

Brain mechanisms of pain affect and pain modulation

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Recent animal studies reveal ascending nociceptive and descending modulatory pathways that may contribute to the affective–motivational aspects of pain and play a critical role in the modulation of pain. In humans, a reliable pattern of cerebral activity occurs during the subjective experience of pain. Activity within the anterior cingulate cortex and possibly in other classical limbic structures, appears to be closely related to the subjective experience of pain unpleasantness and may reflect the regulation of endogenous mechanisms of pain modulation.

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Abbreviations

ACC	anterior cingulate cortex
BA	Brodman area
fMRI	functional magnetic resonance imaging
NAcc	nucleus accumbens
PAG	periacqueductal gray
Pb	parabrachial nucleus
PET	positron emission tomography
rCBF	regional cerebral blood flow
S1	primary somatosensory cortex
S2	secondary somatosensory cortex
VMPPFC	ventromedial prefrontal cortex

Introduction

The International Association for the Study of Pain proposes that pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [1]. This definition implies that pain is a subjective experience, with both sensory and affective dimensions that are usually, but not necessarily, associated with tissue damage (see also [2,3]). Thus, instead of being mistrusted — as implied in some studies — pain reports should be considered important indirect indices of the subjective experience of pain. By contrast, nociception refers to the ‘objective’ presence of, or potential for, tissue damage. Pain research is guided by the neurobiology of nociception, because it provides a primary structure for the analysis of pain-related brain activity. In this review, I first report selected animal studies describing recently discovered ascending nociceptive and putative descending modulatory pathways. The core of the review provides an attempt to describe the neural correlates of the subjective experience of pain in humans in the light of recent functional brain imaging studies on pain, cognitive processes, motivational and emotional states, and self-regulation.

Nociceptive pathways and modulatory circuits

In addition to the classical spinothalamic nociceptive projections, ascending nociceptive pathways originating in the spinal cord and projecting to specific areas of the brainstem and then further rostrally to various brain structures have been mapped in the rat. Recent findings indicate that one pathway projects from the dorsal horn of the spinal cord to the dorsocaudal medulla (subnucleus reticularis dorsalis), then to the ventromedian nucleus of the thalamus, and finally to the dorsolateral frontal lobes [4].

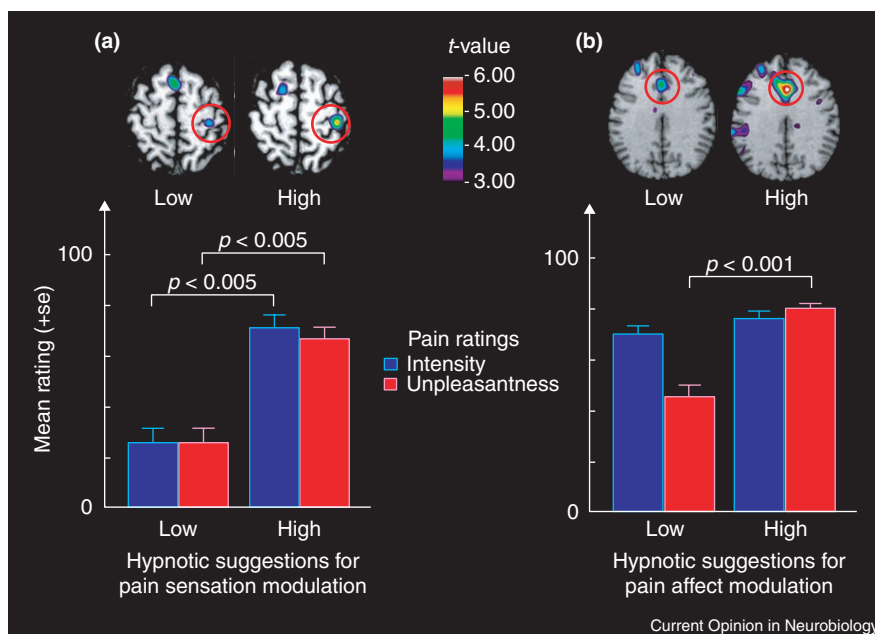
Another ascending pathway projects from the spinal cord to the parabrachial nucleus (Pb), and subsequently to the hypothalamus and the amygdala [5,6]. Additional findings suggest that nociceptive information may be transmitted to the forebrain from the Pb. One pathway could transmit nociceptive activity from the Pb to the intralaminar thalamus, and from there to the frontal cortices [7,8*]. Another pathway involves projections from the Pb to the central nucleus of the amygdala, and on to the basal forebrain [9*]. These pathways may contribute to the emotional aspects of pain and to the interactions between pain and cognitive processes.

In addition to these ascending pathways, recent findings have documented the implication of higher order brain structures in the descending modulation of nociceptive activity. The periacqueductal gray (PAG) area has a key role in descending mechanisms that modulate spinal nociceptive activity [2,10]. Earlier work in rats, cats, and monkeys, showed that there are cortical inputs to the PAG from pain-related cortical areas such as the somatosensory areas, the insular cortex and the medial prefrontal cortex, including the anterior cingulate cortex (ACC) [11,12]. In monkeys, descending projections are found from multiple areas of the ACC including Brodmann area (BA) 25 and BA32, as well as BA24b, the area that receives spinothalamic nociceptive input.

A recent study in rats indicates that the rostral ACC may be involved in pain-induced place-conditioned avoidance [13], and electrophysiological studies in monkeys are consistent with an involvement of the ACC in regulating avoidance behaviors ([14,15*]; see also the studies of Gabriel [16] in rabbits). Recent work also suggests that the amygdala is involved in opioid- and cannabinoid-dependent pain modulation, possibly through descending modulatory processes [17,18]. These studies show that higher order cerebral structures receive and integrate nociceptive information to regulate behavior, and are potential sources of descending influence on nociceptive processes. Future studies will be required to assess the functional significance of these ascending and descending pathways in primates, including humans.

Figure 1

Effects of hypnotic suggestions to modulate pain on pain-related rCBF in normal subjects. In all pain conditions in the two PET studies shown, the left hand of the subject was immersed in hot water maintained at a constant painful temperature. **(a)** Modulation of pain intensity and S1 activity. In this study, hypnotic suggestions to increase ('high') or decrease ('low') the subjective intensity of pain led respectively to increases and decreases in rCBF in the area of S1 cortex where the contralateral hand is represented (red circle) [41^{*}]. In these conditions, pain intensity and unpleasantness were modulated in parallel (bar graph). **(b)** Modulation of pain unpleasantness and ACC activity. In contrast to (a), this earlier study indicated that hypnotic suggestions, specifically directed at the affective dimension of pain, produce a specific modulation of ACC activity and a specific modulation of pain unpleasantness [40]. Results of the recent study showing S1 modulation confirm that the effects reported previously in the ACC (b) are not due to nonspecific cognitive factors associated with the hypnotic procedure, but reflect pain-related modulation associated with the affective dimension of pain and subjectively experienced as pain unpleasantness [41^{*}]. Note that in the study shown in (a), there was no significant modulation of ACC activity in



spite of the significant modulation of pain unpleasantness. This suggests that activity within S1 cortex may also contribute to the subjective feelings of pain unpleasantness when variations in pain unpleasantness are

secondary to the modulation of pain intensity by cognitive factors. ACC may be more critically involved in pain unpleasantness when it is specifically modulated independently from pain intensity (b).

Distributed representation of nociception underlying the experience of pain

Functional brain imaging studies in humans have focused mainly on the classical ascending spinothalamic pathways that convey nociceptive signals to the primary and secondary somatosensory cortices (S1 and S2/parietal operculum), the insula and the ACC (BA24) in primates (recently reviewed in [19]). Electrophysiological and electromagnetic studies in monkeys and humans have provided further evidence that these cortical areas receive contralateral nociceptive input [14,15^{*},20–26]. Additional subcortical activation sites, reported sporadically, include the cerebellum, amygdala, nucleus accumbens (NAcc) and other nuclei of the basal ganglia (with different subdivisions in different studies). Sites of activation in the brainstem have received less attention because of the relatively poor spatial resolution of the functional brain imaging methods. Taken together, functional brain imaging studies of pain indicate that nociceptive information is represented in several areas of the brain that may contribute directly or indirectly to the experience of pain.

The intensity of the experience of pain can be increased by increasing the physical intensity of the experimental noxious stimuli [27,28,29^{*}], by applying successive brief noxious stimulations of identical physical intensity [30^{*}], or as a function of time in response to a sustained noxious stimulus of constant intensity [31]. These manipulations

affect the magnitude of the cerebral response in key cortical areas, especially in contralateral S1 and S2 cortices, the insula and the ACC (but see [30^{*}]), in which a positive correlation is generally observed with ratings of pain intensity. Furthermore, the modulation of pain perception by hypnosis [32–35] and attention [36,37] has been shown to alter brain activity in some of these key pain-related areas. The available results support the proposition that the experience of pain results from the activation of a network of brain structures involving the thalamus, somatosensory cortices S1 and S2, the insular cortex and the ACC.

Cortical activity correlated with sensory and affective dimensions of pain

The functional role of pain-related brain structures in the sensory (e.g. pain intensity) and affective (e.g. pain unpleasantness) dimensions of the pain experience has been examined using combinations of pain scales that measure separately the subjective pain intensity — ‘how intense is the pain?’ — and pain unpleasantness — ‘how much does the stimulation bother you?’. One group of investigators has taken advantage of the specific increases that they observed in pain unpleasantness, but not pain intensity, with the successive application of noxious stimuli [38].

Regression analyses revealed that the subjects’ ratings of pain unpleasantness were correlated with activity in the caudal ACC, which supports the involvement of this

structure in the affective dimension of pain. In a series of studies using hypnotic suggestion [39], my coworkers and I [40] have shown that the specific manipulation of pain unpleasantness produces significant changes in the ACC, whereas the manipulation of pain intensity produces changes mainly in the S1 cortex [41•] (Figure 1).

This result supports our previous interpretation that changes in pain-evoked activity in BA24 of the ACC are associated with subjective changes in pain unpleasantness and cannot be explained by a nonspecific effect of hypnosis. This finding is also consistent with the impairment in pain sensation reported in an individual with a lesion of S1 cortex [42] and supports the contribution of S1 to the sensory dimension of pain perception. Taken together, these results constitute a double dissociation and argue strongly for a ‘relative separation’ of cerebral structures that are involved more directly in sensory and affective aspects of the pain experience.

In studies on the hypnotic modulation of pain, pain unpleasantness was modulated either specifically (Figure 1b) or secondarily to changes in pain intensity (Figure 1a). In this latter condition, the activity in the ACC was not modulated, which suggests that the contribution of the ACC to pain affect may be more critical when variations in pain unpleasantness are determined by cognitive factors that are independent of pain intensity [30•,41•,43]. Additional results examining the nonspecific effects of the hypnotic suggestions for increased and decreased pain suggest that the prefrontal cortices and the dorsal part of the ACC (BA32) may contribute directly or indirectly to the modulation of ACC pain-related activity [44].

Specific mechanisms might involve cortico–cortical interactions between the dorsal and ventral parts of the ACC and between the prefrontal cortices and the ACC, cortical influences on thalamocortical projections to the ACC, and descending projections to subcortical structures such as the amygdala and area PAG (see above).

A role for the ACC in the affective dimension of pain is also supported by studies examining the functional role of the μ -opioid system in pain. Messenger RNA for the μ -opioid receptor is expressed, and the μ -opioid receptor is found, in many areas of the brainstem, thalamus, amygdala, striatum and frontal cortices including the ACC [45–47].

In a recent positron emission tomography (PET) study, the systemic administration of the μ -opioid agonist fentanyl has been reported to produce a hedonic effect and to reduce pain intensity, pain unpleasantness and the pain-related increase in heart rate produced by immersing the hand in cold water [48•]. In this study, fentanyl administration increased regional cerebral blood flow (rCBF) in the ACC under control conditions without pain (also see [49]) and reduced pain-evoked activity in the thalamus and the pain-related cortical areas, including the ACC. More recently, Zubieta *et al.* [50••] have

reported changes in μ -opioid binding during pain using the radioligand [^{11}C]carfentanil and PET. In this study, sustained pain was associated with endogenous activation of the opioid system in the ACC, in the bilateral prefrontal cortices (BA8), in the contralateral insula, thalamus and hypothalamus, and in the ipsilateral amygdala.

Furthermore, stronger endogenous activation of the opioid system in the ipsilateral NAcc, thalamus, amygdala and area PAG was associated with lower pain-related sensory ratings (Figure 2a). In contrast, stronger activation in the ACC, thalamus and ipsilateral NAcc was associated with lower pain-related affective ratings (Figure 2b). These results support the interpretation that the ACC may contribute, independently of pain sensation, to specific changes in pain affect, and might participate in and contribute to the regulation of endogenous pain modulatory mechanisms.

These results also indicate that additional subcortical structures, such as the NAcc, amygdala and area PAG, may contribute to the experience of pain. Recent findings from functional magnetic resonance imaging (fMRI) indicate that these structures are also activated during pain from heat [51•], but future studies will be required to assess their specific role in the subjective experience of pain.

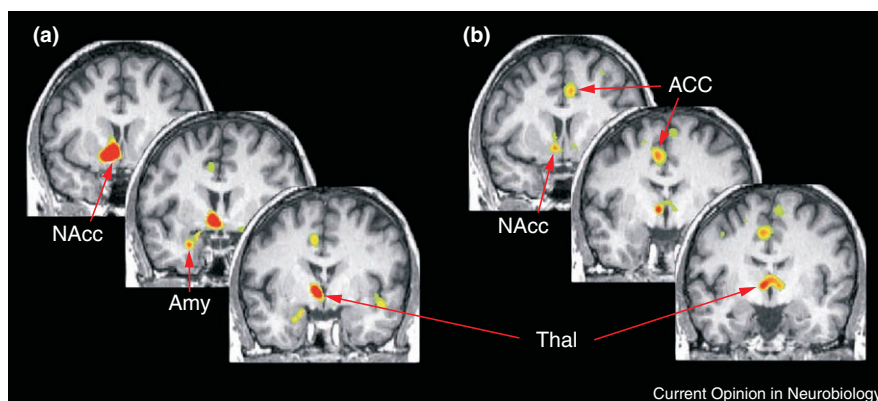
Role of the ACC in affective and cognitive processes

An anatomical–functional segregation of subsectors of the ACC probably depends on the type of input processed and the specific processing and output mechanisms engaged, as has been suggested previously [52–55]. A recent review indicates that pain-related activation is reported most consistently in the ventral part of the supracallosal ACC (BA24), in the dorso-caudal ACC, and occasionally in the perigenual area [19]. Activation within the ventral part of the ACC is consistent with the transmission of nociceptive information through spinothalamocortical projections to BA24 [56]. This area may be involved more specifically when the afferent input is of somatic origin and has an intrinsic affective value, whereas the dorsal sector of the ACC (BA32) may be involved when extrinsic, secondary affective value is attributed to stimuli, such as in cognitive studies.

A direct comparison of the activation of the ACC in response to pain, to other stimuli and to cognitive tasks shows that pain-related foci of activation are found in the anterior ACC, ventral posterior ACC and dorsocaudal ACC [57,58•]. Innocuous thermal stimuli activate mainly anterior sectors of the ACC, and motor tasks activate the dorsocaudal ACC. By contrast, cognitive tasks activate an area that is dorsal to pain-related foci, which is consistent with the location of BA32. The most dorsocaudal part of the ACC may contribute more specifically to motor control during pain, and the activation of more anterior and ventral regions may reflect the arousing effect of painful stimuli, consistent with previous studies and interpretations [53,54,59,60•]. The insular cortex may also have a similar

Figure 2

Endogenous activation of the μ -opioid system associated with the sensory and affective dimensions of pain perception. Changes in μ -opioid receptor availability were evaluated using the radioligand [^{11}C]carfentanil and PET to assess the endogenous activation of the μ -opioid system during sustained pain. The pain test comprised individually adjusted continuous infusions of hypertonic saline in the masseter muscle and was compared against a control nonpainful condition (isotonic saline infused at the same rate). Results of the comparison between the painful and nonpainful conditions showed a reduction in μ -opioid receptor availability in many areas (see text), which suggests that the μ -opioid system is activated endogenously during pain (reduction in binding of the exogenous ligand). **(a)** Correlation with pain sensory scores. Regression analysis with the sensory scores of the McGill pain questionnaire revealed significant negative correlations with the activation of the μ -opioid system, ipsilateral to the stimulation, in the NAcc, amygdala (Amy) and anterior thalamus



(Thal). (A statistical trend was also observed in the brainstem in the region of the periaqueductal gray area [data not shown]; the peak correlation with the sensory score in the ACC was not significant.) **(b)** Correlation with pain affective scores. Results of the regression analysis performed on the affective score of the McGill pain questionnaire

revealed significant negative correlations in the bilateral ACC and anterior thalamus, and in the ipsilateral NAcc. These findings indicate that the experience of pain during nociceptive stimulation is inversely related to endogenous activation of the μ -opioid system in those areas. Results are from Zubieta *et al.* [50**]. Original images courtesy of Jon-Kar Zubieta.

role in the regulation of pain-related autonomic activity, as suggested by the convergence of nociceptive, thermoregulatory, and cardiovascular-related activity in this area [24,60,61]. But the specific relation between physiological arousal and pain-related activity in the ACC and the insular cortex remains to be demonstrated.

The subjective experience of pain unpleasantness may comprise several dimensions that reflect the felt internal state of the body associated with autonomic activity, the desire to produce behavioral responses (thus reflecting the motivational state of the individual), and the anticipated outcome (see below). Evaluating these possibly separable aspects of subjective experience may help to clarify the respective contribution of different subsectors of the ACC, as well as other pain-activated areas, such as the insula, to different aspects of pain unpleasantness.

Pain-evoked activation in the ACC has also been interpreted occasionally as attentional rather than as related to pain [36]. This opposition may be misleading because attention processes refer generally to the information processing analysis of brain function, and pain refers to subjective experience — two complementary levels of description. Activation of the ACC during the application of noxious stimuli may reflect the intrinsic affective value — that is, the primary biological significance — of the stimulus and the priority given to the resources engaged in producing appropriate responses.

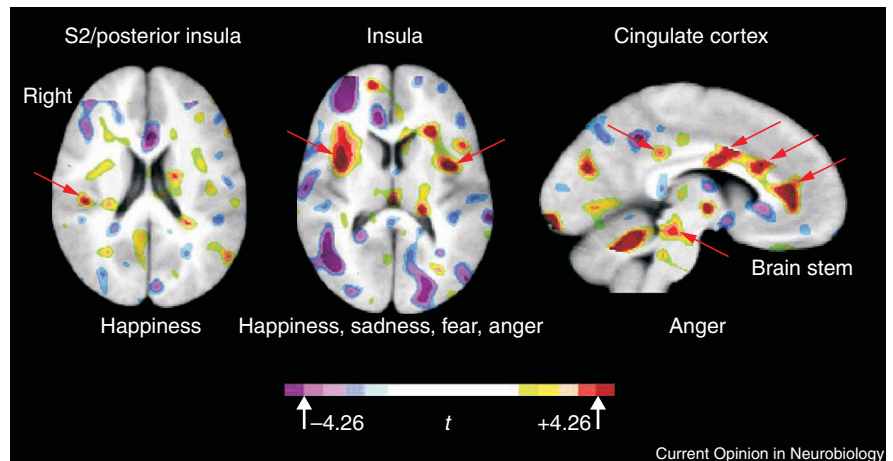
Similarly, the response of the ACC to novel salient stimuli may reflect the intrinsic or primary affective value of stimuli that have the potential to convey relevant

information [62]. In attention tasks, subjects are typically instructed to process targets and ignore distractors. Extrinsic positive/negative affective value is thereby attributed to target/distractor stimuli and processes. In cognitive studies in general, activation of the ACC has been associated with task difficulty [63] and behavioral flexibility [64,65]. Thus, it has been argued that the ACC constitutes an interface between motor, motivational and cognitive processes [54]. Activity in the ACC has also been associated with reward-based decision making [66], detection of errors, monitoring of conflicts and competition between responses [67–69].

A recent model of attention points further to the ACC as a regulator of both affective and cognitive processes [55]. This proposition constitutes a major contribution to our understanding of the function of the ACC and is consistent with a role for the ACC in pain affect to the extent that the subjective experience of pain unpleasantness may be associated with a similar mobilization of resources. Indeed, the activation of the ACC during pain may reflect the role of this structure in the regulation of behavioral and emotional responses to pain, in the regulation of cognitive processes to cope with pain, and in the regulation of modulatory pain mechanisms (see below). The increased demand on those processes depends on the meaning of pain and may be reflected in subjective feelings of unpleasantness. The original contribution of pain studies may be to emphasize that subjective experience is associated with activation of the ACC — an aspect that is often neglected in, but not inconsistent with, cognitive interpretations and information-processing theories. A question left unanswered in most cognitive studies is ‘how does it feel when the ACC is activated during a cognitive task?’

Figure 3

Emotion-related activation in pain-related regions. In this study, brain activity was evaluated in normal subjects during the subjective experience of emotions induced by the autobiographical recall of a personal emotional episode and compared against the recall of an emotionally neutral episode. PET scans were performed specifically when subjects indicated that they started to feel the emotion. Subjective feelings of emotion were associated with brain activation in many areas (see text), some of which are involved in pain. Here, we show a sample of those patterns that illustrate the activation in the parietal operculum in the region of S2/posterior insula during happiness, in the insular cortex during all emotions tested (combined analysis of all emotions compared with the neutral condition), and in the ACC during anger. The functional significance of this overlap of pain-related and emotional feeling-related brain activity is consistent



with the hypothesis that both of these experiences reflect the activity in brain structures involved in the representation of

body states. Results are from Damasio *et al.* [75**]. Original images courtesy of Hanna Damasio.

Given the conditions that lead to ACC activation and the types of processes in which the ACC may be involved, it seems plausible that ACC activation is accompanied by a subjective experience of mental effort and emotional feelings associated with the expected success or failure relevant to performing a difficult task. If this is confirmed, activation of the ACC might contribute to an increase in self-awareness and to feelings of self-agency that are associated with the voluntary engagement of cognitive and behavioral resources in response to novel, salient and affectively loaded stimuli.

Pain anticipation

In many circumstances, the affective aspect of pain goes beyond its immediate unpleasantness, and emotions may be experienced in the anticipation of pain and in response to the meanings and the perceived future consequences of pain [2]. Functional brain imaging studies confirm the activation of a similar network of brain structures during pain and the anticipation of pain, although the specific sites of activation have been shown to shift slightly rostrally in the ACC and the insula in the anticipatory state [70]. Similarly, the S1 and S2 cortices, as well as the ACC, are activated during tickling and the anticipation of tickling [71]. Furthermore, nonpainful stimuli presented in the context of painful stimuli (expectation of pain) can produce feelings of unpleasantness that are correlated with activation of the ACC and the parietal operculum/posterior insula in the region of area S2 [72*].

Pain anticipatory activation has also been reported in the ACC, ventromedial prefrontal cortex (VMPFC) and area PAG [73]. During the anticipatory phase, however, there was also reduced activity in the ACC and VMPFC with increased predictability of pain. Assuming that an

increased predictability may affect the emotional response in the anticipatory phase, activity in the ACC and VMPFC before pain might reflect the emotional response (anxiety) associated with anticipation of an unpredictable aversive event. This role in anticipation may not be restricted to pain but may be involved generally in the expectation of abstract rewards and punishments [74**].

Emotions and motivational states

In contrast to the large body of literature on the cerebral mechanisms underlying the perception of emotions (e.g. see Adolphs, this issue), few studies have examined specifically the neural correlates of the subjective experience of emotions. One of the few recent exceptions is a study conducted by Damasio *et al.* [75**], in which PET scans were acquired at the specific moment when subjects indicated that they experienced an emotional feeling triggered by the autobiographical recall of an emotional experience.

In this study, changes in regional cerebral blood flow (rCBF) were observed in the ACC, insula and parietal operculum in the region of S2 cortex (Figure 3). Additional effects were reported in the orbitofrontal cortices and in subcortical areas that are involved in the regulation of body states including many areas involved in nociception, such as brainstem nuclei, the amygdala and the hypothalamus. Previous studies have also suggested that the rostral ACC is involved in emotions [76,77], particularly in self-awareness of emotional responses [78]. This functional convergence may underlie the interactions between pain and emotions.

Motivational states may also be conceived as affective states with both autonomic and motor components. Consistently, the ACC, posterior cingulate cortex and area

PAG show strong activation during subjective feelings of thirst [79]. Similarly, drug craving produces consistent activation in the perigenual ACC, insular cortex, amygdala and NAcc, and shows strong overlap with anger-related activation [80**].

On the basis of the time course of brain activation in response to heat pain stimuli, Becerra *et al.* [51*] have proposed recently that the patterns observed in brain imaging studies of pain reflect the activation of a reward-related network and a pain-related network. The combination of fMRI with continuous rating methods to monitor moment by moment changes in pain [81–83], emotional feelings [84] and desires may provide the best available approach for investigating the neural correlates of those subjective experiences.

Magnetic resonance spectroscopy of pain and anxiety

Recently, magnetic resonance spectroscopy has been applied to the investigation of pain and anxiety. Results suggest that there is a relative decrease in *N*-acetyl aspartate in the orbitofrontal cortex associated with anxiety [85] and in the dorsolateral prefrontal cortex in individuals with chronic low back pain [86]. Although these studies should be considered preliminary, this technique may yet make a significant contribution to our understanding of the neurophysiological correlates of pain and emotions.

Self-regulation and the endogenous pain modulatory systems

One final note concerning the putative role of the ACC in pain affect and pain modulation concerns its role in self-regulation. The available anatomical data described at the beginning of this review are consistent with a role for the ACC in regulating endogenous pain modulatory mechanisms. Therefore, the ACC may not only be involved in pain perception but may also trigger subcortical pain modulatory mechanisms that may affect brainstem descending inhibitory pathways.

The modulatory effects of hypnotic analgesia on both ACC activity [40] and spinal nociceptive reflexes [2] is consistent with the possibility that descending modulatory mechanisms may be triggered from the ACC, together with the possibility that these mechanisms may, in turn, affect both pain intensity and unpleasantness. A similar involvement of the ACC in self-regulation has been suggested during the voluntary inhibition of sexual arousal [87] and during relaxation biofeedback [88].

Similarly, a reduction in rCBF in the subgenual portion of the ACC and the medial prefrontal cortex during anticipation of electric shocks has been suggested to reflect the engagement of coping strategies to reduce anxiety [89]. This would be consistent with a role of the ACC in the self-regulation of emotional responses. Additional studies will be required to assess the specific mechanisms and the specific role of subsectors of the ACC in the regulation of

pain and emotions by various strategies such as cognitive coping, relaxation or hypnosis.

Conclusions

Accepting the definition of pain as a subjective experience requires that we take a unique approach to the study the neurobiological basis of pain phenomena. Biological or information processing theories of nociception may be viewed as basic approaches that provide some primary constraints to pain theories, but these approaches alone cannot account fully for pain. The experiential approach gives a formal status to subjective experience and is not uncommon in human psychophysics and sensory neurophysiology, although it is acknowledged only rarely (Price DD, Barrell JJ, Rainville P, unpublished data). The investigation of the neurobiology of pain using this approach may provide the most direct test of the role of various brain structures in the experience of pain. Studies that reveal that cerebral activity is correlated with the affective dimension of pain should be considered a small but important step in identifying the neurobiological substrate of pain.

The ACC is one of the key cortical areas, possibly along with the insular cortex, that is involved in regulating nociceptive processes and behaviors in animals and in the subjective feelings of pain unpleasantness in humans. The ACC, along with other structures such as the amygdala and ventral striatum, may contribute further to the self-regulation of endogenous pain modulatory systems. The overlap observed between the patterns of cerebral activity associated with feelings of pain, emotions and motivational states in the ACC, and other body-related structures, such as the insular cortex, is consistent with their contribution to basic aspects of self-representation, self-regulation and consciousness [90].

Update

Two additional important studies have been published recently. In an fMRI experiment, Büchel *et al.* [91[?]] report monotonic increases in activity with increases in pain in several areas of the ACC: in a ventral sector of the supracallosal ACC; and in the perigenual ACC within subsectors of the ACC that overlap with, but are at least partly distinct from, more dorsal areas involved in stimulus registration, orientation and pain-independent attention processes, and more posterior areas involved in motor control. These findings provide further support to previous studies that have demonstrated similar differences between pain and attention-related activity (e.g. [57,58[?]]).

Another recent report by Petrovic *et al.* [92**] provides a first examination of the cerebral mechanisms involved in placebo analgesia. This PET study shows that both the administration of a placebo and a μ -opioid drug activate the rostral ACC, consistent with the previously suggested involvement of the endogenous μ -opioid system in placebo analgesia [2] and with the proposed role of this subsector of the ACC in self-regulation (see also [93]). Placebo

analgesia may involve mechanisms of descending modulation as suggested by covariation analyses showing a coupling between the activation in the rostral ACC and activity in the brainstem. Subjects displaying stronger placebo responses (larger decreases in pain ratings) also showed stronger drug-related activation in the rostral ACC consistent with the possibility that the more potent activation of μ -opioid receptors in the ACC is accompanied by a reduction in pain [50] and may contribute to placebo analgesia. Additional overlap between opioid and placebo responses found in the orbitofrontal cortices of the right hemisphere are suggested to reflect a cognitive modulation of emotional responses resulting from, or interacting with, pain [93]. These findings further emphasize the suggested role of the ACC in pain modulation and more generally in self-regulation, and raise important questions about the neural mechanisms underlying the interactions between pain and emotions.

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putamen, thalamus, ACC and frontal operculum. Right-lateralized activity was found in the thalamus, inferior parietal cortex (BA40), dorsolateral prefrontal cortex (BA9/46) and dorsal frontal cortex (BA6), during both innocuous and painful stimulation to either side of the body. This asymmetry in stimulus-related activation was not specific to pain and did not correlate with the subjects' ratings of pain intensity, which suggests an involvement in orienting, attention and stimulus evaluation that is not specific to pain.

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