PRIMATE ANTERIOR CINGULATE CORTEX: WHERE MOTOR CONTROL, DRIVE AND COGNITION INTERFACE

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Controversy surrounds the function of the anterior cingulate cortex. Recent discussions about its role in behavioural control have centred on three main issues: its involvement in motor control, its proposed role in cognition and its relationship with the arousal/drive state of the organism. I argue that the overlap of these three domains is key to distinguishing the anterior cingulate cortex from other frontal regions, placing it in a unique position to translate intentions to actions.

TEMPERAMENT AND CHARACTER INVENTORY
A self-report measure of seven basic dimensions of temperament (novelty seeking, harm avoidance, reward dependence and persistence) and character (self-directedness, cooperativeness and self-transcendence).

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The past decade saw a surge of interest in the structure and function of the anterior cingulate cortex (ACC) in human and non-human primates. Three key features dominate current discussions on the role of the ACC in behavioural control. First, dense projections from the ACC to the motor cortex and spinal cord seem to implicate this region in motor control. Second, reciprocal cortico–cortical connections of the ACC with the lateral prefrontal cortex (PFC) support its proposed role in cognition. Third, extensive afferents from the midline thalamus and the brainstem nuclei point to the importance of arousal/drive state for ACC engagement. Here I propose that the functional overlap of these three domains distinguishes the ACC from other fronto-cortical regions, and that this overlap provides the ACC with the potential to translate intentions to actions.

Structure

The ACC occupies two tiers on the medial wall of each cerebral hemisphere. The ventral (limbic) tier occupies the surface of the cingulate gyrus and contains Brodmann's areas 24a, 24b and the subcallosal area 25. The dorsal (paralimbic) tier is, for the most part, deeply buried in the cingulate sulcus and contains Brodmann's areas 24c and 32; in the human brain, the paralimbic cortex often extends into the paracingulate gyrus (FIG. 1).

The pattern of cortical folding on the medial wall of the human brain is highly variable from person to person. This is particularly true for the paracingulate sulcus, which is present in only 30–50% of individuals[1]. The incidence[1–3] and volume[4] of the paracingulate sulcus are greater in the left hemisphere; this asymmetry might be related to the involvement of the paracingulate region in speech[5]. Conversely, the volume of grey matter buried in the anterior section of the cingulate sulcus is greater in the right hemisphere, as compared with the left[4]. This is also the case for the surface area of the cingulate gyrus, as it extends from the corpus callosum to the lower lip of the cingulate sulcus (J. Pujol, personal communication). Attesting perhaps to the limbic nature of this part of the cingulate region, the surface area of the right cingulate gyrus seems to correlate with the propensity of the person to show fearfulness, as assessed by the TEMPERAMENT AND CHARACTER INVENTORY (J. Pujol, personal communication).

The variability in gross morphology of the ACC cannot capture the structural heterogeneity of this region, which is evident at the microscopic level. Regional variations in the cytoarchitecture of the cingulate cortex point to the existence of several fields that differ in their connectivity and, presumably, their function. Indeed, important clues about the functional contributions of the ACC have come from the pattern of its efferent and afferent connections. Rather than providing an exhaustive review of ACC connectivity, I shall focus on those aspects that are relevant to the convergence of cognitive and motor processes with those underlying the arousal/drive state of the organism.

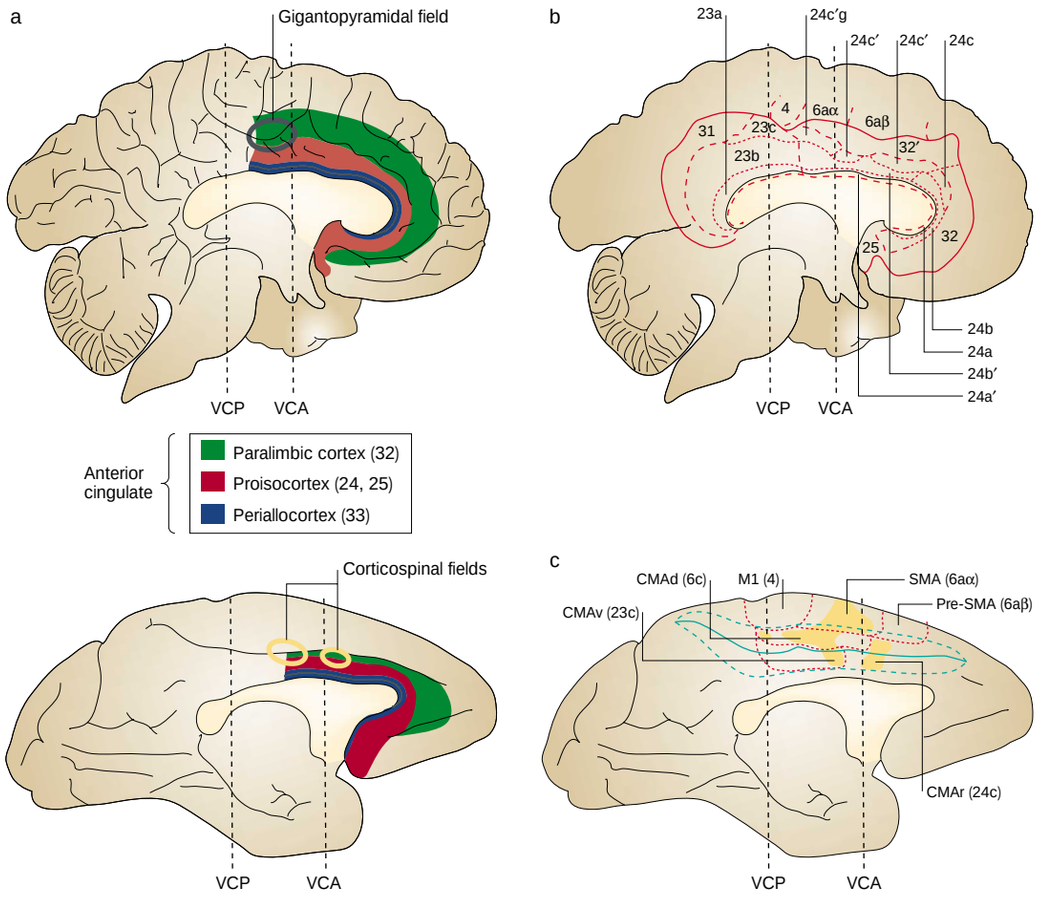

Figure 1 | **Cytoarchitectonic subdivisions of human and monkey cingulate cortex. a** | The cingulate cortex can be divided along a rostro-caudal axis into a posterior granular region (Brodmann's areas 26, 29, 30, 23, 31) and an anterior agranular region (areas 33, 24, 25, 32). A ventro-dorsal distinction on the basis of the degree of laminar differentiation sets apart the old periallocortical areas adjacent to the corpus callosum (area 33) from the proisocortical region (areas 24, 25) and from the paralimbic region on the upper bank of the cingulate sulcus and in the paracingulate gyrus (area 32). In addition to the above distinctions, subtle variations in cytoarchitecture define further subdivisions of area 32, often reflecting structural features of the adjacent neocortical areas[109]. The lower part of the panel shows an equivalent representation of the monkey brain. The approximate position of the gigantopyramidal (human) and corticospinal (monkey) fields is indicated relative to the vertical plane passing through the anterior commissure. **b** | Cytoarchitectural areas superimposed on the flat map of the medial wall of the human brain[110]. The solid lines delineate the cingulate region, the dashed lines show the borders between the cingulate areas (for example, between areas 24 and 23), and the dotted lines indicate the borders between subdivisions of each area (for example, between areas 24b and 24c). **c** | Location of the motor areas on the medial wall of the monkey brain[10]. The dotted lines show the boundaries of the cytoarchitectonic areas. Shaded areas correspond to the territory of origin of corticospinal projections to cervical and upper thoracic segments. The green lines indicate the boundaries of the lower and upper lips of the cingulate sulcus. CMAd, caudal cingulate motor area, dorsal bank; CMAr, rostral cingulate motor area; CMAv, caudal cingulate motor area, ventral bank; M1, primary motor cortex; SMA, supplementary motor area; VCA, vertical plane passing through the anterior commissure; VCP, vertical plane passing through the posterior commissure.

The extent of structural links between the ACC and the lateral PFC is one of the most striking features of cortico–cortical connectivity in the primate frontal cortex. As pointed out by Barbas and Pandya[6], intrinsic connections of the cingulate cortices with other frontocortical areas are not limited to immediate neighbours, but also reach the more distant prefrontal regions, particularly those in the dorsolateral PFC. These projections tend to originate in layer V of the cingulate cortex, and to terminate in the superficial layers of the PFC; this pattern is fundamentally different from the laminar distribution of cortico–cortical connectivity among neocortical regions[7]. Another important feature of PFC–ACC connectivity is the convergence of PFC inputs onto cingulate motor areas located in the cingulate sulcus[8–10]. These fields receive input from the primary motor cortex, premotor cortex and supplementary motor area[11,12], and give rise to corticospinal projections that terminate in the intermediate zone of the spinal cord[11]. Whereas the cingulate motor areas have direct access to the skeletomotor apparatus, a set of fields located more rostrally provides connections with cortical and subcortical regions that are involved in vocalization, including those in the periaqueductal grey

matter[13–18]. It is noteworthy that the cingulate vocalization region also receives extensive input from auditory association cortex[18,19], a feature of potential importance for auditory–vocal interactions.

Overall, the extensive cortico–cortical connectivity between the ACC on the one hand, and the lateral PFC and motor cortices on the other, provides powerful avenues of communication between cognitive and motor systems. Let us now examine the anatomical pathways by which activity in the ACC can be influenced by emotional and motivational states. First, direct relationships of the cingulate cortex with other limbic structures seem to be limited chiefly to the ventral-tier areas 24a, 24b and 25, which are known to receive projections from the amygdala[20] and from the ventral striatum[21]. The limbic influence does reach the dorsal-tier regions (including the cingulate motor areas), albeit indirectly through areas 24a, 24b and 25 (REF. 22). The second important source of input, which might reflect the arousal state of the organism, comes from the thalamus; extensive ACC afferents originate not only in the magnocellular (limbic) part of the mediodorsal and the anterior thalamic nuclei, but also in the midline nuclei[23]. The midline thalamic nuclei are involved in the regulation of cortical arousal[24] and, as such, they might mediate arousal-related changes in cingulate activity (see below). The third and perhaps most important source of arousal-related modulation of cingulate activity comes from the brainstem monoamine nuclei[25,26]. The ACC is the main target area of the mesocortical dopamine system, which originates in the ventral tegmental area. In the human cortex, the highest density of dopamine fibres is found in the paralimbic ACC, where they terminate in all layers[27,28]. A similar laminar distribution is observed in the case of serotonin fibres, but at a much lower overall density[29]. Noradrenaline input from the locus coeruleus preferentially targets deep layers of the ACC, providing a complementary source of modulation of neural activity[25]. Dopamine and noradrenaline are not the only neuromodulators that are present in abundance within the ACC. In addition to monoamines, a number of neuropeptides can also be found at high levels. They include corticotropin-releasing factor (CRF)[30], prosomatostatin-derived peptides[31], neurotensin[32,33] and substance P[34].

Activation

Motor channels. The presence of corticospinal projections from the cingulate sulcus leads to the prediction that electrical stimulation of this region should elicit body movements. In fact, this observation was made in monkey[35,36] and man[37,38] before the discovery of their anatomical substrate. But it was only with the use of intracortical microstimulation that it became possible to reveal the detailed organization of the cingulate motor areas, and to distinguish them clearly from the dorsally located supplementary motor area[39]. Consistent with the known anatomy of the ACC, caudal and rostral cingulate motor areas were found on both banks of the monkey cingulate sulcus; these two areas differ in their stimulation threshold[39], as well as in the type of neural activity recorded during the performance of motor tasks[40–42]. More recently, the existence of the two main cingulate motor areas has also been confirmed in the prosimian galagos, indicating that these motor structures emerged early in primate evolution[43]. Considering the evolutionary significance of vocalization, it is perhaps not surprising that a large expanse of the monkey ACC gives rise to a variety of calls when stimulated electrically. Although detailed microstimulation studies are still needed, the vocalization region seems to be restricted to the peri-genual aspect of areas 24 and 32 (REFS 18, 44–46). As pointed out in the previous section, this region receives significant input from auditory cortex[19]; unfortunately, little is known about the interplay between auditory input and vocalization in the primate ACC. On the other hand, a microstimulation study of the bat cingulate cortex revealed exquisite details in this respect: ultrasound vocalization elicited by electrical stimulation was organized in a tonotopic fashion, providing a highly sophisticated 'acoustic foveation' mechanism for echolocation[47].

In the human brain, functional neuroimaging is the main tool used for mapping the functional organization of the cerebral cortex. Using positron emission tomography (PET) and the water-bolus method, we have embarked on mapping studies of the human ACC by asking two questions. First, is the ACC involved in the WILLED control of actions? And, if so, are different subregions of the ACC engaged, depending on the output system used to execute the response? To answer these questions, we designed a behavioural model in which the execution of a simple response — manual, oculomotor or verbal — was put in conflict with an overlearned stimulus–response alternative[48]. Our findings confirmed both predictions: the ACC was 'activated' under the conflict conditions, and the exact location of these activations varied depending on the output modality (FIG. 2). The manual condition, which required key presses with the fingers of the right hand, revealed likely homologues of the monkey cingulate motor areas in the caudal aspect of the human ACC. These were located just behind and in front of the vertical plane that passes through the anterior commissure (Y=0) (REF. 49). This location of hand representation is a frequent finding, as shown by a meta-analysis of 107 PET activation studies[50]. The verbal condition, which required the utterance of a pronoun, yielded activations in the paracingulate gyrus and the peri-genual aspect of the cingulate gyrus/sulcus (FIG. 2), a finding that is consistent with the original observation made by Pardo *et al.*[51] of a robust ACC response during the STROOP TASK. Such mapping of speech output to the more rostral sections of the ACC fits well with the organization of the monkey vocalization regions, and with the presence of a hemispheric asymmetry in the grey-matter volume of the paracingulate sulcus (see above).

Interactions between ACC and PFC. One of the advantages of functional imaging studies carried out with PET or by functional magnetic resonance imaging (fMRI) is that they allow us to visualize the whole brain. From very early on, investigators noticed frequent CO-ACTIVATIONS of the lateral PFC and the ACC during the

STROOP TASK
In this task, the subject is asked to name the colour of ink in which a word is printed. The task is easy when the ink colour is congruent with the printed word (for example, 'red' printed in red ink). The task becomes difficult when the ink colour is incongruent with the printed word (for example, 'red' printed in green ink).

WILL
A purposeful control over actions.

CO-ACTIVATION
In an imaging experiment, the presence of significant blood-flow responses observed in two brain structures in the same subtraction.

performance of a variety of tasks[48,52,53]. Examinations of such co-activations across 107 PET blood-flow activation studies[54] showed that subtractions that yielded a blood-flow response in the ACC were more likely to be accompanied by a response in the middle frontal gyrus, as compared with subtractions in which the ACC was not activated. This association applied only to the ACC located above the corpus callosum, but not below its GENU, a finding consistent with the presence of widespread cortico–cortical connections of the lateral PFC with the supracallosal areas 24 and 32, but not the subcallosal area 25. The idea that the subcallosal cingulate cortex represents a distinct entity is further supported by frequent observations of blood-flow decreases in this region during the performance of cognitively demanding tasks[50,55]. It has been proposed that these changes are due to anxiety elicited by novelty and unpredictability[56]. Note that exactly the opposite relationship between blood flow and anxiety is observed in the supracallosal ACC.

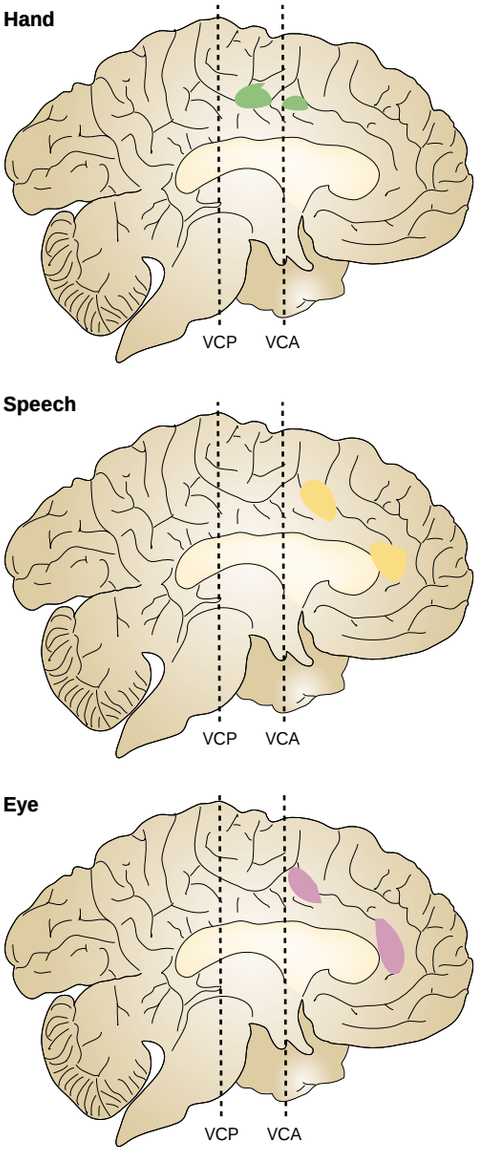

Figure 2 | **Response-related functional subdivisions of the anterior cingulate cortex in the human brain.** Semi-schematic representations of the cingulate locations at which increases in blood-flow response were observed in relation to the performance of stimulus–response conflict tasks requiring finger movements (Hand), speech utterances (Speech) or saccadic eye movements (Eye). Note the good correspondence between the activation in the upper (Hand) panel and the position of corticospinal fields in FIG. 1, and the correspondence between these imaging-derived locations and lesions giving rise to various deficits shown in FIG. 3. The locations are derived, for the most part, from REF. 48.

The presence of a robust functional connectivity between the supracallosal ACC and the lateral PFC has been confirmed with a technique that allows measurements of EFFECTIVE CONNECTIVITY between two brain regions: TRANSCRANIAL MAGNETIC STIMULATION (TMS) during PET. TMS applied over the mid-dorsolateral PFC results in a strong blood-flow response in the paralimbic ACC[57]. The above overview of functional and effective connectivity confirms the importance of fronto–cingulate interactions for task-related changes in neural activity in the ACC. However, the functional significance of such interactions remains unclear. We have suggested that the lateral PFC computes and maintains on-line information necessary for the choice of an appropriate response, whereas the ACC facilitates implementation of the selected action[48]. More recently, two psychological theories have suggested a unique role for the ACC in cognitive control, namely in error detection and in conflict monitoring.

The error-detection theory is based on the observation, originally made by Falkenstein *et al.*[58] and Gehring *et al.*[59], of a large negative scalp-potential time-locked to the onset of an incorrect response. This error-related negativity (ERN) typically peaks about 100 ms after movement onset, and seems to be generated by the ACC[60]. However, subsequent studies challenged the specificity of ERN to error detection. Several authors observed an ERN-like potential, albeit of a smaller amplitude, in correct-response trials[61]. Furthermore, Tucker *et al.*[62] provided evidence that similar potentials are also generated in tasks that involve affective judgements. Interestingly, ERN amplitude is larger in subjects that experience high levels of subjective distress, compared with those with low negative affect[63]. The importance of the PFC–ACC interactions for the generation of ERN has recently been established in a study published by Gehring and Knight[64]. Patients with unilateral lesions to the lateral PFC showed ERN in both error and correct trials and, compared with control subjects, patients were less likely to show 'corrective behaviour'. So, in its original formulation, the ERN-based error-detection theory of the ACC might be too narrow, in terms of both the cognitive processes and the brain structures involved. On the other hand, it does raise the intriguing idea that different cognitive/affective events might lead to a transient synchronization of neural activity in the ACC. It would be interesting to explore the possibility that such synchronization is mediated by, for example, phasic changes in the activity of the locus coeruleus[65,66].

GENU
The corpus callosum has four parts: rostrum, genu, body and splenium. The genu — the C-shaped segment of the corpus callosum — connects parts of the frontal lobe of both hemispheres.

EFFECTIVE CONNECTIVITY
A direct influence that one brain region exerts over another.

TRANSCRANIAL MAGNETIC STIMULATION
A technique used to stimulate relatively restricted areas of the human cerebral cortex. It is based on the generation of a strong magnetic field near the area of interest which, if changed rapidly enough, will induce an electric field sufficient to stimulate neurons.

The conflict-monitoring theory[67] is based on a series of neuroimaging studies that attempted to isolate different cognitive processes engaged during the performance of a Stroop-like colour-naming task. These studies clearly established that the presence of conflict is more important than the actual error[68], and that unpredictable conflict engages the ACC significantly more than a predictable one[69]. In their theory, Carter and colleagues emphasize the 'evaluative' function of the ACC. They suggest that the ACC "provides an on-line conflict signal, indicating the need to engage brain regions such as dorsolateral prefrontal cortex and inferior parietal cortex to implement strategic process"[69]. This theory leads to the prediction that the evaluative function of the ACC should be engaged equally, regardless of whether monitoring for conflict occurs at the level of stimulus presentation or at the level of the response. But neuroimaging data obtained by Milham *et al.*[70] in a variant of the Stroop task do not support this prediction: although the behavioural Stroop effect was present at both stimulus and response levels, the ACC was engaged only in the latter case. Another important issue is the relative involvement of the ACC and lateral PFC during the performance of the Stroop task. Results of an fMRI study carried out by MacDonald *et al.*[71] indicate that the lateral PFC might be involved in the early phase of 'mental-set' preparation, whereas the ACC is engaged later, during the actual response to the incongruent stimuli. These findings are consistent with those made by Banich and colleagues[72]. They observed engagement of the lateral PFC during the performance of a Stroop-like task, even on trials with no response conflict, again indicating a possible role for the lateral PFC in creating an attentional 'set' for task-relevant information. Overall, it is clear that the presence of conflicting response alternatives results in a robust change in ACC activity. But whether this represents a neural correlate of conflict detection or conflict resolution remains unclear.

Arousal and stress. The level of task difficulty seems to be the single most important factor in differentiating between subtractions that yield a blood-flow response in the ACC, and those that fail to show a response; this relationship is particularly strong in the case of the supracallosal and paralimbic ACC[50]. It can be argued that the more difficult a task is, the more likely it is to engage neural mechanisms that are involved in the regulation of arousal and stress responses; the midline thalamus and the mesocortical dopamine system are the prime candidates in this respect.

Arousal-related changes in the ACC have been observed in several PET studies in which the level of arousal varied from full wakefulness[73] to deep sleep[74] or general anaesthesia[75]. Changes in ACC blood flow always covaried with those in the midline thalamus, a part of the ascending reticular activating system[76]. In a vigilance study, blood-flow response in the ACC, midline thalamus and mesencephalic reticular formation decreased at about the same rate over the 50-minute testing period; these changes occurred together with increases in the response latency and in the amount of electroencephalographic activity in the THETA FREQUENCY range[73]. These observations confirm that neural activity in the ACC is modulated by the arousal state of the organism. The presence of such modulations across different stages of sleep and general anaesthesia suggest that the activity of the ACC changes even in the absence of any overt cognitive activity.

Foot-shock-induced stress is a powerful activator of the mesocortical dopamine system in the rat[77,78]. The amount of such stress-induced activation varies across different strains of animal, being especially high in so-called high-avoidance rats[79]. As pointed out above, the highest density of dopamine innervation in the primate cerebral cortex is found in the ACC. This characteristic of the human ACC is reflected in its response to pharmacological agents: both resting and task-related activity in the ACC change in response to manipulations of dopamine-mediated transmission in healthy volunteers. For example, administration of apomorphine, a non-selective dopamine receptor agonist, increased task-related blood-flow response in the ACC[80,81]. Furthermore, administration of haloperidol, an antagonist of D_2 receptors, decreased resting metabolic activity in the ACC[82]. An attenuation of task-related blood-flow response in the ACC was observed after the administration of α-methyl-*p*-tyrosine, a competitive inhibitor of tyrosine hydroxylase, which reduces the rate of catecholamine synthesis[83]. Overall, these results emphasize the potential impact of neuromodulators such as dopamine on neural activity in the ACC. It is likely that behaviours known to increase the activity of monoamine systems will engage this structure. Individual variations in the likelihood and intensity of the stress-induced modulations of the ACC may, perhaps, explain why individuals with a high propensity to show fearfulness appear to have a larger cingulate gyrus and why ERN amplitude is high in subjects experiencing high levels of subjective distress (see above).

Deficit

Patients with medial frontal lobe lesions involving the cingulate cortex often show deficits in spontaneous initiation of movement and speech, and/or show an inability to suppress externally triggered motor subroutines. Akinetic mutism, which is caused by bilateral lesions, is an extreme example of this syndrome[84–88]. Unilateral lesions result in a milder version of mutism: spontaneous speech is scanty and, even on recovery, monotonous[89,90]. The grasp reflex and other forms of externally triggered 'uninhibited' motor subroutines are often found after unilateral lesions of the medial frontal lobe; the involvement of the ACC seems to be a condition *sine qua non* for the appearance of these phenomena[91–93]. The ALIEN-HAND SYNDROME is a curious example of the inability to suppress, at will, externally triggered movements of the hand and arm contralateral to the lesion[94,95]. For example, the patient might reach out with the affected arm and grasp objects such as a doorknob when passing by a door, or a pencil when placed in the patient's sight[95]. In such patients, however, the lesion often encroaches on the supplementary motor area and the middle section of

THETA FREQUENCY
Rhythmic neural activity with a frequency of 4–8 Hz.

ALIEN-HAND SYNDROME
A neurological condition in which the patient denies ownership or is not always in control of his/her own hand.

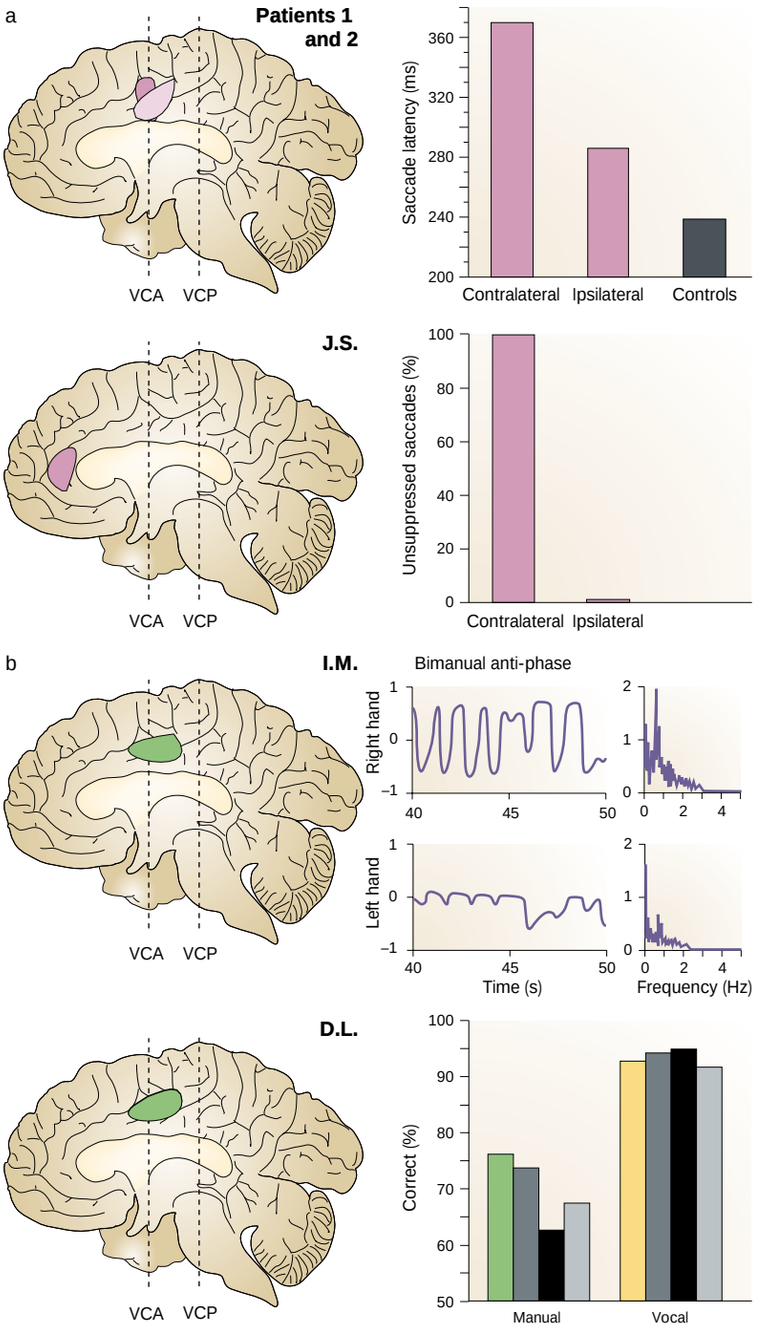

Figure 3 | **Single-case studies of behavioural deficits caused by discrete lesions of the right anterior cingulate cortex. a** | Oculomotor deficits were found in patients with lesions located either in front of the vertical plane passing through the anterior commissure (patients 1 and 2 from REF. 96) or in the rostral ACC (patient J.S. from REF. 97). These deficits involved impaired suppression of reflexive saccades (J.S.), as well as increased latency of visually guided saccades (patients 1 and 2). **b** | Deficits involving hand movements were associated with lesions at the level of the anterior commissure, affecting both rostral and caudal cingulate motor areas (I.M. from REF. 98; D.L. from REF. 99). The observed impairment of bimanual coordination was especially pronounced in one of the patients: I.M. was virtually unable to perform simultaneous finger–thumb opposition when an anti-phase movement was required. Note that the movements of the two hands were repeatedly performed in-phase instead of anti-phase (left panel: movement amplitude) resulting in spectral broadening (right panel: fast Fourier transform spectra) (These panels were adapted with permission from REF 98). Patient D.L. is of particular interest because her deficit was restricted to one output modality: when tested on a series of paradigms, including a Stroop-like task, D.L. showed impairment only if manual (but not verbal) responses were required.

the corpus callosum, and it is therefore difficult to define the precise involvement of the ACC.

Several studies have provided experimental analysis of deficits caused by small lesions restricted to a particular part of the ACC. An overview of the lesion locations and behavioural findings in five such cases is given in FIG. 3. In general, the type of deficit corresponds well with the functional anatomy reviewed above. Oculomotor deficits were found in patients with lesions located either in front of the vertical plane passing through the anterior commissure[96], or in the rostral ACC[97]; these deficits involved impaired suppression of reflexive SACCADES, as well as increased latency and decreased gain of visually guided saccades. Deficits that involved hand movements were associated with lesions at the level of the anterior commissure, therefore affecting both rostral and caudal cingulate motor areas[98,99]. The observed impairment of bimanual coordination was especially pronounced in one of the patients: I.M. was virtually unable to perform simultaneous finger–thumb opposition when an anti-phase movement was required[98]. Patient D.L.[99] is of particular interest because her deficit was restricted to one output modality: when completing a series of tests that included a version of the Stroop task, D.L. showed impairment only if manual (but not verbal) responses were required. This dissociation is indeed consistent with the non-overlapping representations for hand movements and speech within the ACC. Unfortunately, there are no published reports of the effect of restricted cingulate lesions on speech. However, several complementary studies have been carried out in the monkey. Bilateral lesions to the rostral aspect of the ACC, located around the genu of the corpus callosum, significantly impaired spontaneous vocalization, as well as the ability of the monkey to use vocalization in order to obtain reward or to avoid punishment[100–102]. Similarly placed lesions also reduce the number of isolation calls emitted by the monkey to re-establish contact with separated individuals[103]. These studies clearly show that one function of the vocalization regions of the monkey ACC, as defined by electrical stimulation, is the voluntary initiation of calls.

Together, behavioural deficits induced by circumscribed lesions to the primate ACC seem to interfere with the person's ability to initiate movement spontaneously and to resist the potentially interfering effects of automatic subroutines. Although the same type of impairment is observed after lesions affecting different parts of the ACC, the output modality involved seems to vary depending on the exact location of the lesion. This pattern indicates that the same facilitatory mechanisms might act on the separate motor channels that are contained in the ACC.

Willed control of action

Overcoming inertia when initiating actions and fighting competing well-established or innate tendencies are two cornerstones of the willed control of behaviour. Lesions to the ACC interfere with both aspects of willed control. One could argue that the threshold for initiating 'wanted' behaviour is raised, while the threshold is lowered for

SACCADE
A rapid eye movement that brings the point of maximal visual acuity — the fovea— to the image of interest.

all 'unwanted' alternatives. So, the ACC seems to come into play when rehearsed actions are not sufficient to guide behaviour. The results of lesion and imaging studies support this idea: the lesion is more likely to interfere with the acquisition of a novel behaviour[104,105], and activation of the ACC is most frequently observed during the performance of unrehearsed actions[42,106]. Throughout this review, my purpose has been to point out those features of the structural and functional organization of the primate ACC that position it ideally to participate in the willed control of behaviour. The three key elements are: motor channels, which provide access to skeletomotor and oculomotor output systems as well as vocalization; extensive connections with the lateral PFC, which provide access to the cognitive apparatus of this neocortical area; and afferents from the midline thalamus and the brainstem, which provide a strong modulatory influence reflecting the arousal state of the organism.

Conceptually, the ACC is a prime example of a brain structure in which a regulatory network, composed of cells from the modulatory brainstem nuclei, interacts with an executive network, composed of local-circuit neurons interconnected by amino-acid-containing pathways[107]. As suggested by Glowinski[107], "the main operational capacities of this … neural network may be to exert a regulatory or modulatory influence on more defined distributed systems by acting at different levels, modifying the capacities of the local circuit neurons or the transfer of information through connecting pathways". Activation of dopamine and CRF systems by stress, for example, would facilitate information processing within the ACC. The absence of such a modulatory influence would have the same consequences as an ACC lesion; akinetic mutism caused by the interruption of dopamine axons *en route* to the medial frontal cortex is reversed by the administration of dopamine receptor agonists[108]. On the other hand, release of dopamine or CRF during the performance of a challenging task would modulate synaptic activity in this region, and result in task-related increases in blood-flow response. By virtue of their action on ACC neurons, neuromodulators such as dopamine and CRF are in a powerful position to regulate the interaction between cognition and motor control in relation to changes in emotional and motivational states.

Links

MIT ENCYCLOPEDIA OF COGNITIVE SCIENCE Limbic system | Positron emission tomography

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