongue (protrusion) (Escobedo *et al.*, 1973; Talairach *et al.*, 1973; Geier *et al.*, 1977; Stoffels *et al.*, 1980, 1981; Quesney, 1986; Sammaritano *et al.*, 1993). In contrast to gestural automatisms in patients with temporal lobe epilepsy, several groups reported that some patients with automatisms during cingulate seizures can voluntarily inhibit or modify the motor behaviour to blend with ongoing activity (Talairach *et al.*, 1973; Geier *et al.*, 1977). In some cases, ictal or possibly postictal automatisms with aggressive

behaviours led to psychiatric hospitalization or imprisonment (Bancaud and Talairach, 1992).

Electrographic features

Interictal surface recordings may reveal normal background or diffuse or predominently frontal slowing. Bilateral isolated bursts of 1–4 Hz or slightly unilateral predominent spike-and-slow wave activity may be maximal over parasaggital, precentral or prefrontal regions. Interictal depth electrode recordings reveal similar epileptiform discharges which may arise symmetrically in both cingulate cortices spreading initially to the frontal convexities. Such spike-and-slow wave activity often leads on the side of clinical onset by ~60 ms (Mazars, 1970).

Ictal surface recordings reveal bilateral, symmetric, hypersynchronous, fast activity clinically associated with impaired consciousness, staring, speech arrest or head drop. Ictal depth recordings reveal background attenuation and low amplitude fast activity. Onset in anterior cingulate cortex was followed by nearly instantaneous bilateral spread. Onset in posterior cingulate cortex was followed several seconds later by contralateral spread and more often progressed to a tonic-clonic seizure (Mazars, 1970). These differences between anterior and posterior cingulate cortices awaits confirmation.

Interictal behavioural changes

Among the series of patients with cingulate epilepsy, marked interictal behavioural abnormalities have been reported. In Mazars' (1970) report of 36 patients, the majority suffered from fixed or intermittent psychoses or episodic outbursts. The psychoses were clinically different from the ones accompanying temporal lobe epilepsy. Mazars noted that psychotic patients with cingulate epilepsy lacked the hypomania and logorrhea seen with the psychoses of temporal lobe epilepsy but had more paroxysmal aggressive outbursts and greater unsociability. Interestingly, such behaviours were often improved after bilateral cingulectomy. Ledesma and Paniagua (1969) also observed similar aggressive behaviours in epilepsy patients and improved aggression and epilepsy after bilateral cingulectomy.

One of the best documented and most fascinating cases of cingulate epilepsy was reported by Levin and Duchowny (1991). This 11-year-old girl had medically refractory seizures since the age of 2.5 years. Initially, her seizures were atonic, but later she developed complex partial seizures with impaired consciousness, eye blinking, and oroalimentary (e.g. lip smacking), vocal (e.g. humming), and gestural (e.g. hair fixing) automatisms. At the age of 3 years she developed obsessive features and by the age of 8 years she had pathological obsessive and compulsive symptoms. She was preoccupied with Satan and feared punishment for imagined and real behaviours, and she spent long periods at hand-washing, toothbrushing and showers. Her CT and MRI studies were normal. Scalp video-EEG recordings showed partial seizures arising from the right frontal region. Depth electrode recordings documented seizure onset from the right anterior cingulate cortex with secondary generalization of the 3–3.5 Hz spike-wave activity. Surgical destruction of 4 cm of right anterior cingulate cortex eliminated seizures and markedly reduced obsessive–compulsive behaviours during the first 15 post-operative months. Two additional cases, not previously reported, provide further insight into the features of seizures that originate in anterior cingulate cortex. Of note, both patients were followed by psychiatrists for many years with the diagnosis of non-epileptic psychogenic seizures.

Epilepsy Case 1

A 43-year-old man had a 15-year history of medically intractable complex partial seizures. Seizures initially occurred 3–20 times a week but increased to 10–20 seizures a day on presentation. The seizures were stereotyped, characterized by laughter, repetitions of the phrase 'Oh my God,' small repetitive neck and trunk flexion, and bilateral arm extension followed by repeated touching of the forehead and mouth. The duration of the seizures never exceeded 10 s and there was no pre- or post-ictal behavioural alterations. The patient was amnestic for the seizures. There were no risk factors for epilepsy. Because of the seizures, the patient lost a job of many years. He became more reclusive and returned to his parents' home.

Ictal recording with scalp and sphenoidal electrodes revealed rhythmic bifrontal theta. An FDG-PET scan was normal. A brain MRI revealed mild and diffuse cortical atrophy. An ictal SPECT scan showed increased blood flow to the right mesial frontal lobe. Depth electrodes were implanted in right and left orbitofrontal cortex with the long axis parallel to the gyrus rectus, ending anterior to the corpus callosum. Subdural strip electrodes were placed in the following locations: four along the right interhemispheric fissure and one along the left, with the distal contacts of two of the right interhemispheric strips and the left interhemispheric strip corresponding to anterior cingulate cortex; lateral frontal to orbitofrontal strips were placed bilaterally. Seizures arose as low amplitude fast activity consistently from electrodes recording from the right anterior cingulate cortex spreading within 250–500 ms to the left cingulate and right orbitofrontal cortices. The patient underwent a resection of the right anterior cingulum. Pathology revealed a low grade glioma. The patient's seizures have resolved over the first year of follow-up. He is living independently and has entered into a romantic relationship. He remains unemployed.

Epilepsy Case 2

A 42-year-old man had medically intractable complex partial seizures and sociopathic behaviour over 15 years beginning 1 year after a motorcycle accident associated with mild head trauma. Seizures were primarily nocturnal and as frequent as 10–20 a night, each lasting <1 min. Stereotyped behaviours

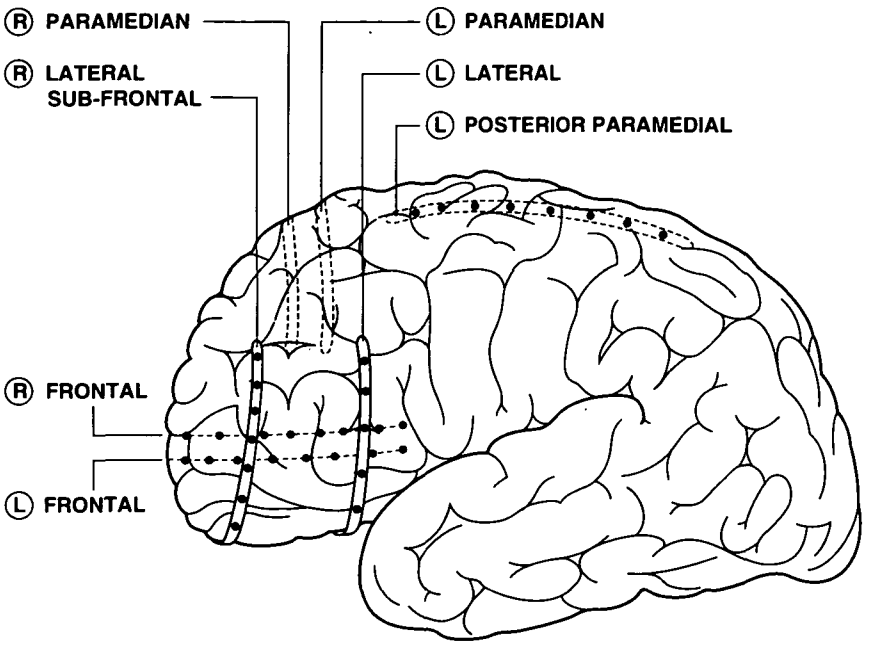

Fig. 5 Location of the intracranial electrodes in Seizure Case 2. Left and right frontal electrodes are depth electrodes; other electrodes are subdural strips.

included grotesque facial contortions, tongue thrusting, a strangulated yell, neck and trunk flexion, bilateral arm and leg extension with side-to-side thrashing and occasional progression to a generalized tonic-clonic seizure. There was no pre- or post-ictal phenomenon. Consciousness was preserved unless the seizure was secondary generalized. Behavioural abnormalities included excessive irritability, poor impulse control, and sexual preoccupation and deviancy. For example, he propositioned women medical staff and attempted to lick a nurse's face. He had been dismissed from the police force because of brutality, and then from the Drug Enforcement Agency because of brutality and use of confiscated drugs and was unemployed at the time of presentation. He was a black belt in karate and would strike out at anyone who attempted to restrain him during or after a seizure.

Ictal scalp and sphenoidal EEG showed rhythmic bifrontal theta. An FDG-PET scan was normal. A brain MRI showed a left parietal cryptic arteriovenous malformation. As shown in Fig. 5, intracranial electrodes were implanted including bilateral orbitofrontal depth electrodes with the long axis parallel to the gyrus rectus, ending anterior to the corpus callosum; two subdural electrodes in the right interhemispheric fissure and two in the left, with distal contacts corresponding to anterior cingulate cortex; and bilateral lateral-frontal to orbitofrontal subdural strip electrodes. A subdural strip was also placed adjacent to the cryptic arterovenous malformation. All seizures arose from the right cingulate gyrus, as shown in Fig. 6. Spread to contralateral anterior cingulate cortex and to ipsilateral orbitofrontal cortex occurred within 300 ms. He underwent resection of the right cingulate gyrus and an anterior corpus callosotomy. He has experienced more than a 90% reduction in seizures. The residual seizures are characterized only by brief axial flexion. Family members also describe behavioural improvement with diminished irritability and better social conduct. He is now employed as a manager at a fast-food restaurant and has married his girlfriend of many years, assuming the care of her three children.

Cingulate epilepsy syndrome

Although recognition remains elusive and documentation challenging, these patients express a spectrum of features associated with anterior cingulate cortex seizures. The extensive sampling of frontal cortex allowed onset to be precisely localized to the anterior cingulate cortex. The variability in ictal behaviours probably reflects different spread patterns. These seizures often include changes in level of attention or consciousness, activity in autonomic and skeletomotor systems, automatisms which occur early in the seizure and may be suppressed or modified voluntarily. Cingulate seizures are often frequent, under 45 s in duration, stereotypic, and include prominent affective vocalization, axial flexion, appendicular extension, facial contortion, and gestural automatisms. In some seizures, consciousness is maintained despite bilateral motor involvement. Patients with cingulate seizures may be diagnosed with psychogenic seizures. A non-epileptic diagnosis may be prompted by the significant behavioural abnormalities exhibited interictally and because of subtle or no alteration in the pre- and postictal states.

In many patients, even those with only neuronal loss documented pathologically in anterior cingulate cortex,

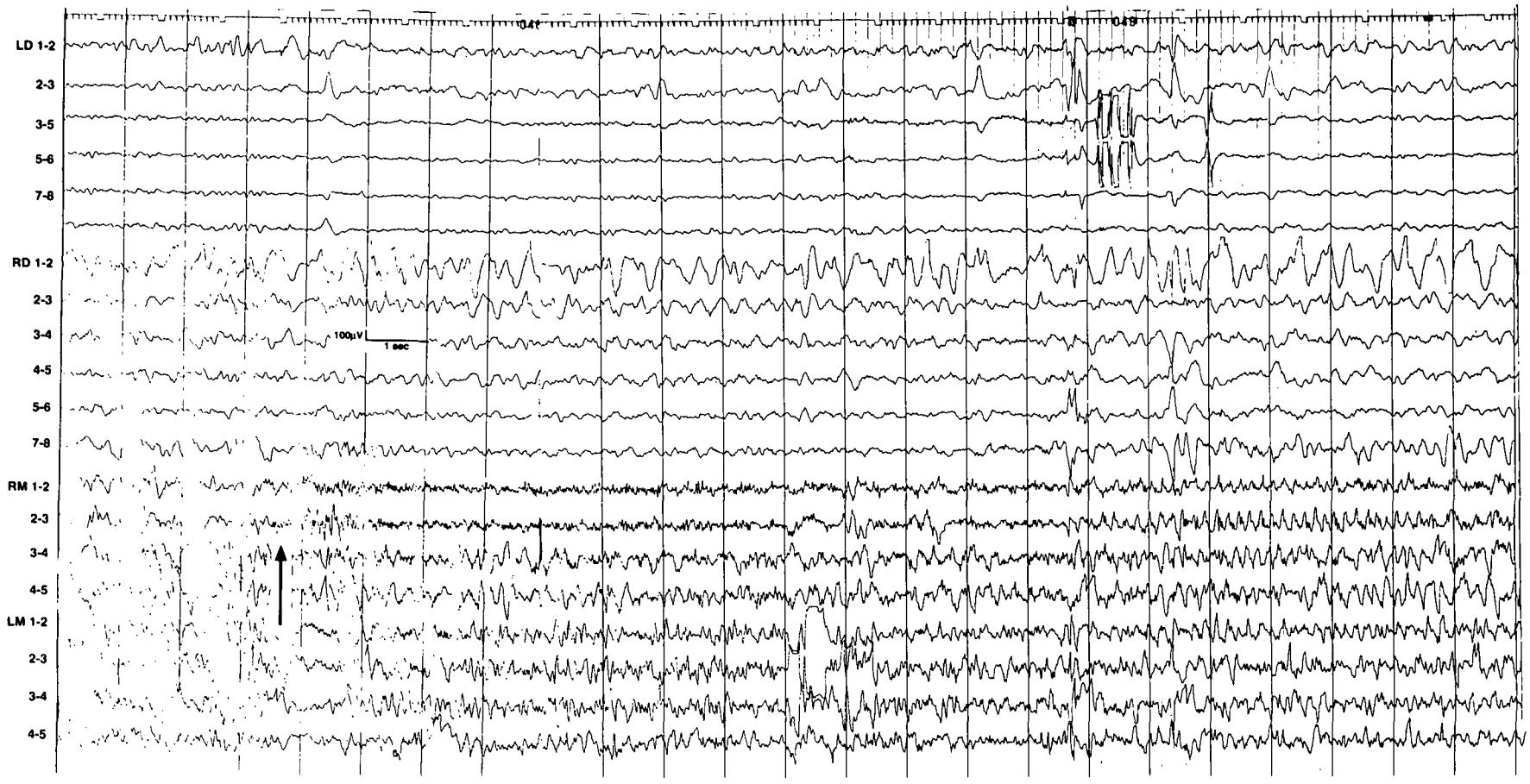

Fig. 6 EEG obtained from electrodes surgical implanted in right frontal lobe of Seizure Case 2. RD/LD = right/left depth electrode; RM/LM = right/left mid interhemispheric fissure (*see* Fig. 2). Contact point 1 is most distant from the point of entry. Contacts 1, 2 and 3 of RM record from the right cingulate gyrus. The seizure begins at the arrow, with low amplitude fast (>15 Hz) activity.

prominent interictal behaviour changes occur. These behavioural changes contrast markedly with those reported in patients who have undergone bilateral cingulectomy. Indeed, many patients with such behavioural changes reported in the earlier literature (Mazars, 1970) as well as more recently (Levin and Duchowny, 1991) and here (Case 2), the behaviours improved after unilateral or bilateral cingulectomy. These behaviours may, therefore, result from some pathological amplification of cingulate activity, perhaps reflecting abberent connections between affects, ideas, and actions.

Akinetic mutism and cingulate strokes

Akinetic mutism is a condition in which the subject appears to be awake and to visually track objects without spontaneous motor and verbal responses (Cairns *et al.*, 1941). Akinetic mutism occurs with bilateral cingulate and adjacent frontal cortical lesions as well as with lesions of the paramedian reticular formation in the midbrain and diencephalon (Cravioto *et al.*, 1960; Kemper and Romanul, 1967; Skultety, 1968). There are no reports in animals or in humans with neurosurgically produced or spontaneous lesions limited to the cingulate gyri in which either akinesia or mutism persisted more than a few days. In the case of transient deficits, it is impossible to exclude injury to neighbouring cortical areas or white matter.

Akinetic mutism is most often associated with bilateral anterior cingulate cortex lesions. One young alcoholic man developed akinetic mutism after bilateral anterior cerebral artery infarcts with maximal destruction in area 24 (Amyes and Nielsen, 1953). The lesion, however, extended to the corpus callosum and left frontal pole. He was eventually able to feed himself on occasion and respond to questions with yes/no answers. Another akinetic mute man had bilateral haemorrhagic lesions in area 24. He was unresponsive to noxious stimuli, incontinent of urine and lay with his eyes open, unable to swallow food or drink (Barris and Schuman, 1953). The lesion involved contiguous cortical areas including medial and inferior portions of areas 4 and 6, and slight involvement of area 32. Old lesions, consistent with previous head trauma, were in both orbitofrontal areas and the inferior surface of the left temporal lobe. Other cases of akinetic mutism with bicingulate lesions resulting from rupture of anterior cerebral artery aneurysms, strokes in the territory of the anterior cerebral artery, or tumours have been reported (Faris, 1969; Buge *et al.*, 1975; Laplane *et al.*, 1981; Nemeth *et al.*, 1988). In all cases, the lesions were maximal in anterior cingulate cortex, but extended to other regions of the frontal, and in some cases, other cortical and subcortical regions.

The most severe deficits in spontaneity and motor activation probably follow bilateral lesions of anterior cingulate cortex and the supplementary motor area. Laplane *et al.*'s case (1981) is remarkable because there was extensive bilateral anterior cingulate (and fornix) damage with indifference, docility, amnesia and prominent inattention, but motor activity was normal (i.e. no akinesia or mutism). These investigators suggest that the preservation of motor activity was related to sparing of the supplementary motor area and caudal anterior cingulate cortex. As animal studies have shown, the caudal cingulate area 23c contains a motor area. Neuropsychological, metabolic, and clinical studies document the role of the supplementary motor area in preparing and initiating movement (Laplane *et al.*, 1977; Deecke and Kornhuber, 1978; Orgogozo and Larsen, 1979; Roland *et al.*, 1980; Verfaellie and Heilman, 1987). In many clinical cases, lesions encompassed both anterior cingulate cortex and supplementary motor area (Laplane *et al.*, 1977; Verfaellie and Heilman, 1987). Unilateral neurosurgical resections of the supplementary motor area cause only transient mutism or contralateral hemiplegia (Laplane *et al.*, 1977). The motor defect in these patients improves to a point where there is slight hesitation during rapid alternating movements, lack of fluidity in contralateral movements and speech in the case of dominant hemisphere lesions (Laplane *et al.*, 1977). The reciprocal connections between anterior cingulate cortex and supplementary motor area may in part explain why unilateral supplementary motor area lesions can cause transient mutism or transcortical motor aphasia (Laplane *et al.*, 1977; Masdeu *et al.*, 1978; Brust *et al.*, 1982; Rubens and Kertesz, 1983). In many cases with supplementary motor area lesions and reduced vocalization, there was also cingulate injury. Both the supplementary motor area and anterior cingulate cortex may activate vocalization, especially when responding to an emotional stimulus.

Damasio and Van Hoesen (1983) report a 35-year-old woman with a left cingulate and supplementary motor area embolic infarct. Initially, she had no spontaneous speech but was able to repeat. She made no response to questions but did not appear frustrated. One month later, after a significant recovery, she commented that 'she did not talk because she had nothing to say.' Her mind was 'empty'. 'Nothing mattered.' During the initial illness she could follow the doctors conversations, but 'felt no will to reply' to the questions. They interpret the findings in this and other cases of combined cingulate and supplementary motor area damage to indicate that such lesions cause a profound behavioural disturbance, preventing the normal expression and experience of affect.

Both anterior cingulate cortex and supplementary motor area receive dopaminergic input from the ventral tegmental area (Ungerstedt, 1971). Akinesia can result from specific anatomical or neurochemical lesions: destruction of the ascending forebrain dopaminergic fibres or drugs decreasing dopaminergic activity (e.g. receptor blockers like phenothiazines), depleting storage (reserpine) or blocking synthesis (alpha-methylparatyrosine) (DeLong and Georgopoulos, 1981). Dopaminergic agonists can improve akinesia and mutism when there are lesions of the ascending dopaminergic fibres and limbic regions are intact (Ross and Stewart, 1981) but not when the lesions include the areas where these fibres

terminate (e.g. cingulate, orbitofrontal and septal areas) (Devinsky *et al.*, 1987).

In summary, isolated bilateral cingulate damage or supplementary motor area damage does not cause persistent akinesia or mutism. However, when lesions involve both of these areas or one of these areas together with other pathways or areas involved in motor activation, akinesia and mutism can occur and may be permanent.

Gilles de la Tourette Syndrome

Gilles de la Tourette Syndrome (GTS) is a chronic motor and vocal tic disorder associated with obsessive thoughts and compulsive behaviours, sleep disorders, echolalia, and echopraxia. Obsessions and compulsions affect the majority of patients (Eldridge *et al.*, 1977; Cummings and Frankel, 1985). Obtrusive sexual and aggressive thoughts and actions are common, as are other obsessive–compulsive behaviours such as touching specific objects or people, hand-washing, ritualistic behaviours, fears about failure to lock doors, and ego–alien intrusive thoughts.

A biological basis for GTS is widely supported from genetic, biochemical, neuropharmacological and electrophysiological studies (Bulter *et al.*, 1979; Cohen *et al.*, 1979; Nee *et al.*, 1980; Obeso *et al.*, 1981; Pauls and Leckman, 1986). The pathogenesis and anatomical basis of GTS, however, remains unknown. Neuropathological studies have generally been unrevealing (Dewulf and van Bogaert, 1941; Balthasar, 1957), although diminished or absent dynorphin-like staining in the globus pallidus was found in one case (Haber *et al.*, 1986).

A potential role of the anterior cingulate cortex in GTS (Devinsky, 1983) was suggested because: (i) electrical stimulation of the anterior cingulate gyrus in monkeys evokes guttural sounds and calls (Robinson, 1967; Jürgens and Ploog, 1970); (ii) connections between the anterior cingulate cortex and structures are involved in vocalization (Müller-Preuss and Jürgens, 1976; Baleydier and Mauguiere, 1980); (iii) there is a a dopaminergic pathway from the ventral tegmental area to anterior cingulate cortex and dopaminergic hyperactivity is postulated as the principal neurochemical abnormality in GTS (Singer, *et al.*, 1982; Devinsky, 1983); (iv) there are similarities between complex, coordinated movement patterns evoked by electrical stimulation of the anterior cingulate cortex in humans and those observed during tics; (v) a 15% decrease in cerebral glucose utilization in the anterior cingulate cortex and insular cortices is observed in patients with GTS (Chase *et al.*, 1986); and (vi) lesions of anterior cingulate cortex or the cingulum bundle can relieve obsessive–compulsive behaviours (Ballantine *et al.*, 1987). Furthermore, several groups have found that cingulumotomy reduced obsessive–compulsive behaviours in GTS patients (Baker, 1962; Kurlan *et al.*, 1988; Robertson *et al.*, 1990). The intralaminar and medial thalamic nuclei have also been neurosurgically ablated with reduction in tics and obsessive–compulsive behaviours in GTS (Hassler and Dieckmann, 1970; de Devitiis *et al.*, 1977). These thalamic areas have strong connections to anterior cingulate cortex as noted previously. Notably, Rauch *et al.* (1994) found increased regional cerebral blood flow in the right caudate, left anterior cingulate cortex and bilateral orbitofrontal regions during obsessive–compulsive syptoms.

The unique clinical aspects of GTS may derive from the unique contributions of anterior cingulate cortex to behaviour. It is one of the only neurological disorders in which simply thinking about a symptom—the tic—can evoke it. The patient who sees an obese person and uncontrollably vocalizes loudly 'fat fat lady' as a verbal tic may have cingulate dysfunction. The integration of thought, motivation and emotion with movement are critical aspects of cingulate function. In GTS, anterior cingulate cortex may discharge autonomously without the control of other areas such as prefrontal cortex which may be capable of inhibiting cingulate function (Cohen *et al.*, 1988). Whereas many people may pass an obese individual and make note of their distinctive morphology with an internal verbalization, the GTS patient lacks conscious control of the motor act. In other instances, they can consciously suppress the tic at the cost of hightened emotional tension. This semi-volitional component is reminiscent of motor acts observed during cingulate seizures and with electical stimulation of anterior cingulate cortex.

Psychiatric disorders

Effects of cingulectomy

Surgical removal of the anterior cingulate gyri for treatment of psychiatric disorders began in the late 1940s (Ward, 1948*b*; Mettler *et al.*, 1949; Scoville, 1949; LeBeau and Pecker, 1950). Whitty *et al.* (1952) reported 29 cases with bilateral ablations limited to area 24. During the initial post-operative period, patients made small, repetitive, seemingly purposeless movements such as patting the bedclothes or rubbing the face. There was often a transient reduction of aggression and tension in patients with psychosis. In contrast, patients with obsessive–compulsive disorder and anxiety neurosis enjoyed a long-lasting improvement in these disorders with minimal undesirable personality changes. LeBeau (1954) partially removed area 24 bilaterally in patients with epilepsy and aggression or psychosis, reporting behavioural improvement in most cases.

Tow and Whitty (1953) reported eight cases with bilateral area 24 ablations for depression, anxiety, and obsessive–compulsive disorder. Psychiatric symptoms, especially anxiety and obsessiveness were significantly improved, and there was little change in personality. Some subjects were, however, unduly tired in the afternoon, less meticulous in their habits, slower in thoughts and actions, less self-conscious and timid, more irritable, had shallower and less sustained affect, and had impaired judgment in personal and social situations. There were no changes in memory, religious thought, sexual desire or humour. Subsequent studies con-

firmed that cingulectomy reduces aggression and affective range and relieves chronic pain (Jimeno and Paniagua, 1969; Wilson and Chang, 1974). No post-cingulectomy deterioration in cognition or personality has been found using the Wechsler Adult Intelligence Scale, Halstead–Reitan Test Battery, Wechsler Memory Scale, Minnesota Multiphasic Personality Inventory (Long *et al.*, 1978). The only significant change was a decrease in anxiety.

Schizophrenia

Several lines of evidence suggest that structural, neurochemical and physiological disorders of the anterior cingulate cortex, as well as other areas such as the hippocampus and dorsolateral frontal cortex, are involved in the pathogenesis of schizophrenia (Benes, 1993). Post-mortem studies reveal a significant reduction in the number of small neurons (interneurons) throughout the anterior cingulate cortex in schizophrenic brains, with the changes maximal in layer II (Benes *et al.*, 1991). These structural changes were not related to age or treatment variables.

Post-mortem studies suggest a selective loss of glutamatergic neurons and altered GABA-A binding on pyramidal cells in the superficial layers of the anterior cingulate cortex in schizophrenics. Benes *et al.* (1992*a*) found increased biccuculine-sensitive and [^{3}H]muscimol binding to GABA-A receptors on neuronal cell bodies in anterior cingulate cortex layers II and III and the neuropil in layer I. These changes did not appear to result from antipsychotic medication exposure as similar findings were present in one drug naive patient and in another patient exposed to only small doses of such medications. Benes *et al.* (1992*b*) also found significantly increased density of small-calibre (78%) and large-calibre (30%) glutamate-immunoreactive vertical fibres in anterior cingulate cortex layers II and IIIa of schizophrenic brains when compared to age-matched controls. Flunitrazepam binding is reduced in the anterior cingulate cortex and hippocampus of post-mortem schizophrenic brains, suggesting a loss of glutamatergic neurons (Squires *et al.*, 1993). These post-mortem studies suggest a disturbance of inhibitory activity in these superficial layers of the anterior cingulate cortex.

Metabolic, blood flow and receptor-labelling studies also implicate anterior cingulate cortex dysfunction in schizophrenia. Patients with schizophrenia have significantly lower regional cerebral metabolic rate of glucose in the hippocampus and anterior cingulate cortex (Tamminga *et al.*, 1992). During the Wisconsin Card Sorting Test (which assesses shifting behavioural sets), schizophrenic patients, but not normal controls, had reduced regional cerebral blood flow in the medial frontal regions (Kawasaki *et al.*, 1993). Behavioural tasks that increase anterior cingulate cortex blood flow in normals (i.e. Tower of London) do not activate this cortex in neuroleptic-naive or non-naive schizophrenic patients (Andreasen *et al.*, 1992).

Conclusions

The anterior cingulate cortex may be essential in making a transition from early premotor to behavioural states. The clinical and experimental observations reviewed here suggest that anterior cingulate cortex subserves three levels of premotor processing. First, when a response selection is to be made, including the decision not to move, area 24′ is engaged, while attending to non-challenging sensory stimuli such as different frequency tones or neutral visual stimuli may be associated with reduced activity in these areas. Secondly, the expression of specific movement sequences that require little or no autonomic activity is probably directed by the CMAs in the depths of the cingulate sulcus. Finally, when autonomic activity is required there may be coactivation of visceromotor and skeletomotor areas in anterior cingulate cortex.

One consequence of these generalizations is that anterior cingulate cortex and its connections provide mechanisms by which affect and intellect can be joined. The cingulate gyrus may be viewed as both an amplifier and filter, interconnecting the emotional and cognitive components of the mind. Under normal conditions, behavioural responses such as vocalization in response to emotional stimuli are facilitated through circuits in anterior cingulate cortex and the adjacent supplementary motor area. Similarly, affective states are in part modulated by anterior cingulate cortex. Thus, after bicingulate lesions, a noxious stimulus may still be localized on the body surface, but will not trigger the unpleasant affective pain perception and avoidance responses that normally occur. The anterior cingulate cortex may also be responsible for activating circuits associated with emotional states (e.g. 'getting psyched') in response to intellectual ideas such as going to a sporting event. Obsessive–compulsive disorder, pathological anxiety, and behavioural problems associated with cingulate epilepsy (i.e. intermittent and fixed psychoses, disordered impulse control and aggression, irritability, obsessions and compulsions, and sexual preoccupation) may, in part, be a disorder of excessive amplification of emotional signals. Tics and impulsive movements may reflect pathological amplification of spontaneous motor behaviour. The diminished motivation, lethargy, loss of interest in reading and sports, and decreased affective range after cingulate lesions also may reflect diminished amplification of emotional willpower.

Most of the dramatic behavioural changes following anterior cingulate cortex lesions are associated with other lesions. Thus, when combined with orbitofrontal lesions, a devastating 'social agnosia' results. When combined with supplementary motor area lesions, akinesia and mutism result. One may speculate that the combination of lesions in the anterior cingulate cortex and other areas may cause severe neurobehavioural disorders such as schizophrenia. For example, impairment of willed actions (anterior cingulate cortex and dorsolateral prefrontal cortex), attention to action (anterior cingulate cortex and dorsolateral frontal and/or

parietal cortex), memory (anterior cingulate cortex and septum or hippocampus). The functions of the anterior cingulate cortex, a component of several vital networks and subserving a diverse range of functions, are difficult to quantify or even describe, and have eluded the traditional 'localized lesion-behavioural correlate' approach. Understanding the anterior cingulate cortex may require new methodologies and new frames of reference. One such perspective is that of the rostral limbic system. This concept proposes that a select group of forebrain structures including anterior cingulate cortex are involved in affect and regulating context-relevant motor behaviours. Each part of the rostral limbic system has direct access to autonomic and skeletomotor brainstem systems for implementing behaviour.

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