Cognitive and emotional influences in anterior cingulate cortex

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Anterior cingulate cortex (ACC) is a part of the brain's limbic system. Classically, this region has been related to affect, on the basis of lesion studies in humans and in animals. In the late 1980s, neuroimaging research indicated that ACC was active in many studies of cognition. The findings from EEG studies of a focal area of negativity in scalp electrodes following an error response led to the idea that ACC might be the brain's error detection and correction device. In this article, these various findings are reviewed in relation to the idea that ACC is a part of a circuit involved in a form of attention that serves to regulate both cognitive and emotional processing. Neuroimaging studies showing that separate areas of ACC are involved in cognition and emotion are discussed and related to results showing that the error negativity is influenced by affect and motivation. In addition, the development of the emotional and cognitive roles of ACC are discussed, and how the success of this regulation in controlling responses might be correlated with cingulate size. Finally, some theories are considered about how the different subdivisions of ACC might interact with other cortical structures as a part of the circuits involved in the regulation of mental and emotional activity.

Recently, the search for a unifying concept of the functional nature of anterior cingulate cortex (ACC) has become an important topic of research in cognitive neuroscience[1,2]. Neuroimaging[3] and electrical recording methods[4] have led to related but somewhat different conceptions for the role of ACC in information processing.

A comprehensive theory of ACC function, however, must account for the entire body of evidence accumulated by a variety of scientific methods. From this perspective, we outline three general ideas for which various theories must account:

(1) Cingulate cortex includes specific processing modules for sensory, motor, cognitive and emotional information.

(2) As a whole, cingulate cortex integrates input from various sources (including motivation, evaluation of error, and representations from cognitive and emotional networks).

(3) Cingulate cortex acts by influencing activity in other brain regions and modulating cognitive, motor, endocrine and visceral responses.

In this review we examine commonalities and differences among different literature, and show the involvement of ACC in a variety of cognitive and emotional tasks, especially the higher cognitive and emotional influences of ACC. Several important domains in which cingulate cortex is involved, such as pain processing, visuospatial processing and memory retrieval will not be considered[5,6].

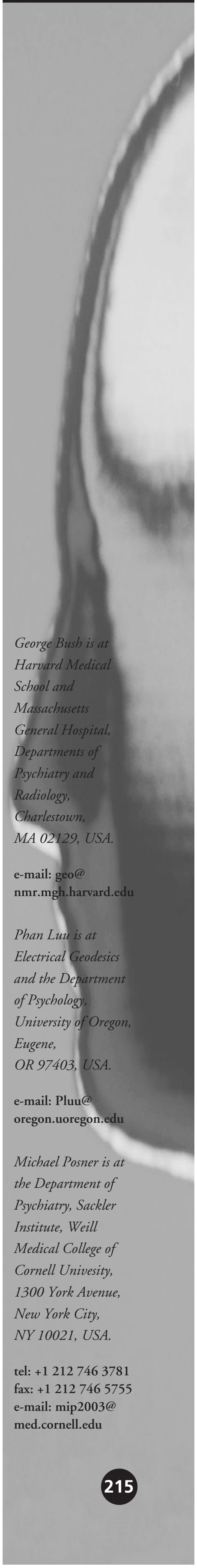
We start with a brief review of the classical studies. Next, we review imaging studies and then electrical recording data related to error processing. We then place these efforts within a developmental context. Finally, we present an analysis of the theories of the function of ACC in relation to other brain areas. Although none of the theories can fully qualify as a unifying theory, each is built upon a strong foundation and addresses an important facet of cingulate functioning.

Anatomy and lesion studies

The cingulate gyri were broadly defined by Broca as belonging to the limbic lobe. With the advent of more-precise methods for studying anatomical connectivity, cytoarchitecture and function, it is now clear that cingulate cortex encompasses numerous specialized subdivisions that subserve a vast array of cognitive, emotional, motor, nociceptive and visuospatial functions[5].

Anterior cingulate cortex can be differentiated from posterior cingulate cortex on the basis of cytoarchitecture and patterns of projections, as well as function. The anterior part has been characterized as 'executive' in function, whereas the posterior region is characterized as 'evaluative'[5]. Within ACC, further parcellations can be made based upon cytoarchitecture and connectivity (see Fig. 1).

An important guiding principle about ACC function is that cognitive and emotional information is processed



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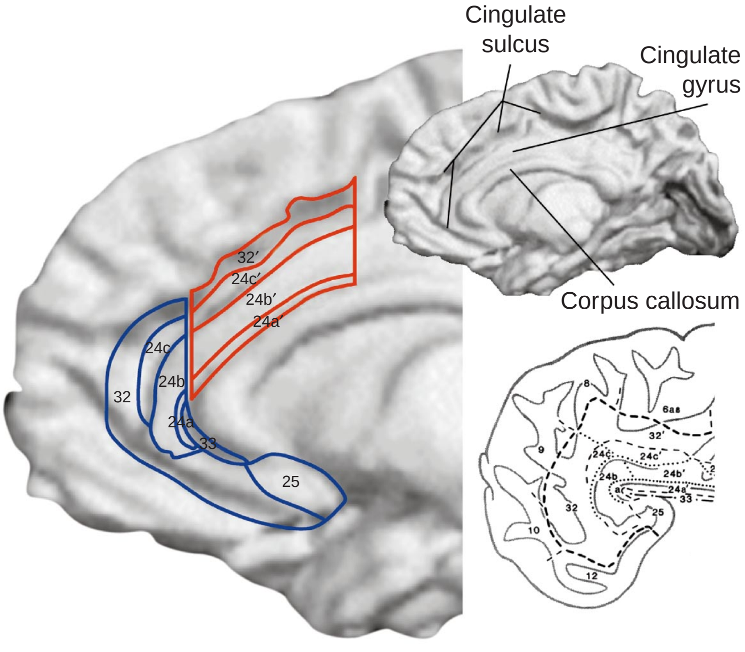

Fig. 1. Anterior cingulate cortex (ACC) anatomy. The upper right part of the figure contains a reconstructed MRI of the medial surface of the right hemisphere of a single human brain (anterior towards the left, posterior towards the right). The cortical surface has been 'partially inflated' to allow simultaneous viewing of gyri and sulci. In this example, a single cingulate gyrus lies between the cingulate sulcus and the corpus callosum. A schematic representation of cytoarchitectural areas (numbered) of ACC is shown on the enlarged section (left). Cognitive division areas are outlined in red and affective division areas are outlined in blue. These simplified localizations are only approximations for illustrative purposes. A schematized flat map of actual anterior cingulate cortical areas is shown in the bottom right panel. The borders of each sulcus appear as thin unbroken black lines, whereas a combination of broken and dotted lines outline cingulate areas. (Adapted, with permission, from Ref. 7.)

separately. Its two major subdivisions subserve distinct functions. These include a dorsal cognitive division (ACcd; areas 24b′-c′ and 32′) and a rostral–ventral affective division (ACad; rostral areas 24a–c and 32, and ventral areas 25 and 33). It has been observed that these two sub-territories are distinguishable, based on convergent data from cytoarchitectural, lesion and electrophysiology studies, combined with a knowledge of differential connectivity patterns and a limited number of imaging studies[5,6].

Lesions of ACC have produced a host of symptoms, which include apathy, inattention, dysregulation of autonomic functions, akinetic mutism and emotional instability[8–10]. Indeed, even earlier evidence of behavioral and physiological changes produced by callosal tumors encroaching upon ACC was used by Papez to argue for the role of cingulate cortex in emotional experience[11]. In humans, lesions of ACC for the treatment of affective disorders produce striking personality changes, including lack of distress and emotional liability[10], which parallels the results of ACC lesions in cats reported by Kennard[8]. Later observations and experiments have essentially confirmed much of the earlier findings of inattention and akinetic states[12]. Some reports have also suggested specific cognitive deficits in Stroop interference, although the strength and transience of these deficits are controversial[12,13].

Imaging studies

Functional neuroimaging techniques, which include PET and fMRI, have provided invaluable insights into the roles that ACC has in cognitive and emotional processing. The cognitive subdivision is part of a distributed attentional network. It maintains strong reciprocal interconnections with lateral prefrontal cortex (BA 46/9), parietal cortex (BA 7), and premotor and supplementary motor areas[6]. Various functions have been ascribed to the ACcd, including modulation of attention or executive functions by influencing sensory or response selection (or both); monitoring competition, complex motor control, motivation, novelty, error detection and working memory; and anticipation of cognitively demanding tasks (see Refs 1,3,5,6,14–17 for reviews).

The affective subdivision, by contrast, is connected to the amygdala, periaqueductal gray, nucleus accumbens, hypothalamus, anterior insula, hippocampus and orbitofrontal cortex[6], and has outflow to autonomic, visceromotor and endocrine systems. The ACad is primarily involved in assessing the salience of emotional and motivational information and the regulation of emotional responses[5,6,15,18].

Meta-analyses of brain-mapping studies of cognitive and emotional tasks strongly support this functional delineation of ACC into cognitive and affective subdivisions. Although other meta-analyses of cognitive–motor tasks by Picard and Strick[16], and Bush *et al.*[17] did not include studies that involved processing of emotional information, the fact that the ACC activations reported by these authors were clustered in the dorsal ACcd further supports the cognitive versus affective distinction.

Figure 2 extends the work of these four prior meta-analyses[3,15–17]. It includes all functional neuroimaging studies in the cited studies, together with data from 10 additional recent studies. Together, this represents 132 data points from 64 studies. Activations (blood flow/fMRI signal increases) and deactivations (blood flow/fMRI signal decreases) are depicted separately (Fig. 2a and b, respectively). The reciprocal nature of increases and decreases in the cognitive and affective divisions are both interesting and informative.

The cognitive division (ACcd) has been activated (Fig. 2a) by cognitively demanding tasks that involve stimulus–response selection in the face of competing streams of information, including Color Stroop and Stroop-like tasks, divided-attention tasks, verbal- and motor-response selection tasks and many working-memory tasks.

The affective division (ACad) has been activated (Fig. 2a) by affect-related tasks, including studies of emotional processing in normal healthy volunteers and symptom provocation studies in a number of psychiatric disorders (anxiety, simple phobia and obsessive–compulsive disorder). It has also been activated repeatedly by induced sadness in normal subjects and in individuals with major depression. Notably, a direct comparison of two versions of the Counting Stroop task (one involving cognitive interference, the other emotional words) activated the two ACC subdivisions differentially (see Box 1).

Although brain-mapping studies report activations (increased blood flow) much more frequently than deactivations (decreased blood flow), a review of deactivations (Fig. 2b) also supports the cognitive- versus affective-division distinction. As discussed in greater depth by Drevets and Raichle,

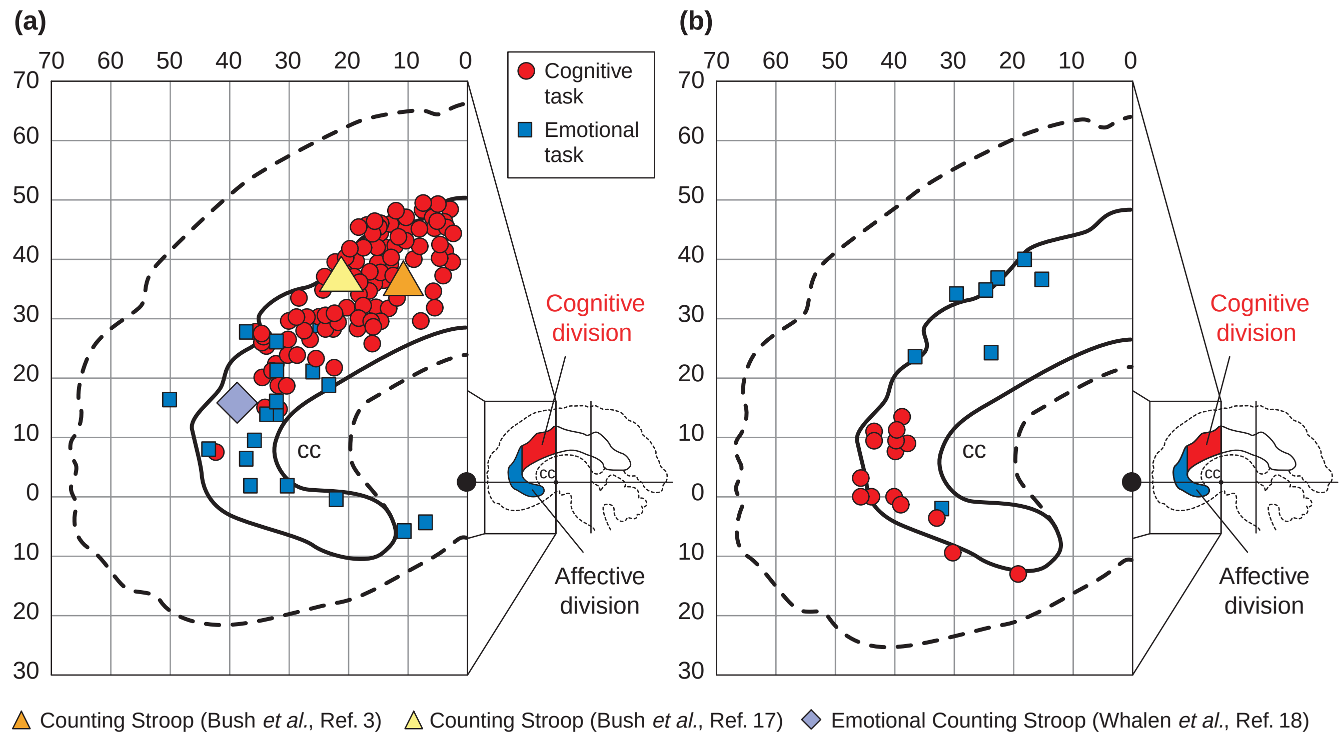

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Fig. 2. Meta-analysis of activations and deactivations during cognitive and emotional studies. Activations **(a)** and deactivations **(b)** are shown in 2-D spatial coordinates**.** The cognitive division is activated by Stroop and Stroop-like tasks divided attention tasks, and complex response selection tasks. It is deactivated (i.e. shows reduced blood flow or MR signal) by emotional tasks. The affective division is activated by tasks that relate to affective or emotional content, or symptom provocation. It is deactivated by cognitively demanding tasks. A direct comparison within the same subjects supports the cognitive versus affective distinction. The orange triangle indicates the activation of the cognitive division during the cognitive Counting Stroop[3]. The same group of subjects activated the affective division (blue diamond) while performing the Emotional Counting Stroop[18]. Although matched normal controls activated the cognitive division during the Counting Stroop (yellow triangle), subjects with attention-deficit/hyperactivity disorder failed to activate the region[17]. Abbreviation: CC, corpus callosum.

reciprocal suppression of the affective subdivision during cognitive tasks (and vice versa) is often observed[15]. For example, two groups of normal subjects performing the cognitively demanding Counting Stroop task[3,17] showed increased fMRI signal in the cognitive subdivision. The same groups also showed decreased fMRI signal in the affective subdivision when comparing the cognitively demanding neutral task to fixation. Similarly, the same subjects who had shown activation of the affective subdivision during the Emotional Counting Stroop showed deactivation of the same area when contrasting the cognitively demanding neutral part of that task to fixation[17]. Drevets and Raichle cite numerous examples of deactivation of the affective subdivision during the performance of divided attention, antisaccade, working memory, sequence learning and visuospatial tasks.

Reciprocal suppression of the cognitive subdivision during intense emotional states has also been observed (Fig. 2b). Individuals with severe depression[19,20], and normal subjects anticipating pain[15] and experiencing film-induced emotion[21] all showed deactivation of the cognitive subdivision.

Behavioral studies suggest that emotion and cognition might also interact in other ways. For example, it has recently been argued that Stroop interference can be modulated by positive affect[22] and positive affect has been shown to have lasting effects on later decision making[23]. Combining functional imaging, anatomical and behavioral methods will be important for understanding the interaction between cognition and emotion.

Electrical studies of error monitoring

Recent electrophysiological studies using event-related potentials (ERPs) have shown that when subjects make an erroneous response in a behavioral task there is a negative deflection in the stimulus- and response-locked ERP (Refs 24,25) called the error-related negativity (ERN)[25]. The ERN is sharper and clearer in the response-locked averages and has a centromedial scalp distribution. Its onset is simultaneous with the erroneous response and peaks approximately 100 ms after response onset (see Fig. 3a).

Source localization algorithms designed to identify the neural generators of scalp-recorded ERP (Ref. 26) indicate a location in the midline prefrontal cortex. A generator in the vicinity of ACC can account for the appearance of the ERN as recorded from the scalp. Animal studies of error processing are consistent with this dipole model of the ERN. Cortical depth recordings in behaving monkeys have shown that there are cells within ACC that increase firing (with a time course similar to the scalp-recorded ERN) when the animal makes an erroneous response (see Box 2 for additional animal studies).

Initial studies attempted to clarify the nature of the cognitive process indexed by the ERN. Bernstein compared the ERN amplitude of similar and dissimilar stimuli, and found that they did not differ[27]. However, the amplitude of the ERN was larger for similar response representations than it was for dissimilar response representations. Thus, it was argued that the ERN reflects a process that compares a representation of a correct response with the actual response. Additional

Box 1. Separating cognition and emotion in ACC

Convergent evidence from cytoarchitectural, connection, electrophysiology and lesion studies, together with earlier versions of the imaging meta-analysis data, certainly suggested that separable cognitive and affective divisions of anterior cingulate cortex exist.

To test this hypothesized dichotomy directly, two Stroop-like interference tasks with differing causes of interference (i.e. one cognitive and one affective) were validated in fMRI studies run with the same subjects during the same scanning session. During the cognitive version of this task, sets of up to four vertically tiled words appeared on the screen every 1500 ms. Subjects were instructed to report by button press the number of words in each set, regardless of their meaning. Neutral trials contained single semantic category common animals (e.g. 'dog' written three times). Interference trials contained number words that were incongruent with the correct response (e.g. 'three' written four times). In contrast, during the interference portion of the Emotional Counting Stroop, emotionally valenced words were substituted for the number words (e.g. 'murder' written four times). In addition, a different set of emotionally neutral words was used for comparison. Nine normal adult volunteers participated.

As predicted (and shown in Fig. I), the cognitive version of the Counting Stroop activated the cognitive subdivision, and the Emotional Counting Stroop activated the affective subdivision. Taken together, these results confirm that manipulating the type of information being processed can recruit activity selectively in different regions of anterior cingulate cortex. Specifically, processing of cognitive information enhances activity in the cognitive division and processing of affectively valenced information enhances activity in the affective region. In keeping with the reciprocal suppression model (Refs c,d), the cognitively demanding neutral parts of both tasks (i.e. those involving word reading, word counting, response selection and button pressing) both produced fMRI signal decreases in the affective subdivision (when compared with fixation).

Many important components of the limbic system (anterior cingulate affective division, orbitofrontal cortex, amygdala and insular cortex) were suppressed (or biased against) during the cognitively demanding neutral portions of the Counting Stroop tasks. Notably, in a meta-analysis of common blood flow decreases during nine visual tasks using a different imaging modality (PET), Shulman *et al.* reported decreases in these same areas (Ref. e). This supports the conclusion that the observed fMRI signal decreases were veridical, as PET is immune to the susceptibility artifacts that might potentially interfere with fMRI measures at the base of the brain. The fact that the affective division of ACC was suppressed, together with other elements of 'emotional circuitry', during the neutral part of the task and, conversely, was the only one of these areas to show significant activation during the interference part of the task suggests that it might have a special role in emotional processing of more complex stimuli (i.e. evaluation of the emotional valence of words).

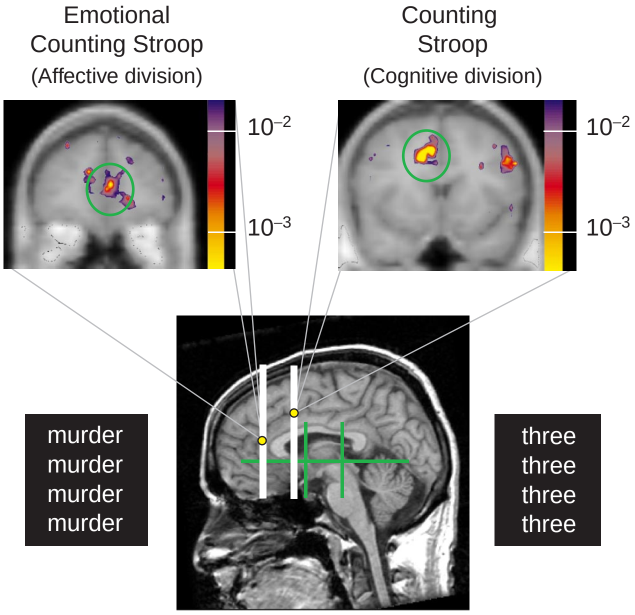

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Fig. I. Emotional and Cognitive Counting Stroops modulate different anterior cingulate cortex (ACC) divisions. In companion studies performed using the same group of young adult subjects during the same scanning session, the Emotional Counting Stroop activated the affective division (Ref. a), whereas the cognitive version of the Counting Stroop activated the cognitive division (Ref. b). Examples of the interference portions of the two tasks are displayed beneath the scan data (for example, the correct answer would be to press button number '4' to indicate four items in the display).

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evidence shows that the ERN reflects the functioning of an error detection system and not a system that is responsible for error correction or inhibition of the erroneous response[28].

However the ERN also has been found to have an affective–motivational dimension. The effects of motivation on the process of error detection can be readily observed when accuracy on a task is emphasized over speed. In this situation, the ERN amplitude for accuracy instructions is significantly bigger than the amplitudes of the ERN under speed conditions[25]. More-recent evidence on the relationship between motivation and the ERN comes from studies of variations in human emotions and motivations. Gehring *et al.* showed that the ERN was larger in individuals with obsessive–compulsive disorders than in matched controls[29]. Furthermore, these authors found that the amplitude of the ERN was associated with symptom severity. Dikman and Allen found that subjects who scored low on a scale that measured socialization showed smaller ERN amplitudes in conditions under which they were punished for errors than in conditions under which they were not rewarded because of an incorrect response[30].

A recent study examined the relationship between the ERN and the personality and affective dimensions of distress, known as negative emotionality and negative affect. It was found that in the initial stages of the experiment, ERN amplitudes were larger in high negative-emotionality and affect subjects than in low negative emotionality and affect subjects[31]. However, as the experiment progressed, the high negative emotionality and affect subjects became less involved

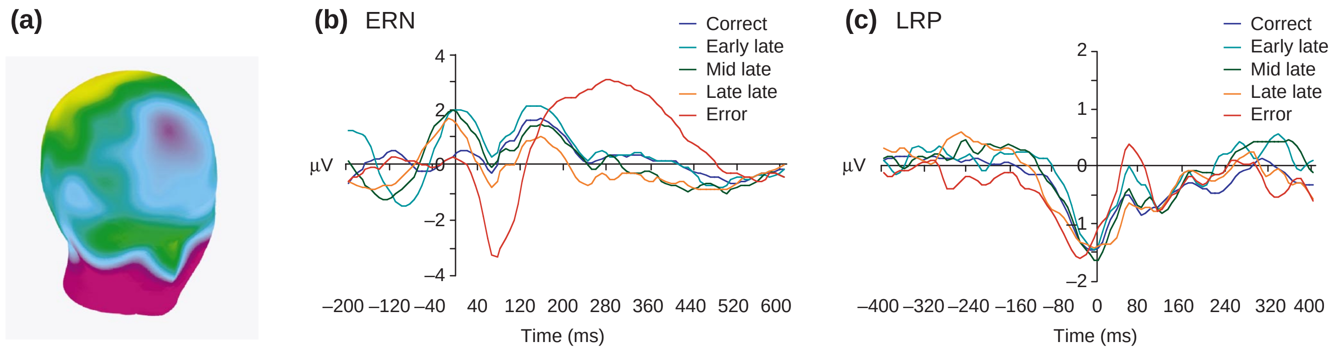

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Fig. 3. Electrical studies of error-related negativity (ERN). (a) Scalp distribution of the error related negativity (the purple area shows the center of scalp negativity following an error). **(b)** Electrical tracing showing that errors produce the largest ERN, but later responses, owing to strong conflict, produce some ERN. **(c)** The lateralized readiness potential (LRP) before emission of the response already shows differences related to how late the response will be[4].

and, accordingly, their ERN amplitudes decreased. One way of synthesizing the results from several studies that show the influence of affect and motivation on the amplitude of the ERN is to invoke a dimension of distress. The idea is that affective evaluation occurs during error detection and this evaluation varies along a continuum related to the distress of making an error.

Developmental studies

Although the cingulate cortex is an ancient structure, there is evidence that it has undergone changes in recent evolution[32]. There is no doubt that cingulate cortex, like other frontal areas, undergoes a long developmental process. Conel has shown extensive development of the connectivity of cingulate cortex from infancy to late childhood[33]. However, few studies to date have related these changes to behavior.

During later childhood, neuroimaging methods can be applied. In one study of 5- to 16-year-old children (see Fig. 4), a significant correlation was found between the volume of the area of the right ACC and the ability to perform a go/no-go task. The go/no-go task requires inhibiting a prepotent response, which is similar to tasks found to activate the ACC in adults[34]. There was no significant correlation between ACC activation and reaction time in a task involving no inhibitory control. In an fMRI study, performance of children aged seven to twelve and of adults was studied in a go/no-go task. In comparison with a control condition, in which children responded to all stimuli, the condition that required inhibitory control activated prefrontal cortex in both children and adults, and the number of false alarms in this condition correlated significantly with the extent of cingulate activity[35] (see Fig. 4). This finding agrees with the error detection data obtained from electrical recording studies (see, for example, Refs 25,26).

Posner and Rothbart have speculated on the relationship between several behavioral findings in infants[36] and young children, and maturation of the ACC (Ref. 37). During early infancy, signs of distress (including crying) can be blocked temporarily by orienting of attention to an interesting object[36,37]. This finding could be related to the findings discussed above concerning the reciprocal relationship between the ACC cognitive and emotional subdivisions.

Other evidence to indicate that developmental changes are involved in the ability to control conflict comes from a study using Stroop-like conflict tasks adapted for children[38,39].

Box 2. Animal studies

Animal studies of anterior cingulate cortex functioning demonstrate consistencies with the blood flow and electrical neuroimaging studies in humans, and might provide valuable clues for integrating the various findings that implicate anterior cingulate cortex in the regulation of adaptive behavior, such as learning.

Similar to the findings in humans, animal research has shown that the anterior cingulate cortex is part of a larger network that might be involved in the early stages of learning where effort and flexibility are important control parameters. It has been shown that lesions to the anterior cingulate cortex affect the early stages of learning (Refs a,b) (e.g. animals take longer to achieve above chance level performance but not in achieving higher levels of accuracy). These findings are similar to the animal studies showing the relationship between anterior cingulate cortex and non-reinforced error responses. In these studies, the error potentials recorded in the anterior cingulate cortex are observed in the early stages of learning, when the animal is gaining insight into the nature of the task (Refs c,d). After achieving an accuracy rate between 60 and 70%, the error potentials are no longer apparent.

Gabriel (Ref. c) has outlined a model of how the early learning supported by the anterior cingulate cortex supports a more general start and stop system (made up of the anterior and posterior cingulate, subiculum, anterior ventral and mediodorsal nucleus of the thalamus) involved in conditioned response learning. In addition to being part of the start and stop system, the anterior cingulate cortex demonstrate other interesting functional characteristics. First, it is sensitive to reversal training. Second, it appears to be able to weigh the duration of the conditioned stimulus. Finally, it is sensitive to the probabilistic occurrence of the condition stimulus.

In summary, evidence from animal studies might provide the necessary information to integrate data from the human neuroimaging studies. For example, it could provide a way to understand the host of frontal midline potentials observed in the ERP literature, such as the NOGO N2 (a mediofrontal component seen after successful witholding of a response, i.e. negative wave peaking at about 300 ms), ERN (error-related negativity is seen as a mediofrontal negativity in response to an error), and P3a (a mediofrontal positivity usually elicited by a novel stimulus approximately 300–400 ms after stimulus onset).

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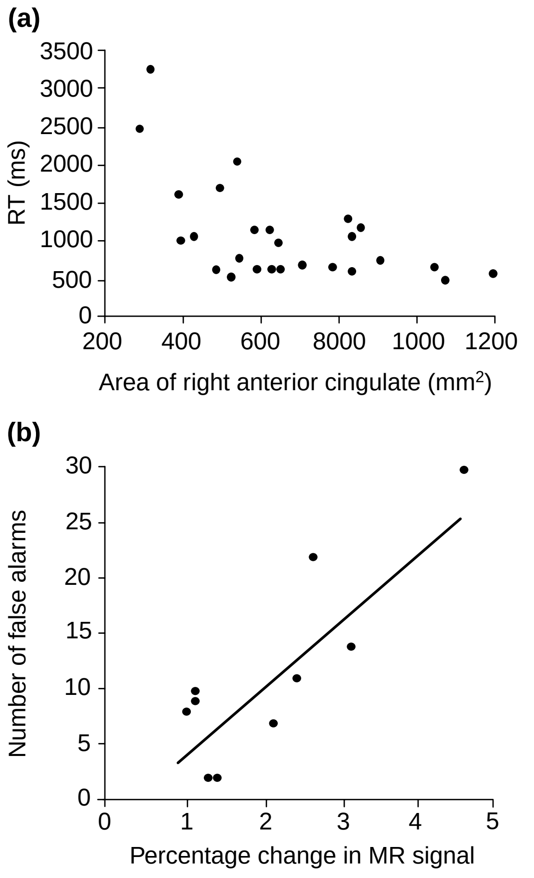

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Fig. 4. Developmental studies of anterior cingulate cortex (ACC). (a) The size of the right anterior cingulate correlates with reaction time (RT) in controlled but not in simple tasks. The study covers an age range of 5–16 years, but the correlation with cingulate size holds constant with age[34]. **(b)** The number of false alarms in a go/no-go controlled RT task is correlated with the amount of cingulate activity[35].

A substantial development of this ability was found between two and five years of age. Children who were relatively less affected by spatial conflict also received higher parental ratings of their ability to control behavior in natural settings (effortful control) and higher scores on laboratory measures of inhibitory control[39]. Although there are no imaging studies that relate these changes in behavior to ACC maturation directly, it seems reasonable to suppose, on the basis of Fig. 2, that conflict tasks would activate this area in children as they do in adults.

Functional theories

Before attempting to synthesize and integrate existing theories, it is important to emphasize that ACC does not act in a vacuum. Many researchers have identified ACC as an important component of parallel distributed attentional[40–43] and emotional[5,6] networks. Imaging studies have begun to provide a basis for exploring frontal networks involved in effortful control[44]. These studies suggest that both dorsal ACC and areas of the lateral prefrontal cortex operate together during tasks that involve high levels of mental effort. It has been proposed that medial and lateral frontal areas act in concert to exert a common influence during many diverse mental processes[44,45]. However, neuroimaging studies of orienting of attention to visual stimuli show that within the large-scale distributed network found to orchestrate shifts of attention, each specific area has a different role[46]. We expect that a similar story will eventually emerge with respect to the lateral and medial frontal structures involved in focal attention.

We now give a brief commentary on several theories that specify ACC function, often in combination with other brain areas. For each, we will attempt to emphasize major strengths and identify weaknesses or shortcomings. Of the proposals that have been made regarding the roles ACC has in cognitive processes and motor control, none has support in the current data as a unifying theory of ACC function. At the end of the article, however, we place each in the context of the larger framework outlined at the start.

One view that seeks to relate medial and lateral frontal areas suggests that lateral areas are involved as holding circuits in which domain-specific activity is represented while it is acted upon by midline circuits. This would fit with the role of lateral frontal cortex in working memory[47]. Consider, for example, generating the use of a noun (e.g. given ‘scissors’, answer ‘cut’). The word name might have to be held in a system during the process of evaluating candidate uses. Focal attention would include both the representation of the input (lateral frontal) and the control operations that would co-activate areas of semantic memory where associated concepts might be stored. Although such cingulo–frontal interactions are, no doubt, important in many processes, this theory does not address directly the mechanism by which cingulate cortex might act within the network.

A different idea about how lateral and medial frontal areas interact centers on the hypothesis that there are separate ‘automated’ and ‘attended’ routes to output, and that a switch in response pathways occurs when the same response is practised several times[48]. In processing words, the anterior insula represents a more-automated pathway to word output. The insula is active in reading aloud and in generating uses when the association has been practised recently. ACC, by contrast, is part of a pathway used when effortful control is required, for example, when generating the use for the first time. This theory does a valuable service in highlighting the interconnected nature of cingulate cortex with other areas. In addition, data from clinical studies[17] do give it tacit support in that individuals with attention-deficit disorder (who as a group did not activate the cognitive subdivision of ACC during the Counting Stroop) do show strong bilateral activation of anterior insula (potentially compensating for a dysfunctional cingulo–frontal network). However, the narrow focus of this theory on response output does not account for other aspects of cingulate function, such as emotional processing and error detection.

The error detection theory has been discussed at length above, and obviously has a great deal of supporting evidence to indicate that error detection and monitoring is an important function of ACC. However, a single-trial fMRI study showed that the ACcd was active during both error and correct trials[49], a finding that was supported by the ERP study of Luu *et al.*[4]. In addition, the theory would need to be elaborated to deal with evidence of affective processes in error detection. Thus, while the role of ACC in error monitoring demands further study, once again we see it falls short as a unifying theory.

Another approach has been to identify cingulate activation with the type of supervisory or executive attention outlined by Norman and Shallice as a cognitive theory[50].This approach would identify cingulate activation with a wide variety of control operations in handling novel situations, dealing with errors and conflict. However, this view lacks precision and is difficult to use in making predictions despite some efforts to do so[51].

More-precise views have generally emphasized the role of ACC in processing conflict or competition. These views tie together the idea of conflict and error monitoring, in agreement with the data of Figs 2 and 4. Stroop-like and generation tasks that activate the ACC's cognitive division do involve competition. The theory carrying the most explicit statement of this view is the competition monitoring hypothesis[1,51,52]. According to this hypothesis, the cognitive division of the ACC serves to monitor crosstalk or conflict between brain areas, and this computation signals the need for control processes. Lateral areas of the cortex are then activated to provide control operations, which might include increasing or inhibiting neural activity within distinct brain areas so as to eliminate the confusion between modules.

This theory does an admirable job of explaining the results of many studies that activate the cognitive division, and in setting forth empirically testable predictions. However, it also leaves some puzzles. As an inherently stimulus-driven or 'bottom-up' theory (which maintains that the role of ACC is to detect and report competition within response channels), the monitoring view has difficulty in dealing with the anticipatory nature of cingulate activity in many tasks[53,54] (in which ACC activation is obtained after task instructions are given but long before any stimulus is presented), and with findings that cingulate activity can come very early in the processing sequence[55]. It is also curious that the cognitive division of the ACC is activated above baseline in the absence of conflicting information (e.g. during the display of congruent information in both the Color Stroop Task[56,57] and the Eriksen Flanker Task[51], as well as during simple speeded response tasks[58]). The monitoring view has trouble explaining cingulate activity involved in processing error feedback[59] and with the finding that ERN amplitude can be independent of the degree of prior response competition[4].

Although it does not put forward a mechanistic theory, the work of Paus and colleagues[60] is illuminating. Based on a review of PET studies, they concluded that increases in task difficulty and the inclusion of a remote memory component leads to increased ACC activity. Furthermore, they discuss evidence suggesting that somatopic differences exist (i.e. findings that manual responses tend to be located in caudal portions of ACC, which are in line with work cited above[16,58]).

None of the above-mentioned theories could qualify as a unifying theory of ACC function as none accounts for the observed separateness of its cognitive and emotional subdivisions. In fact, the main reason the final section on theories concentrated on the cognitive division is that researchers are just beginning to undertake investigations that attempt to establish a specific role for the affective division within emotional brain circuitry. As discussed in Box 1, the affective division of the ACC displayed an interesting unique response pattern during the Emotional Counting Stroop: its activity decreased (in concert with other limbic areas) during cognitive information processing, but uniquely increased during the display of emotionally valenced words. Future research might seek to build upon these findings and those of the meta-analysis to extend our understanding of the specific role ACad has in emotional processing.

Several of the theories we have discussed provide ideas about how to break down executive attention or emotional processes into components and preserve the general approach to studying brain activity in which specific anatomical locations are related to mental operations. These efforts fit into the framework outlined at the beginning: cingulate cortex is a network that integrates input from various sources and contributes to the modulation of processing in other brain regions. The challenges ahead lie in determining both the specific roles the individual subdivisions have in cognitive and emotional processing, and in elucidating how the subdivisions interact with one another (and other brain areas) to guide human perception and behavior.

Outstanding questions

- What is the nature of the interaction between lateral prefrontal cortical areas and the various subdivisions of the cingulate cortex?
- What types of interaction between cognitive and emotional processes are possible? Do they always work by mutual inhibition?
- Does the ERN that follows an error and the ERN that follows feedback come from the same or different areas of the cingulate, and how do their locations relate to the cognitive and emotional subdivisions?
- When do the cognitive and emotional functions of the cingulate develop in childhood and does the development of one depend upon the other?
- Are the monitoring and control functions related to the role of the cingulate in cognitive regulation truly separate?

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