PAIN AND EMOTION INTERACTIONS IN SUBREGIONS OF THE CINGULATE GYRUS

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Abstract | Acute pain and emotion are processed in two forebrain networks, and the cingulate cortex is involved in both. Although Brodmann's cingulate gyrus had two divisions and was not based on any functional criteria, functional imaging studies still use this model. However, recent cytoarchitectural studies of the cingulate gyrus support a four-region model, with subregions, that is based on connections and qualitatively unique functions. Although the activity evoked by pain and emotion has been widely reported, some view them as emergent products of the brain rather than of small aggregates of neurons. Here, we assess pain and emotion in each cingulate subregion, and assess whether pain is co-localized with negative affect. Amazingly, these activation patterns do not simply overlap.

Pain is evoked by noxious body stimulation or through negative emotional events and memories. To understand pain we need to consider how and where it affects the brain. In previous decades the emphasis was on pain 'sensation', which involves assessing the location and intensity of noxious stimuli. However, somatosensory localization and intensity coding are not necessarily linked with emotional responses if they are processed in different parts of the brain . Moreover, the linkage of pain and its affective (autonomic) substrates in the brain was not a viable research target until functional imaging allowed conscious reporting by human subjects to be related to changes in the brain during noxious stimulation. Imaging psychophysics allows brain changes to be correlated with sensory stimulation parameters. In terms of pain, this means that modulating the level of unpleasantness might provide insight into the substrate of affect.

Just as important, and carried out in parallel during the past decade, are a series of studies on the emotional modulation of brain circuits, which was assessed using scripts, faces or films with emotional or non-emotional content. These provided control conditions and reports from participants — which were not previously possible in experimental animals — as well as methods of relating emotion to specific brain circuits. The value of human functional imaging is apparent in studies of the amygdala during fear conditioning. An integrated study of the nociceptive connections, emotional activation and behavioural conditioning has provided important insights into the sensory inputs to the amygdala and its projections to the networks that are generally termed the emotional motor systems. This has been pivotal to driving new research paradigms[1,2]. Despite the wealth of information about the amygdalar substrates of emotion, this mechanistic approach must be broadened to investigate the great expanse of the limbic cortex that is presumed to subserve many painful and emotional functions and diseases.

One of two views guide investigators in their analysis of the cerebral mechanisms of pain and emotion. The global model posits that most of the cerebral cortex is involved, in some way, in emotion, and that perceptions that are associated with emotional experiences are an emergent property of the brain. Although many parts of the brain contribute to emotion, each area does not necessarily make an equal contribution.

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The alternative view is that some areas store memories with positive or negative valences and drive associated autonomic outputs, whereas other areas provide sensory and short-term memory substrates that are not specific to emotion, and cannot access autonomic outputs. Systems involved in all short-term memory, including, for example, emotional memory, are not emotion-specific processors. Although the circuits that engage the cingulate cortex in pain processing have long been known, we are only now in a position to link specific aspects of pain perception with its localized emotional substrates, which was not possible without human functional imaging.

The two-domain pain model and cingulate gyrus

Traditionally, pain processing has been viewed according to two cognitive domains[3]. The sensory-discriminative domain involves stimulus localization and intensity, which can be assessed in a number of ways, including using the visual analogue scale, whereas the affective-motivational domain involves the affective component of pain, which can be measured using ratings of unpleasantness. Before human functional imaging came into general use, the emphasis of research was on sensory-discriminative processing in the somatosensory system, which includes the primary and secondary somatosensory cortices and posterior parietal cortex. With the introduction of positron emission tomography (PET) and functional MRI (fMRI), it has become clear that other telencephalic regions are also engaged during acute noxious stimulation. These include the prefrontal cortex, anterior insula, premotor areas (supplementary and premotor cortices), the cerebellar cortex and the striatum, which are active during acute noxious stimulation[4,5] but do not fit easily into the two-domain model of pain processing.

Most important in the present context is the fact that several limbic structures are activated during noxious stimulation of the body, and these medially-located structures are collectively referred to as the medial pain system. These include the midline and intralaminar thalamic nuclei (MITN), which project to the limbic cortex, the periaqueductal grey, the amygdala and the anterior cingulate cortex (ACC)[6]. In addition, it is possible that the anterior insula lies between the two pain systems and is involved in aspects of processing associated with both, including sensory coding, body state assessment and autonomic regulation. Although the two-domain model might have general utility, noxious stimuli can activate eight to ten areas in the brain, which indicates that there might be more than two domains of pain processing. Indeed, studies of the cingulate cortex indicate that this region might be involved in three aspects of pain processing, which does not fit the two-domain model.

Human functional imaging studies indicate that the ACC might mediate affective responses to noxious stimuli. The extensive studies of MacLean[7] and others support the general idea that the cingulate cortex is a pivotal region for emotion. Interestingly, there are several caveats to the simple proposition that pain and emotion are linked in the cingulate gyrus. So far, most studies of cerebral activation during acute noxious stimulation have not taken into account the fact that the ACC is involved in other functions unrelated to pain, which include coding for the reward properties of particular behaviours[8,9] and activation during romantic love[10]. The 'pain-centred' view seeks to identify pain-specific processing functions and raises many interesting paradoxes about the organization and functions of the cingulate cortex.

First, the effort to identify pain-specific, cingulate processing derives from nociceptive-specific lamina I neurons in the spinal cord, where LABELLED-LINE THEORIES trace pain-specific processing through the mediodorsal thalamic nucleus[11]. Unfortunately, these connections have not been demonstrated experimentally, and their specificity to any part of the cingulate cortex has never been shown. This is because many thalamic nuclei project to many parts of the cingulate cortex rather than to a single, nociceptive nucleus. Moreover, there are many thalamic nuclei that provide nociceptive input to the cingulate cortex (see below), and these are not limited to one nucleus, as labelled-line theorists assume.

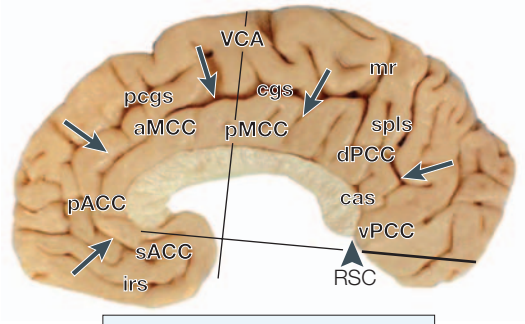
Second, only part of the ACC is involved in emotion. According to electrical stimulation and neuron recording studies, the subgenual part of the ACC (sACC) is involved in autonomic and classical conditioning functions[12,13], whereas activity associated with emotion is not evoked in a region of the posterior ACC (also known as the midcingulate region) that is frequently activated by pain. The question remains: does the entire ACC contribute equally to the affective responses that are associated with pain?

Third, no part of the cingulate cortex is activated only by noxious stimulation, although there could be small aggregates of purely nociceptive neurons[14] that might respond under other, as yet untested, cognitive conditions. In addition, it does not seem that a cingulate region, subregion or area is engaged only by noxious stimulation; that is, no cingulate region or area appears to be nociception specific. So, what is the relationship between pain and affect with regard to autonomic regulation, and pain in relation to premotor planning and motor output? The answers to these questions derive from the four-region model of the cingulate gyrus.

New approach to cingulate pain and emotion

Studies of the role of the cingulate cortex in nociception should not be based on labelled-line theories, particularly as, so far, no pain-only processing inputs or areas have been identified. Rather than asking where pain processing occurs, we apply a new logic by considering what the structural and functional organization of the cingulate gyrus is and how nociceptive signals are used in the cingulate cortex to accomplish behavioural goals, such as avoiding noxious stimuli. This approach requires a multidisciplinary view of the functions of the cingulate cortex for both monkey and human brains[15,16]. FIGURE 1

LABELLED-LINE THEORIES
These predict that a line or projection from lamina I of the spinal cord is specific for nociceptive stimulation and that this line is maintained throughout the CNS; that is, through the thalamus and directly to parts of the cerebral cortex. There is no evidence for a labelled line in the cingulate gyrus.



ACC: emotion
- sACC, visceral integration

MCC: response selection
- aMCC, fear-avoidance
- pMCC, skeletomotor orientation

PCC: personal orientation
- dPCC, visuospatial orientation
- vPCC, self-relevance assessment

RSC: memory formation/access

Figure 1 | **Distribution of the four cingulate regions and subregions.** Region borders are marked with arrows and were determined in this and six other postmortem cases that were coregistered to a stereotaxic atlas with the vertical plane at the anterior commissure (VCA) and the anterior–posterior commissural line. A functional overview, derived from the analysis of a large volume of literature, is provided. This illustrates general regional function and, where known, subregional specializations. aMCC, anterior midcingulate cortex; cas, callosal sulcus; cgs, cingulate sulcus; dPCC, dorsal posterior cingulate cortex; irs, inferior rostral sulcus; mr, marginal ramus of cgs; pACC, pregenual anterior cingulate cortex; pcgs, paracingulate sulcus; pMCC, posterior midcingulate cortex; RSC, retrosplenial cortex; sACC, subgenual anterior cingulate cortex; spls, splenial sulci; vPCC, ventral posterior cingulate cortex.

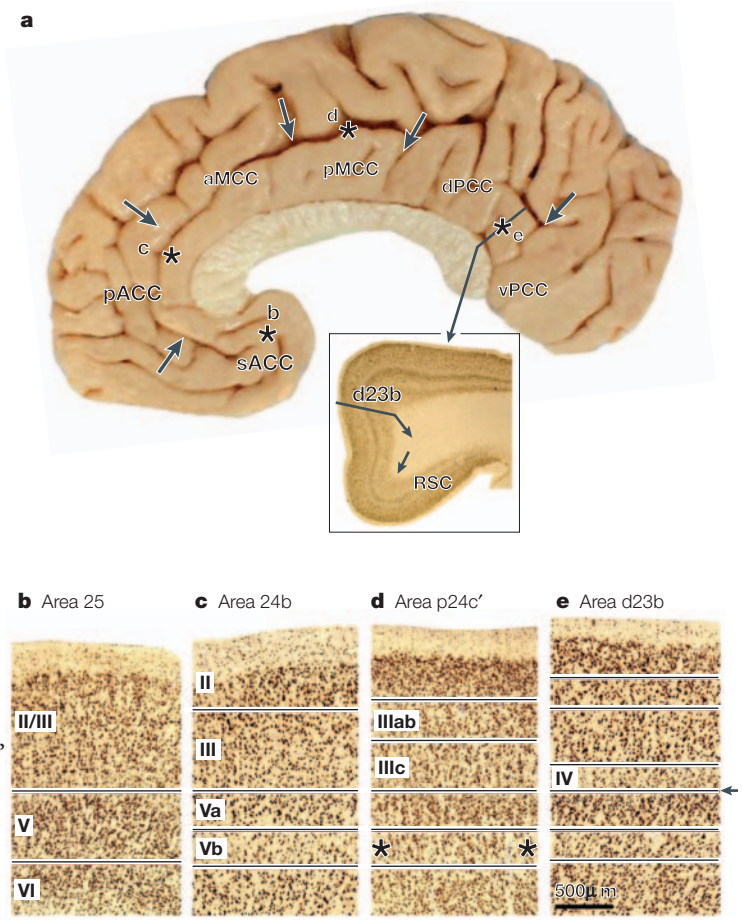
summarizes the four regions and their subregions that have emerged from integrated neurobiological assessments. A cortical region is an aggregate of areas that have a similar underlying cytoarchitectural motif, and common circuitry and functions. These regions and their subdivisions are the ACC (s, subgenual; p, pregenual), the midcingulate cortex (MCC; a, anterior; p, posterior), the posterior cingulate cortex (PCC; d, dorsal; v, ventral), and the retrosplenial cortex (RSC) on the ventral bank of the posterior cingulate gyrus that is not exposed on the gyral surface. The borders of each region were defined with cytoarchitectural analyses of postmortem cases and then coregistered to the Talairach and Tournoux stereotaxic atlas in the human[17] and the vertical plane at the anterior commissure (VCA) in the monkey[18]. The cellular organization of each area implies differential functions that are still not understood. For example, the presence of a layer IV provides for an intracortical stage of processing in areas 23 and 31 that is not present in areas 25, 24, or 24′. BOX 1 documents the cytological basis of the four-region model by showing key neuronal and laminar differences between each region, using an antibody for neuron-specific nuclear-binding protein (NeuN).

In terms of a neurobiological model, the organization of the cingulate gyrus does not simply reflect locations in a three-dimensional coordinate system. As discussed previously, the regions reflect circuitry and functional organization[15–17]. Indeed, the four-region model predicts the outcomes of information processing in the cingulate gyrus, and the following facts are of particular relevance. The ACC is involved in autonomic control and the storage of emotional memories. However, each region is not uniform, because particular connections that alter processing can result in different subfunctions within different regions. Although a considerable volume of literature documents the role of the ACC in autonomic regulation and emotion[12,13], one of the first human imaging studies on this subject showed that the sACC subregion is involved in negatively valenced affect in healthy women[19]. A review of human imaging studies in the context of the four-region model showed prominent brain activation during both sad and happy emotions. The sACC is activated during sad events; whereas when individuals experience happy emotions, the pregenual ACC (pACC)[17], which is located in a rostral position in the ACC, is activated. In terms of pain processing, a pain response has been shown in the pACC with magnetoencephalography (MEG), and might be associated with C-fibre activation and the 'suffering' component of pain[20]. Finally, subgenual area 25 has many autonomic projections — including those to the central nucleus of the amygdala, parabrachial nucleus and periaqueductal grey — and light projections to the nucleus of the solitary tract and dorsal motor nucleus have been reported[12]. These autonomic projections and emotion functions ensure that this region is qualitatively distinct from the cortex dorsal to the corpus callosum.

The MCC is involved in response selection and has two separate cingulate motor areas that project to the spinal cord and motor cortices[21,22]. This region, and the cortex dorsal to it, can be engaged in cognitive tasks that do not necessarily require movement and decisions, and that are based on the reward value of particular behavioural outcomes[8,23]. In terms of premotor functions, parts of the MCC might have little or nothing to do with pain sensation *per se*. Büchel *et al.*[24] used high resolution fMRI to show that caudal parts of the aMCC are separately activated by innocuous and noxious activity, and might be related to a third site for cognitive processing other than nociception and intensity ratings. Finally, the PCC is involved in visuospatial orientation that is mediated through its extensive parietal lobe connections and assessment of self-relevant sensation. The dorsal part of the PCC (dPCC) might be involved in orienting the body toward innocuous and noxious somatosensory stimuli, and might share some functions with the pMCC. Although the RSC is poorly understood, it seems to have a role in memory access, particularly for valenced information, and probably contributes to the functions of the PCC through its substantial connections with area 23.

Box 1 | **Cytoarchitectural bases of cingulate gyrus regions**

A region comprises a number of areas with a common circuitry and information processing activity (panel **a**). For example, the anterior cingulate cortex (ACC) is a region that regulates autonomic motor function and has extensive interactions with the amygdala, and the midcingulate cortex (MCC) is a region that projects to the spinal cord and regulates skeletomotor function. In addition, there are subregions with specialized connections and functions — for instance, the subgenual subregion of the ACC (sACC) stores negatively valenced memories and interacts with the central nucleus of the amygdala, whereas the pregenual region (pACC) is engaged in positively valenced events and is more heavily connected with the lateral basal and accessory basal nuclei of the amygdala. The MCC has an anterior part (aMCC), which contains the rostral cingulate motor area and interacts with the amygdala, and a posterior part (pMCC), which contains the caudal cingulate motor area and interacts with the posterior parietal cortex. Pivotal to the regional and subregional organization is the topography of cytologically unique areas.



This postmortem cingulate gyrus was cut in the coronal plane and an example section is shown through the posterior cingulate gyrus, in which the ventral bank is comprised of retrosplenial cortex (RSC) dorsal to the corpus callosum (inset in panel **a**). The section was labelled with a neuron-specific nuclear-binding protein. No glia or vascular elements were stained, which ensures that only neuronal architecture is considered when analysing an area. In the inset, the short arrow indicates the border between the RSC and area 23 above it, whereas the long arrow represents the section level for area d23b and the arrow points to the section shown in panel **e**.

A sample from one area of each region is shown (asterisks at **b**–**e**) and they are aligned at the top of layer Va (as indicated by the arrow). As the architecture differentiates in the rostrocaudal direction, samples are shown in this sequence and emphasize the progressive laminar differentiation. The laminar designations (I–VI) are placed at the points at which each layer is first differentiable, and it continues, from (**b**) to (**e**), without labels. Area 25 is the least differentiated, with layers II/III, V and VI (panel **b**). Area 24b (panel **c**) has clearly defined layers II and III, and layer V is differentiated into 'a' and 'b' divisions. These laminar differences are based on the size, shape and density of neurons in each layer. Area 24′ (panel **d**), which is sampled in the cingulate sulcus at area p24c′, has two crucial differentiations — layer III contains a deep 'c' division of large pyramidal neurons, and layer Vb (between the asterisks) is quite dense with large pyramidal neurons, many of which project to the spinal cord. Area d23b (panel **e**) has a prominent layer IV, a thick layer IIIc, and the neurons in layer Va are densely packed, as are those in area p24c′. aMCC, anterior MCC; dPCC, dorsal posterior cingulate cortex; pMCC, posterior MCC; vPCC, ventral PCC.

Nociceptive neurons and aggregate responses

Noxious somatic stimuli provoke pain and avoidance behaviours, which are impaired in humans[25] and experimental animals[26] that have lesions of the cingulate gyrus. Moreover, destruction of the somatosensory cortex greatly impairs stimulus localization without altering pain affect; presumably because the medial pain system, including the cingulate cortex, remains intact[27]. Based on neurosurgical outcomes and connections with the MITN[28], we studied neuron discharge properties in relation to noxious stimulation in the halothane-anaesthetized rabbit preparation[14]. Our findings are summarized in FIG. 2 and demonstrate the following essential facts. First, neurons in the ACC do not recognize where on the body surface a noxious stimulus is located, because stimulation anywhere on their body

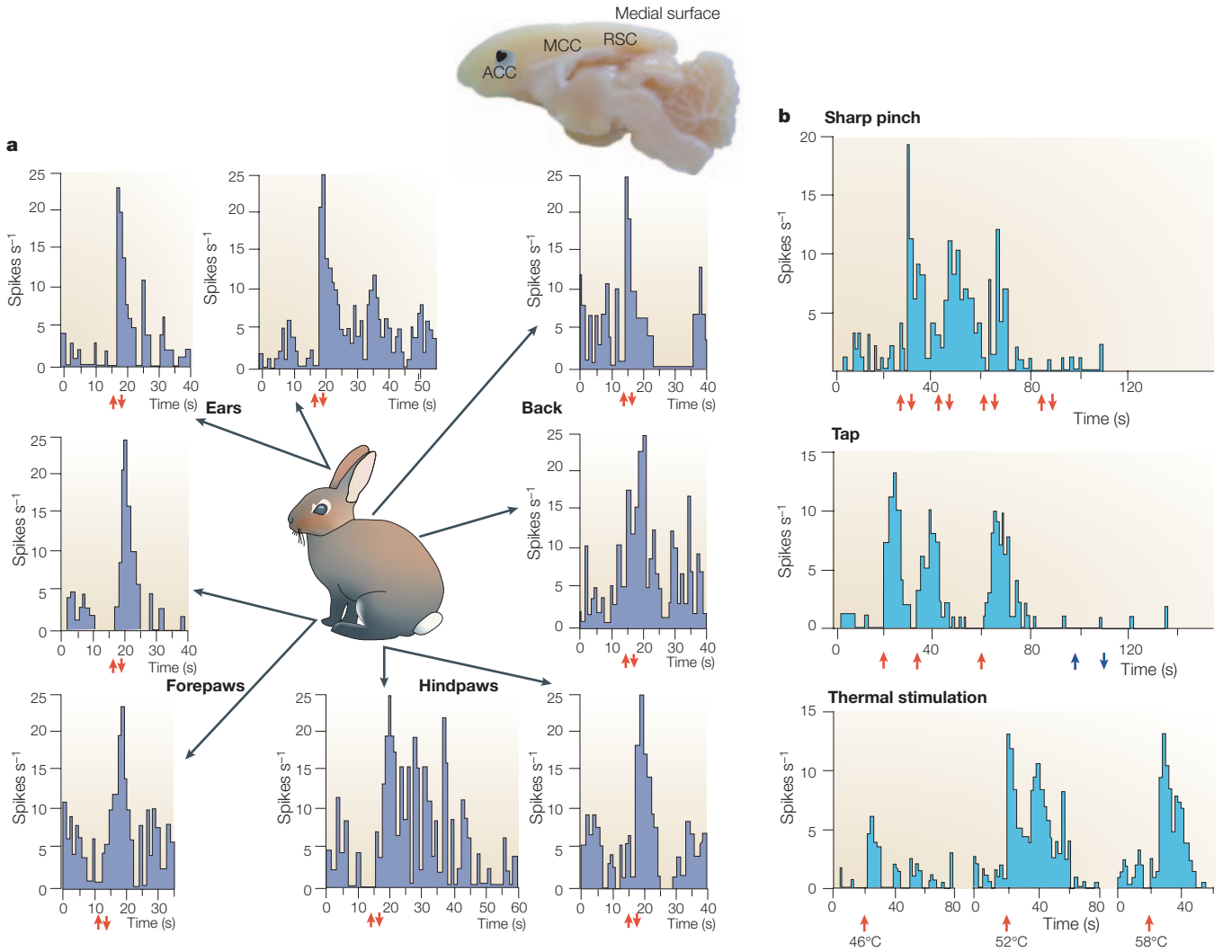


Figure 2 | **Nociceptive cingulate neurons.** The medial surface of a rabbit brain, showing its cingulate regions (anterior cingulate cortex (ACC), midcingulate cortex (MCC) and retrosplenial cortex (RSC)) and areas containing a high density of nociceptive neurons (black) and a low to moderate density of these neurons (grey). Unlike primates, the rabbit does not have posterior cingulate cortex areas 23 and 31. **a** | The rasters show neuron spike discharges for one neuron in response to stimuli applied at different physical locations. The arrows indicate stimulus onset (↑) and offset (↓). Noxious mechanical stimulation with serrated forceps evoked a response from the neuron regardless of where the stimulus was applied to the skin, which shows that no one neuron in the ACC can determine where on the body a noxious stimulus is located.**b** | The neuron studied is a multimodal nociceptive neuron because it responds briskly to both noxious mechanical and heat stimulation. Although the neuron did respond to tap stimulation, light brushing of the skin (blue arrows) failed to evoke a response. These multimodal nociceptive neurons provide little information about the characteristics of particular noxious stimuli.

can evoke a discharge. Note that the responses of the rabbit in FIG. 2a are recorded from a single neuron. Second, neurons respond mainly to noxious stimuli, including pressure and temperatures over 46°C. Tapping the skin is the only innocuous stimulus to drive these neurons. Third, there is a major aggregate of nociceptive neurons just dorsal and rostral to the genu of the corpus callosum. Interestingly, in many ways these responses reflect the properties of those neurons in the MITN that have projections to the cingulate cortex, with large and bilateral receptive fields that are mainly nociceptive but have some tap responses, and a large percentage of nociceptive multimodal responses[29,30].

Acute nociceptive responses in humans include those that are mediated by the cingulate cortex, which is one of the most frequently activated regions in the pain neuromatrix[4,5]. Lenz *et al.*[31] used subdural recording electrodes to show that laser-evoked, nociceptive potentials could be evoked directly from the MCC with latencies of 211–242 ms for negative and 325–352 ms for positive potentials. A response has also been evoked in the pACC by Ploner *et al.* using MEG[20]. The latency of this latter response was 0.5–1.5 s, indicating that it is associated with the perception of secondary pain, which is characterized by greater unpleasantness and a burning sensation. Validation of

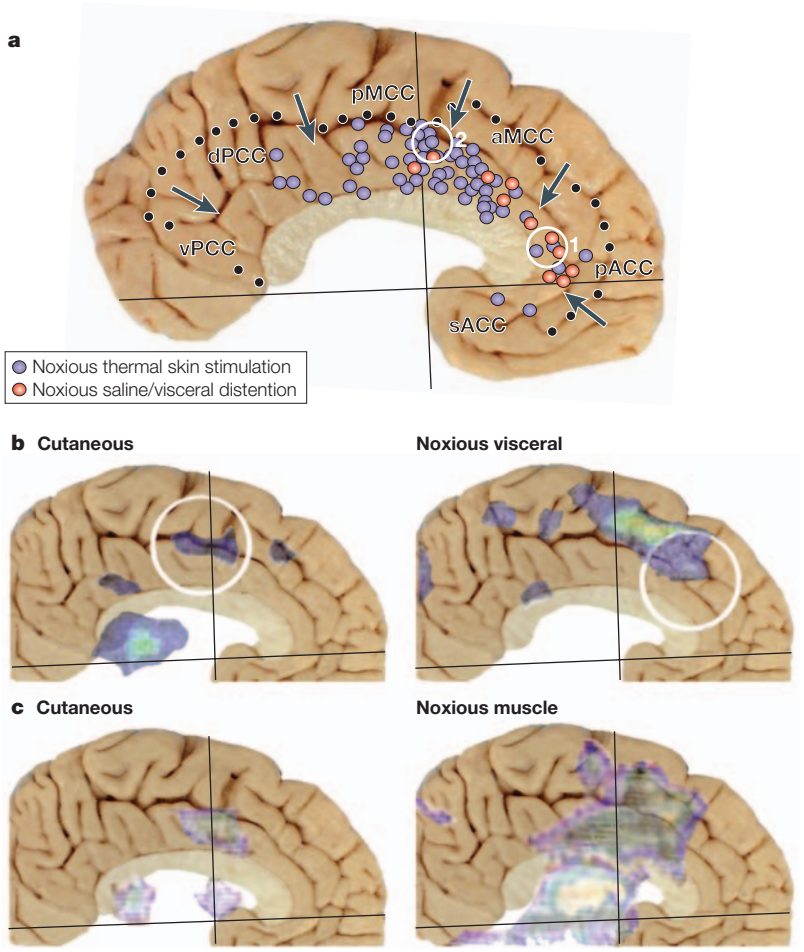


Figure 3 | **Human imaging during acute nociceptive stimulation. a** | Summary of 40 studies showing peak activation sites during noxious thermal stimulation of the skin and noxious hypertonic saline or visceral distention[33–43,59,60,62,65–90]. Cutaneous activations were almost homogeneous throughout the midcingulate cortex (MCC), with somewhat fewer in the rostral part of the anterior MCC (aMCC) and the greatest number in the dorsal and rostral parts of the posterior MCC (pMCC). Visceral activity was greatest in the pregenual anterior cingulate cortex (pACC) and some activity was seen in the rostral aMCC. The white circles indicate activations associated with the placebo anagesia in opioid studies (1)[62] and the acupuncture placebo induced by retractable placebo needles (2)[64]. The black dots represent the outer border of the cingulate gyrus. **b**,**c** | The activation sites of two studies were coregistered to the postmortem control case because two different noxious stimulation paradigms had been applied to the same individuals, providing a more accurate differentiation of the topography of activation sites. As a rule, noxious cutaneous stimulation evoked smaller, more caudal activity in the pMCC, whereas noxious oesophageal distention (**b**)[36] or electrical stimulation of muscle (**c**)[43] evoked larger and more rostral activity in the aMCC. Differential activation of parts of the MCC probably reflects the differential recruitment of the caudal and rostral cingulate motor areas and their associated cognitive functions. Yellow, green and blue represent t-values of 5+, 4 and <4, respectively. dPCC, dorsal posterior cingulate cortex; sACC, subgenual ACC; vPCC, ventral PCC.

the role of the pACC in unpleasantness comes from a recent study in which the intensity and unpleasantness of noxious cutaneous thermal, laser-evoked responses were independently manipulated, which resulted in a significant elevation in pACC activity[32]. Interestingly, although the sACC is a site of negatively valenced memory storage (see below), it was not involved in either of the latter studies.

A summary of peak voxel activation during acute nociceptive responses in the cingulate cortex is shown in FIG. 3. We studied nociceptive responses in the context of the four-region model using PET, and showed that both the pACC and MCC had elevated cerebral blood flow when noxious heat was applied to the back of the hand compared with the control (innocuous heating applied to the same skin)[33]. FIG. 3a shows that most cutaneous activity is evoked in the MCC, with almost no preference for its anterior or posterior divisions, whereas there are fewer activation sites in the pACC and almost none in the sACC or dPCC. Human imaging studies also show coding for the intensity of noxious stimulation in the pACC and MCC, as occurs in other components of the pain neuromatrix[34,35]. Finally, although there are relatively few studies of nociceptive visceral responses, they show a preference for the pACC and, to a lesser extent, the aMCC. These responses were evoked with hypertonic saline (applied either to the tongue or administered intravenously) or with noxious distention of the bladder, oesophagus, colon or rectum[36–42].

Plots of peak voxel activations must be viewed critically because they are generated in many separate subject populations and this type of analysis does not take into consideration the full distribution of an activation site. Together, these facts might lead to misinterpretation of the actual size of the activations and make comparisons among conditions difficult. Two studies provide important evidence that noxious stimulation of deep tissue or viscera activates a larger, and different part of the cingulate cortex from noxious cutanous stimulation, because both modalities of stimulation were used in the same participants. Strigo *et al.*[36] tried to balance noxious stimulation of a similar intensity in visceral and cutaneous sites, and observed activation of the pMCC by cutaneous thoracic stimulation, whereas oesophageal distention evoked activity more dorsally and anteriorly, in the aMCC (FIG. 3b). Svensson *et al.*[43] showed that a similarly sized, laser-evoked noxious cutaneous activation of the pMCC compared to that of Strigo *et al.*[36], whereas intramuscular electrical stimulation evoked a substantially larger and more anterior site in the aMCC and pMCC. Therefore, deep tissue stimulation activates the aMCC and this could be related to the generation of emotion and/or avoidance behaviours. It also seems that deep tissue/visceral activations enhance the activation of the rostral cingulate motor area in the rostral part of the cingulate cortex, whereas cutaneous nociceptive stimuli primarily activate the caudal cingulate motor area in the pMCC. These activations do not simply differ in size; they activate qualitatively unique cortical subregions.

Sources of nociceptive cingulate gyrus inputs

The well-documented responses of the cingulate cortex to nociceptive stimulation require a source by which such information can access this cortex. Our hypothesis that the MITN provide the primary source of nociceptive information is based on several observations. Nociceptive responses are of short latency (see above), occurring within 200 ms of stimulus onset, which does not favour prior processing through other cortical sites. Also noted above, some of the MITN share nociceptive response properties with cingulate neurons, which

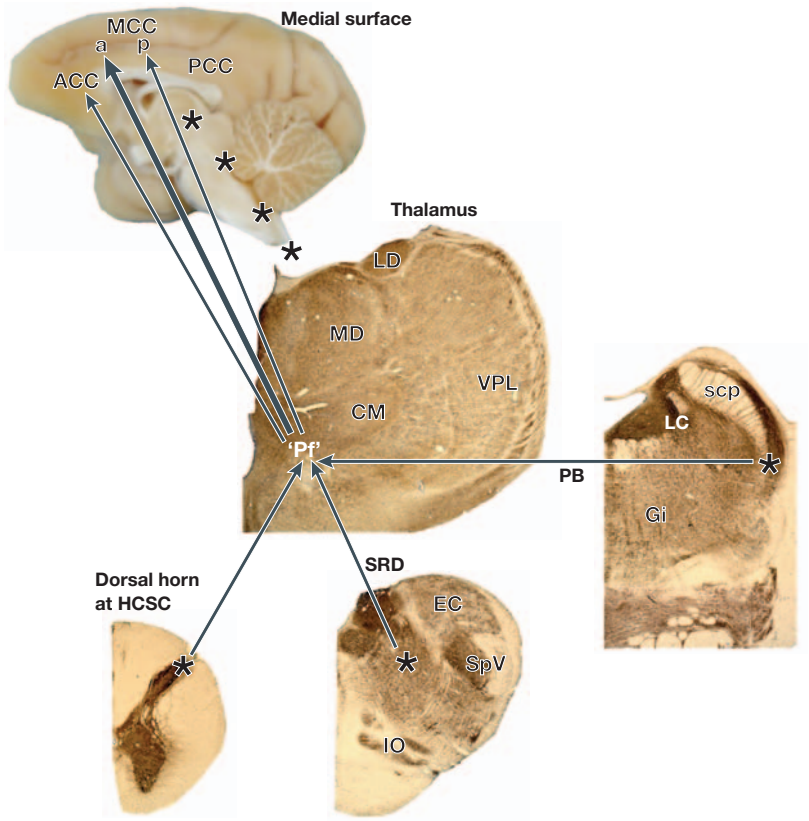


Figure 4 | **Nociceptive afferents to the cingulate cortex.** Shows three sources of nociceptive inputs to the parafascicular nucleus 'Pf' that arise from lamina I of the spinal cord, the subnucleus reticularis dorsalis (SRD) and the parabrachial nucleus (PB). The four asterisks along the medial surface of the monkey brain show (from top to bottom) the levels at which the thalamic, PB, SRD and high cervical spinal cord (HCSC) sections were photographed. The asterisks indicate exactly where each nucleus is in the section. The sections were stained for an antibody to microtubule-associated protein 2 (MAP2), which labels neuronal dendrites, and they were counterstained with thionin because some neurons do not express MAP2. The Pf is enclosed in quotation marks because it is representative of the MITN, of which there are many nuclei that receive nociceptive spinothalamic inputs and project, in turn, to the cingulate cortex (see BOX 2). We believe the greatest density of nociceptive inputs is to the anterior midcingulate cortex (aMCC), indicated by the large arrow, whereas more modest projections are made to the anterior cingulate cortex (ACC) and posterior midcingulate cortex (pMCC). CM, centre medianum thalamic nucleus; EC, external cuneate nucleus; Gi, gigantocellular reticular nucleus; IO, inferior olive; LC, locus coeruleus; LD, laterodorsal thalamic nucleus; MD, mediodorsal thalamic nucleus; PCC, posterior cingulate cortex; scp, superior cerebellar peduncle; SpV, spinal nucleus and tract of the trigeminal nerve; VPL, ventral posterolateral thalamic nucleus.

indicates a functional linkage. Ablation of most cortical inputs to the rabbit nociceptive region does not block the nociceptive responses, whereas lidocaine block of MITN activity abolishes such activity[14].

FIGURE 4 summarizes the primary sources of nociceptive inputs to the cingulate cortex. The 'Pf' refers to the parafascicular nucleus, which is representative of as many as ten MITN that receive differing amounts of spinothalamic input and project to the cingulate cortex. A discussion of MITN organization and projections is provided in BOX 2. The three main nociceptive inputs to the MITN arise from the spinothalamic tract (for a review, see REF. 6), the pronociceptive subnucleus reticularis dorsalis[44,45], and the parabrachial nucleus[46,47]. Each of these inputs to the parafascicular nucleus might transmit cutaneous, muscular and visceral nociceptive signals, and the net consequence of these inputs is that neurons in the cingulate cortex have almost full body receptive fields for cutaneous, muscle and visceral noxious stimuli.

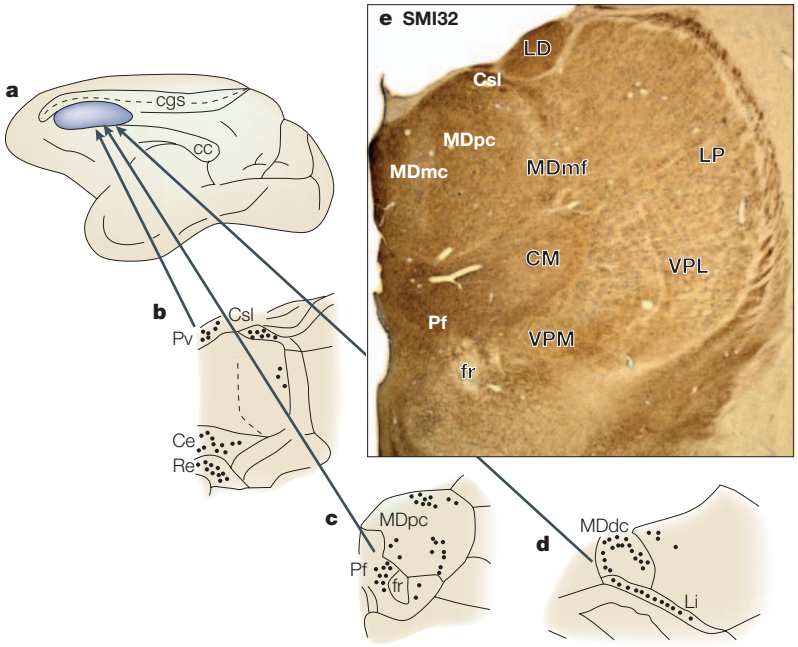
FIGURE 4 also indicates that a more dense projection of nociceptive inputs from the MITN terminates in the aMCC than in the ACC and pMCC. This idea is supported by a study in which tracers were injected into the rostral cingulate motor area in the aMCC and the caudal cingulate motor area in the pMCC[48]. After injection into the aMCC, 39% of thalamic neurons in the centrolateral, centre medianum thalamic nucleus (CM) and Pf nuclei were labelled, whereas 14.6% were labelled in the same nuclei after injection into the pMCC. As these nuclei transmit nociceptive information, this substantial difference indicates that there is a higher level of nociceptive activation in the aMCC than in the pMCC, and differential involvement of the cingulate motor areas in pain processing.

Role of the pMCC and dPCC in nociception

Most studies of nociceptive processing in the cingulate cortex emphasize the ACC and MCC because these parts of the cingulate cortex are thought to mediate the affective component of pain. FIGURE 3 shows that the PCC is rarely activated during acute noxious stimulation of either cutaneous or visceral tissues. However, activation of the pMCC could certainly be associated with a different type of nociceptive response, particularly given that nociceptive MITN inputs to this region are less extensive than those to the aMCC. Indeed, the cingulate subregion model requires that the pMCC activation be considered in a different light compared with more rostral activations. For example, the cingulate motor areas contain neurons with different properties — neurons in the caudal area have shorter latencies to movement and weaker links to reward contingencies than those in the rostral cingulate motor area[23].

Reports of early responses using electrophysiological techniques implicate the pMCC in sensory orientation rather than affect *per se*. Nociceptive stimulus discrimination has a peak latency at 172 ms after noxious stimulation in the dorsal PCC[49], and Bentley *et al.*[50] used cranial surface electroencephalographic recording to show that both the pMCC and dPCC have short-latency, nociceptive responses. Furthermore, Niddam *et al.*[51] used evoked potentials to show that painful and non-painful electrical stimulation of muscle activated the caudal cingulate motor area and the dPCC, and Huang *et al.*[52] evaluated movement-associated activity during simple finger movements and showed sites of activation in the caudal cingulate motor area and the dPCC with MEG. These observations indicate that the pMCC and dPCC are involved in orienting the body in response to sensory stimuli, including nociceptive stimuli, and it is unlikely that nociceptive activations of the pMCC are specific for noxious stimuli. The extent to which pain activates the pMCC and dPCC depends on the role of both regions in emotion.

Box 2 | **Midline and intralaminar thalamic nuclei**



The nociceptive gateway to the cingulate gyrus originates in the midline and intralaminar thalamic nuclei (MITN)[28]. Following an injection of horseradish peroxidase into the anterior cingulate gyrus (panel a, blue ellipsoid on medial surface), projections from the MITN to the cigulate gyrus were shown with retrograde labelling (indicated by black dots; panels b–d). Each dot in panels b–d is approximately equal to 3–5 labelled neurons. The midline nuclei include the paraventricular (Pv), central (Ce), reuniens (Re), mediodorsal densocellular (MDdc) and parvocellular (MDpc), limitans (Li), and parafascicular (Pf) nuclei; and the intralaminar nuclei, including the paracentral, centrolateral and superior centrolateral (Csl) nuclei. Each of these nuclei receive some spinothalamic input, and most project to the cingulate cortex. The histological section (panel e) was stained for an antibody (SMI32) to intermediate neurofilament proteins and shows two divisions of MD, Csl, and Pf. cc, corpus callosum; cgs, cingulate sulcus; CM, centre medianum; fr, fasciculus retroflexus; LD, laterodorsal; LP, lateral posterior; MDmc, magnocellular MD; MDmf, multiformis MD; VPL, ventral posterolateral; VPM, ventral posteromedial.

Cingulate emotion processing

Although emotion, like pain, is consciously perceived as a uniform experience, it is not equally engaged throughout the brain or the cingulate gyrus. Our view is that, rather than being an emergent property of the whole brain, emotion is processed in different areas according to the memory valence, autonomic associations and sensory driving that are necessary for the internal content and behavioural output relevant for each class of emotion. This hypothesis can be applied to the entire brain and the regionalized cingulate gyrus. Phan *et al.* carried out a meta-analysis of simple emotions[53], plotting functional response peaks in the brain during happiness, sadness, anger and fear generated by word pairs, scripts or faces with emotional valence. At first glance, it appears that the cingulate gyrus is more or less completely engaged during emotion; a reassuring conclusion for those who view the cingulate cortex as a unitary component of the limbic system that subserves emotion. Indeed, the idea of the limbic cortex requires that emotion be a primary function of a region/subregion/area for it to be part of this system. Are all parts of the cingulate cortex equally involved in emotion? The answer to this question can be found in the cingulate regions and subregions, and will have profound implications for how the cingulate cortex processes nociceptive information.

An assessment of responses during emotion considered the proposition that cingulate emotion processing is not equally distributed in the gyrus because the four-region model, which is based on cytoarchitectonics, circuits and functions, predicts specialized contributions from each region and subregion[17]. The goal of this study was to link activations seen during the experience of simple emotions to particular cytoarchitectural entities. Emotion involves events, objects and memories that have a positive or negative valence, and these can be associated with affective (autonomic) changes. The valance of simple emotions, such as happiness and sadness, is easily attributed, whereas valance attribution of complex emotions, such as anxiety and guilt, requires subtle interpretations of events and cues that often depend on context. For example, 'slashing knife' is usually an unambiguous and negatively valenced object, 'carrying a knife' could cause anxiety if one is observing another person on a dark street, or might be a positive event if one is preparing for an evening dinner. Therefore, the former is a simple emotion, whereas the latter is a complex one that depends on context. As shown in FIG. 5, most of the MCC was not active during simple emotions, whereas the cortex around the genu and splenium of the corpus callosum (perigenual and perisplenial cortex, respectively) were highly active. Only the rostral part of the aMCC was active during fear. This distribution supports the prediction that the cingulate cortex is not uniformly involved in emotion.

FIGURE 5 can be taken much further in terms of the 'submodal' processing of emotion in the cingulate gyrus. Emotion submodalities refer to direct autonomic regulation, valenced memories and skeletomotor responses that show valence, such as facial expressions and crying. Indeed, there are four aggregates of emotion-generated activity numbered in FIG. 5 and we conclude the following from each.

First, activity during sadness is greatest in the sACC, a localization that was first reported by George *et al.*[19]. Importantly, this site of memory storage for negatively valenced events is comprised mainly of area 25, which has many direct projections to subcortical autonomic centres, and we generally refer to its function as autonomic integration (FIG. 1). No other region has these specific connections[12,15].

Second, activity during happiness occurs more rostrally and dorsally in the pACC. Differentiation of these emotions into subregions of the ACC emphasizes their specific role in mediating internal responses to different emotional states.

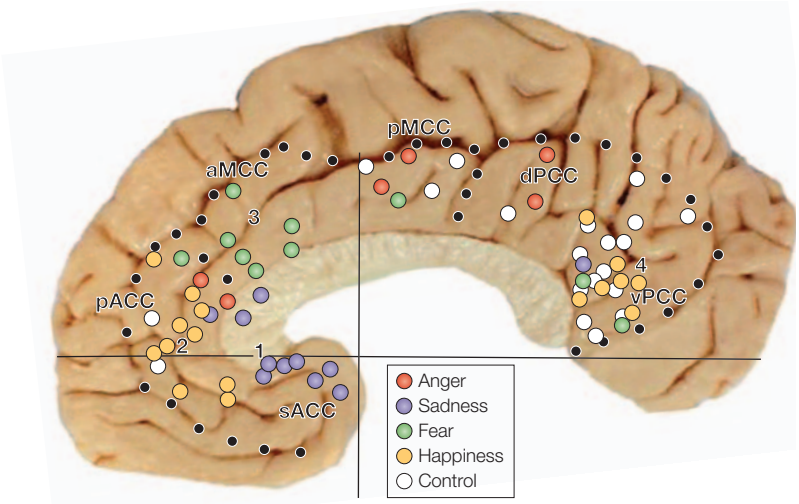


Figure 5 | **Cingulate emotion processing.** Summary of 23 studies showing peak activation sites during simple emotions in the context of the regionalized cingulate gyrus[17,19,91–112]. Four groups of active sites are numbered. Control conditions involved non-emotional scripts and faces. Each numbered aggregate of sites is located in a different subregion, which indicates that they each have a different role in the processing of emotional information; that is, a different relevance to autonomic integration, skeletomotor output and personal orientation, as predicted by the four-region neurobiological model. The black dots represent the outer border of the cingulate gyrus and borders between the regions. aMCC, anterior midcingulate cortex; dPCC, dorsal posterior cingulate cortex; pACC, pregenual anterior cingulate cortex; pMCC, posterior MCC; sACC, subgenual ACC; vPCC, ventral PCC.

Third, fear is mainly associated with activity in the aMCC. This part of the MCC receives input from the amygdala[54], which has been implicated in fear[55]and nociception[56]. No other cingulate region has high and direct amygdala input as well as a significant role in fear.

Fourth, the vPCC shows a high level of activity during happiness, which might be construed as equivalent to the activation seen in the pACC. However, the four-region model and observation of control condition activity prevents this spurious conclusion. The vPCC is active during both emotion and non-emotion conditions, which is not true for the pACC. The vPCC does not have autonomic projections to subcortical autonomic motor nuclei, nor does electrical stimulation evoke autonomic changes. The role of the vPCC can be better characterized in terms of assessing the self-relevance of emotional events and stimuli — it is more of an emotional pre-processor that allows emotional information to gain access to the cingulate emotion subregions. Indeed, the vPCC has reciprocal connections with the sACC[54], which might assist in establishing the personal relevance of sensory information that comes into the cingulate gyrus.

Therefore, there are four levels of emotion-relevant activity in the cingulate cortex, which are sorted according to subregions in the four-region neurobiological model. Having plotted pain and emotion-evoked activations into the same coordinate system as the postmortem histological analyses, we are in a position to consider direct relationships between pain and emotion in subregions of the cingulate gyrus.

Pain and emotion linkages

A new perspective on the literature about pain and emotion processing in the cingulate gyrus is provided by the four-region neurobiological model and its associated subregions. Indeed, rather than attempting a single group analysis, linkages can be made on the basis of numerous studies, which provides added confidence in the conclusions. Furthermore, both matches and mismatches with expected parallels between processing in these two distributed networks become more apparent in this context. Amazingly, the most common acute pain and simple emotion plots indicate that there are complex relationships between these cortical functions rather than a simple overlap of negative emotions and pain affect, as predicted from the dual cognitive model of pain processing. Of course, it must be reiterated that these plots are of peak voxel activity from many studies — they do not represent the full extent of activation — and that the studies used were only those reporting cingulate activations. However, despite these caveats, the following observations seem to be justified.

First, the fear and pain sites overlap in the aMCC and validate the general conclusion of this region's involvement in avoidance behaviours. This overlap occurs in the context of heavy MITN inputs to the region.

Second, it is surprising that the pMCC has no consistent emotion activations, yet has robust nociceptive responses. Assuming that nociceptive responses are generally short-latency, it seems reasonable to conclude that these evoke skeletomotor body orientation to the noxious stimulus without affective (autonomic) or emotional (valenced) content. This would probably be mediated through the caudal cingulate motor area, which seems to operate more as a skeletomotor integrator than in the assessment of behavioural outcomes using valence-coded information.

Third, visceral nociceptive activity is mainly associated with the pACC, yet this is not an autonomic integrative centre like the sACC. Although this region is most often associated with happiness in studies of simple emotion, amplification of unpleasantness during noxious stimulation enhances activity in the caudal part of the pACC, but not the sACC[32]. The four-region model predicts preferential sACC activation during noxious stimulation of the skin and viscera, and this is one of the most striking incongruities of these observations, and requires further explanation. Although the sACC is sensitive to susceptibility artefacts with high field strength magnets, many studies of acute pain were done with PET, for which this was not an issue. It is also true that pain anticipation can reduce cerebral blood flow in the sACC[57,58], which could contribute to a general lack of signalling in this region during acute pain. Finally, sad events that evoke sACC activity tend to be associated with personally relevant events and not a simple external noxious stimulus. It is possible that pain could engage the sACC in a person-specific manner, and the stimulation paradigms that are used currently are not relevant to the internal states of individual participants. Another way to express this

is to say that the unpleasantness of a noxious thermal stimulus does not generate an adequately negative and personal emotional event to drive the sACC.

Fourth, acute nociceptive stimulation does not activate the vPCC as part of a generalized self-relevance assessment. It seems that the MITN-mediated nociceptive signal bypasses processing in the vPCC and this latter system is primarily involved in visual stimulus assessment. Indeed, nociceptive stimulation actually shuts off much of the PCC's activity[33,35]. Therefore, emotion activations of the vPCC have little or nothing to do with pain affect because this subregion does not receive MITN inputs, and there might be a cognitively-mediated mechanism whereby activity in this area is inactivated during noxious stimulation. Inactivation of the vPCC could be one mechanism by which the overall perception of noxious stimulation and suffering might be reduced.

Fifth, the dPCC does not seem to have a specific role in pain processing because it can be activated by both noxious and innocuous stimulation. Importantly, this region and the adjacent pMCC probably dominate activity in the caudal cingulate motor area and mediate rapid body orientation to somatic stimuli, and both have little or nothing to do with emotion.

It seems that the four-region neurobiological model of the cingulate gyrus and its subregions is constructive for studying interchanges between pain and emotion networks in the cingulate gyrus. We predict that this will be true for many of the other essential functions of this region. Surprisingly, the cingulate cortex is not uniformly involved in emotion, and not all pain-activation sites are associated with affect or emotion — facts that should lead to a better understanding of how each is processed. Although the MITN provide direct circuits to each cingulate region, the density of these projections differs between each subregion and each subregion uses information from this area differently for pain processing. In conclusion, the cingulate gyrus mediates three main aspects of pain processing: fear-avoidance in the aMCC, unpleasantness in the pACC, and skeletomotor orientation of the body in response to noxious stimuli in the pMCC and dPCC. The MCC and dPCC are generally engaged in premotor planning, and might have little involvement in sensation. Even the fear signal in the aMCC might be more closely associated with predicting behavioural outcomes than sensory affect *per se*.

Hypnoanalgesia and placebo effects

Pain regulation and its associated negative affect might eventually be resolved clinically in the context of the cingulate subregions. Induction of analgesia by hypnosis targets the aMCC[59,60] which is consistent with the idea that fear reduction is part of the analgesic effect mediated by the cerebral cortex. The mechanisms of opiate analgesia are less clear, but seem to be in line with the distribution of subregions. The highest level of opioid receptor binding is in the pACC[61], which is the site of the opioid placebo effect[62], as shown in FIG. 3a. This is the same region in which elevated activity occurs during attention to the unpleasantness of nociceptive cutaneous stimulation[32], and the point at which negative affect displaces binding of the μ-opioid agonist carfentanil in the pACC[63]. Therefore, hypnoanalgesia, opioid drugs and the opioid placebo target different subregions that have emotional functions and regulate autonomic outputs.

Interestingly, different placebo effects are mediated by different cingulate subregions. In patients with painful osteoarthritis, acupuncture using either proper needles or retractable placebo needles activates the dorsal part of the pMCC[64]. It is striking that the somatic acupuncture placebo response is located in the region that has the highest density of acute somatic pain sites (FIG. 3a), whereas the opioid placebo response is located in the region of highest visceral activation and opioid receptor density (FIG. 3a). Therefore, there may be a map of placebos that is organized according to the distribution of the cingulate subregions. Moreover, hypnoanalgesia and opiate analgesia could provide important and independent tests of the subregion model. They might also aid our understanding of the aetiologies of chronic pain and stress syndromes, as well as mood, motor and thought disorders, and allow us to design effective treatments for each.

Concluding remarks and future perspectives

The four-region model is a theoretical construct. That is to say, the MCC is more than a location on the cingulate gyrus in the sense of the posterior ACC, caudal ACC, dorsal ACC and the many other terms used to identify activity in this region. The MCC is a region and a concept that represents a circuitry with a limited number of functional outputs. Although less apparent in the nomenclature, we also use the terms ACC, PCC, and RSC to represent theoretical constructs as well as structural entities. The value of the regional model derives from its ability to make specific, *a priori* predictions about experimental outcomes. Interestingly, it is not expected to be 'correct' in all instances, and some of the more profound outcomes arise when an observation cannot be predicted and forces a new functional perspective, as occurred when co-localizing pain and emotion.

Since the four-region model was first proposed in 1993 (REF. 6), our main concern was ensuring the accuracy of the anatomical and functional criteria. Further observations have meant that changes to the model were required. For example, amygdala connections, differential properties of the cingulate motor areas and studies of simple emotions indicated that subregions existed for the MCC and, recently, the PCC[18]. However, it now seems that defining the cingulate regions and subregions is essentially complete, and their cytoarchitectures are well understood.

Is the research into the structure and functions of the cingulate gyrus complete? There are three major areas of investigation now opening and these will keep us occupied for the twenty-first century. First, we know little of the distribution of particular transmitter receptor systems and their transduction mechanisms in any

area of the primate brain. New neuronal phenotypes will certainly become apparent as the molecular biology of the cingulate cortex evolves over the coming decades. Second, the functions of each subregion are still poorly understood. Interactions of reward and punishment systems are not understood because their dynamics are usually evaluated in the contexts of different theoretical and disciplinary frameworks. Third, the relationship between each neuronal phenotype and the aetiology and progression of many diseases is not understood but will be uncovered in the context of the regional and subregional organization. Alzheimer's disease, obsessive-compulsive disorder, post-traumatic stress disorder, depression, chronic and functional pain disorders, and many other diseases might be linked to the cingulate cortex through their primary aetiology.

The theoretical model of the cingulate cortex will continue to evolve as our understanding of its neuronal features increases. Most importantly, the initiation and progression of many diseases across the cingulate gyrus will continually drive evolutionary changes in how we model this part of the brain.

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Competing interests statement

The author declares no competing financial interests.

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