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# Review

# Cortical modulation of pain

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**Abstract.** The sensation commonly referred to as 'pain' has two components. The first is the sensory-discriminative component and provides information on location, modality and intensity of stimuli. The second is the affective-motivational component and refers to the emotional responses (fear, distress etc.) and the urge to respond evoked by the somatic sensation, and at the cortical level these two components appear to be located in different regions. The cortex probably influences pain by two different mechanisms. There is good evidence that the cortex can reduce pain by interrupting the transmission of noxious information from the spinal cord level by activating descending pain modulatory systems located in the brainstem. Less well established is the idea that modulation can also occur at the cortical level to change the affective-motivational aspects of nociception so that pain is perceived but looses its emotional and aversive component.

**Key words.** Spinal cord; nociception; thalamus; descending inhibition: somatosensory; insular cortex; cingulate cortex.

## Introduction

We might all understand what 'pain' means in a colloquial sense, but it is not clear that pain is experienced by all individuals and by all species in the same way. Although the physical structures involved with pain sensation appear the same, the report of, or reaction to, pain varies considerably. A concept that has been useful in dealing with these issues is the broad division of somatic sensation into 'sensory-discriminative' and 'affective-motivational' components [1, 2]. The sensory-discriminative component is possibly the easiest to understand, and as the description implies, this component provides information on location, modality or intensity of stimuli. The neuronal structures, pathways, physiology and biochemistry associated with sensory-discriminative aspects of somatic sensation are relatively well established in the normal condition, although much less is known about the same structures once they have undergone reorganization in response to injury.

The affective-motivational component refers to the emotional responses (fear, distress etc.) and the urge to respond evoked by the somatic sensation. This aspect of pain is most obviously present in the language associated with pain. A commonly used assessment of pain, the McGill Pain Questionnaire, includes phrases like 'exhausting', 'sickening' and 'fearful' to describe pain and it is obvious that such phrases are not a description of the sensation itself but of a response to the sensation. Physically measurable aspects of the affective-motivational component are autonomic responses (e.g. blood pressure, skin galvanomic response) [3, 4] associated with painful stimuli and are mediated by common substrates in the central nervous system (CNS). Unlike sensations such as vision, it is very rare for somatic nociceptive stimuli not to evoke an affective-motivational response, and there is no easy means to escape from the sensation similar to closing one's eyes.

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The CNS structures and pathways subserving the affective-motivational responses are not quite so well defined as for the sensory-discriminative pathway, and this is, in part, because emotions involves mostly the cerebral cortex, large portions of which are uncharted. In other words, we are not trying to examine how stimulating a receptor in the periphery leads to activation of neurons in the cortex that code for location or intensity, but rather how that sensation is perceived as painful, i.e. generating a sense of urgency and attendant complex responses. Ultimately, the goal of studying pain is to be able to control or prevent pain. Presently, most strategies involve some means of blocking nociceptive signals somewhere along the path from the periphery before it reaches the cerebral cortex. Here we want to examine whether it is possible to control pain at the level of the cortex.

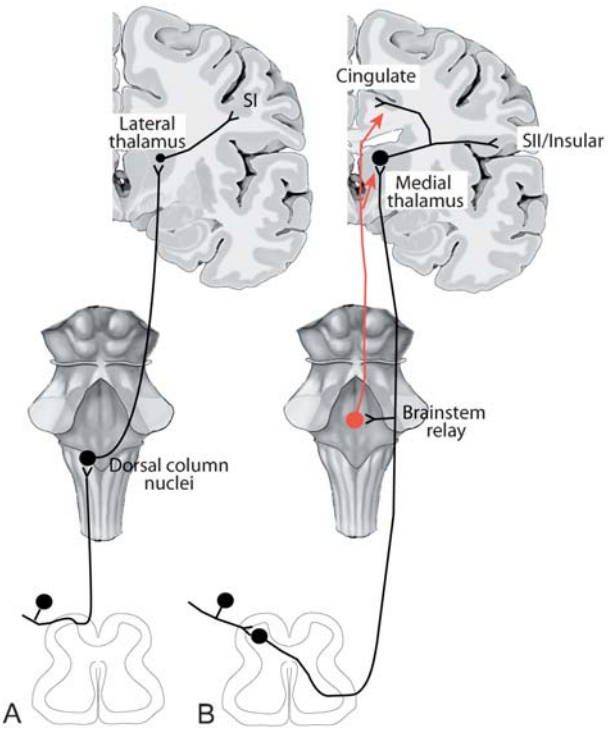


Figure 1. Schematic representation of the conceptual pathways subserving pain. The dorsal column medial lemniscal pathway (*A*) is generally associated with innocuous sensation, including fine touch, vibration and proprioception. The spinothalamic pathway (*B*) subserves nociceptive sensation. The classic pathway is indicated in black and includes relays through the spinal cord dorsal horn and medial thalamic nuclei before terminating in frontal and insular regions of the cerebral cortex. A parallel pathway is shown in red and arises from a number of sites in the brainstem, including the parabrachial nucleus, and eventually reaches the cortex either by direct projection or through relays in the thalamus and amygdala (not shown).

## Peripheral nociceptive pathways

From a practical point of view, if we define 'pain' as the responses associated with tissue injury, we can at least begin to define anatomic substrates underlying modulation of pain-generated responses. The sensation associated with tissue injury, generally called nociception, is transduced by peripheral nerve endings and carried to the CNS by axons with characteristic morphology, ion channels and neurochemical signature. The pathways and structures subserving somatic sensation are well established and can be found in standard neuroscience textbooks and will be only briefly reviewed here (fig. 1). The sensory receptors in the periphery that are activated by potentially tissue damaging stimuli are generally free nerve endings but occasionally more complex receptors [5]. These sensory endings may be activated by a variety of stimuli, including hydrogen ion concentration, histamine, capsaicin, heat and possibly mechanical deformation. The axons associated with the free nerve endings are small diameter non-myelinated (C) or thinly myelinated (Aδ) fibers, and their central branch terminates in the dorsal horn of the spinal cord. Axons of second-order neurons ascend in the contralateral spinal cord spinothalamic tract to terminate in a number of brainstem sites as well as several thalamic nuclei. In general, fibers from the spinothalamic tract terminate in more medially located thalamic nuclei that in turn project to the cortex. Some brainstem nuclei receiving nociceptive information also send projection to widespread areas of the cortex.

## Central pathways

Innocuous information is carried in large-diameter peripheral fibers (Aβ) that ascend in the dorsal columns of the spinal cord to terminate on second-order neurons in the dorsal column nuclei. These second-order neurons then relay the incoming information to the thalamus. This pathway terminates in nuclei located in the lateral thalamic nuclei that in turn project to several cortical areas but most densely in the primary somatosensory cortex.

Many details can be added to the above description, but the most important detail from our perspective is that this description of the classic 'labeled line' pathway should be regarded more as a conceptual pathway rather than a physical entity. Although it is clear that nociceptive information is conveyed by a very well defined class of fibers in the periphery, once these fibers enter the spinal cord, the path becomes muddied and not easily categorized. For example, some nociceptive projections from the spinal cord terminate in the brainstem sites such as the parabrachial nuclei where there is a convergence of inputs from visceral related structures and the cerebral cortex [6]. The parabrachial nuclei in turn project to the cortex directly and via the thalamus, hypothalamus and amygdala [7–10]. Thus, in addition to the classic spinothalamic path, the cortex receives nociceptive information that has

passed through the parabrachial nuclei, and in turn some of the cortical output passes through the parabrachial nuclei en route to the spinal cord. Recently, Craig [11–13] presented strong arguments that cutaneous nociceptive information becomes part of an interoceptive sensory system that involves relays through the parabrachial nucleus, and this pathway gives rise to the affective-motivational attributes of nociception.

## Non-cortical modulation of pain

There are two widely recognized sites involved in modulation of nociceptive transmission. The first is the spinal cord dorsal horn, where a number of different mechanisms have been shown, or postulated, to mediate interruption of transmission of nociceptive information to higher centers [14, 15]. The second site is the periaqueductal gray matter, which is firmly established as a region that when appropriately activated is able to interrupt pain transmission from the spinal cord and is considered a key component of the system generally referred to as the 'descending pain inhibitory system' [16–18]. Do these brainstem and spinal mechanisms interrupt both the discriminative and affective dimensions of pain equally? We known that some sensory discrimination can occur at a sub-cortical level. Rossetti and colleagues describe a subject with a thalamic lesion who was unaware of a stimulus applied to the affected arm but could point to the site of the stimulus using the opposite hand [19]. Similarly, studies on normal subjects showed that stimuli perceived without conscious awareness facilitated a motor response [20]. There are some remarkable reports of anencephalic children [21] who show a range of emotional and cognitive behaviors that appears mediated entirely by sub-cortical structures.

## Cortical substrate for pain modulation

Most would agree that immediate, conscious awareness of any sensation is a cortical phenomenon. Several cortical areas have been shown in animal and human studies to be specifically activated by noxious stimuli. Since the primary somatosensory cortex (SI) has long been established as the cortical site of innocuous somatic sensory discrimination, it was a reasonable assumption that nociceptive stimuli would also be represented in SI. In actuality, identifying nociceptive responses in SI proved elusive for many years [22, 23]. As early as 1911, Head and Holmes showed that large lesions of the primary somatosensory cortex in humans rarely disrupted pain sensation and as a consequence postulated that pain was a subcortical phenomenon [24]. The development of functional magnetic resonance imaging (MRI) in the early 1990s held the promise of resolving many issues of cortical function, at least in the human, but obtaining consistent results has been frustrating. Thus, using regional cerebral blood flow (rCBF) to examine cortical activation, a number of studies have described significant increase in cortical activation of SI following nociceptive stimuli, but a comparable number of reports using similar methods have failed to find any changes. In a review of the literature, Peyron et al. [23] found that for 30 experiments (from 24 studies) on somatic pain, significant SI activation was observed in 15 (63% of cases), but no significant change in the 9 other studies (46%). Despite the inconsistency of findings, it seems that some neurons in SI cortex are activated by nociceptive input, but the intensity, amount and character of the activation is different [25, 26] from non-nociceptive input to the same area.

One result of the human functional imaging studies is that it has become possible to define functions for large areas of cortex, sometimes referred to as 'association cortex' for which there was previously no definitive function. This has been true for nociception, and in contrast to SI activation, a large number of studies using rCBF and functional MRI show that the cortical regions exhibiting most reliable pain-related activity are bilateral and located in a broad region extending from the anterior insula to the second somatosensory cortex (SII) and associative parietal cortex, including the depth of the Sylvian fissure and the parietal and frontal operculi. Other cortical areas consistently reported to be activated by nociceptive stimuli are the anterior cingulate, prefrontal and supplementary motor cortices. These observations suggested that the representation of pain involves many cortical regions, and activation of different sites is responsible for the division of discriminative and affective components of sensation.

The location of cortical representation of nociception has been as problematic in animals as it has been in humans. It was not until relatively recently that nociresponsive cells were recorded in the rat SI region [27–29] using a variety of mechanical or electrical stimuli. Even so, the percentage of cells responding to noxious stimuli was low and raised questions about the relevance of the primary somatosensory cortex in nociceptive processing. A similar situation pertains to cats and non-human primates, where studies report relatively few nociresponsive neurons in the SI [30–32]. Nociceptive responding neurons have been recorded in other regions of the cortex in all species, but these cells tend to have large, often bilateral receptive fields that argue against a role in discriminative aspects nociception. As will be detailed below, the non-SI areas of cortex in animals, just as in the human studies, have come to be associated with affective aspects of nociception.

The synthesis of this material is that the role played by the SI in nociception is not yet completely established, but

what evidence there is shows it is not involved in the affective-motivational aspects of pain. In contrast, the evidence for involvement of other areas in nociception, notably the opercular, cingulated and prefrontal cortices, appears solid. A number of lines of evidence, outlined below, implicate these latter regions in the emotional, affective aspects of nociception. Interestingly, it is somewhat easier to carry out these studies in humans than in experimental animals. Human functional imaging technology permits mapping the entire brain relatively easily, and one obtains reports of the subjective experience of any stimulus. Nonetheless, behavioral, electrophysiological and anatomical studies in the rat, cat and non-human primate support the idea that the cingulate, opercular and prefrontal cortex have a function similar to that in the human.

**Cortical sites of nociceptive modulation** (fig. 2)

As already noted, lesions of the primary somatosensory cortex do not have a profound affect on nociception, but there is a large literature showing that manipulation of other cortical regions, notably the prefrontal and cingulate cortices, do play important roles in pain modulation. One of the earliest experimental demonstrations showed that anesthetizing a region of the prefrontal cortex of rats [33] using bilateral injections of procaine hydrochloride (Novocaine) lowered the flinch threshold. That is, the animal exhibited increased pain response, and to explain how anesthetizing the cortex could have this effect, it was suggested that this cortical region normally 'acts to limit the response to painful footshock'. Additional findings were that only bilateral injections of procaine were effective, and that cortical injections of morphine had no effect. Although this study produced different results than later studies, including our own [34–36], it did show that changing cortical function in a region other than the somatosensory cortex could alter the response to pain.

Subsequent studies have shown that the ventrolateral orbital (VLO) region of the frontal cortex receives somatosensory information and is activated by nociceptive cutaneous and visceral information both in normal [37–39] animals and in animals with peripheral nerve injury [40]. Morphine injected into the VLO results in an increase in tail-flick latency (antinociception) as well as analgesia in neuropathic pain [41]. In both cases the antinociceptive effect was reversed by administration of mu-opioid receptor antagonist, naloxone, showing the effect was receptor mediated and not a non-specific effect of the morphine injection. Baliki and colleagues also found that reducing VLO activity using a variety of anesthetic or lesion methods all produced analgesia [42]. These results are consistent with our own studies [35] showing that morphine injection into the rostral agranu-

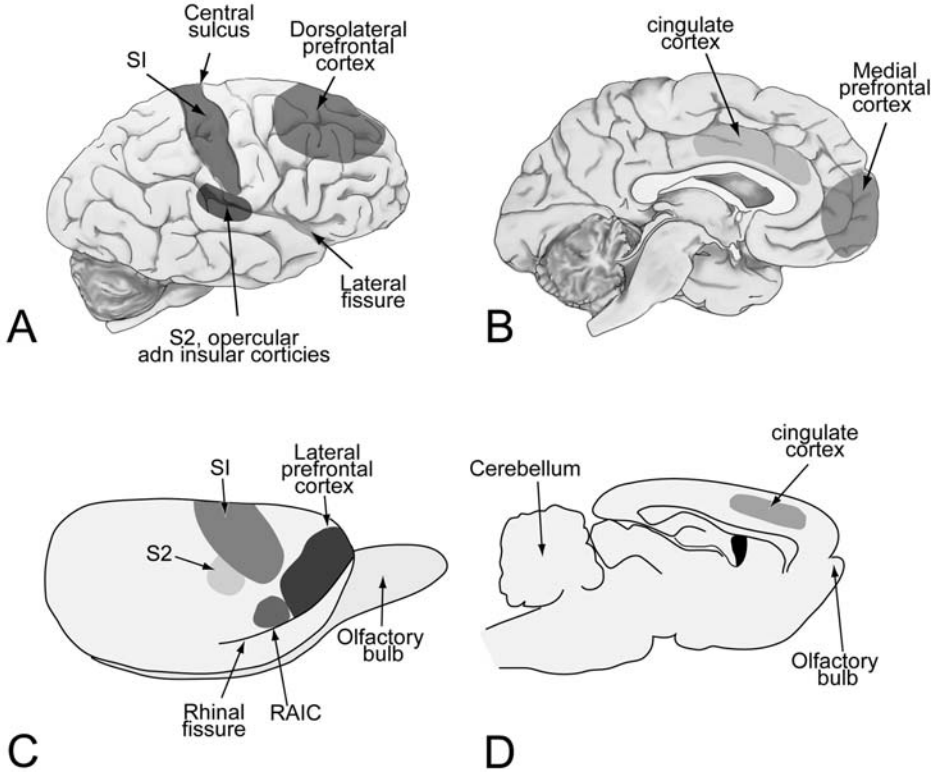


Figure 2. Diagrams to illustrate the approximate cortical regions of the human (*A*, *B*) and rat (*C*, *D*) referred to in the text. *A* and *C* are views of the lateral cortex while *B* and *D* show regions on the medial cortex

lar insular cortex, a region immediately caudal to the VLO, resulted in analgesia that was naloxone reversible and mediated through descending inhibitory systems. Studies that have activated the VLO using electrical or neurochemical (glutamate) stimulation have produced inconsistent results. In some cases stimulation produced analgesia [43–45], and in others the effect was pronociceptive and reduced pain thresholds [46]. However, all these studies are consistent in finding that the effects of stimulation of the VLO can be blocked by anesthetizing or lesioning the PAG. The conclusion is that manipulation of the VLO can change nociceptive thresholds but that the effect is mediated through the PAG by activating the descending pain inhibitory system.

The anterior cingulate cortex (ACC) is the second most reported site that is activated following nociceptive stimulation in human functional imaging studies [23]. The cingulate region is subdivided into a rostral (perigenual) and mid-cingulate (area 24) region. The mid-cingulate region is further separated into an anterior and posterior portion [47, 48]. The cingulate does not appear to play a role in discriminative aspects of nociception [49–51], and there is some question whether the anterior cingulate is related to the affective component, with some studies suggesting it is [48, 52, 53] while others have not [54, 55]. There is considerable evidence for mid-cingulate involvement in nociception [56, 57], and Vogt [47] proposed that the posterior mid-cingulate cortex coordinates the earliest skeletomotor reflex responses and the anterior mid-cingulate cortex coordinates fear and avoidance.

In addition to human functional imaging studies, there is considerable experimental evidence from animal studies implicating the cingulate cortex in modulation of nociception. Several electrophysiological studies have shown that the ACC receives nociceptive input [58, 59] but that the cells in this area have large receptive fields, suggesting they are unlikely to be involved in the discriminative aspects of sensation. Behavioral studies show that lesion of, or opioid injection into, the ACC in mice has an antinociceptive effect [60], while electrical stimulation or application of glutamate agonists in ACC results in hyperalgesia (increased pain response) [61]. In the latter cases the effects of ACC activation could be blocked by anesthetizing the rostro-ventral medulla, suggesting that the ACC, similar to the VLO, exerts its effect on nociceptive threshold by modulating the descending inhibitory pathway [18, 62] and presumably changing sensory transmission in the spinal cord. Other studies on the medial prefrontal cortex had documented an opposite effect, although a similar mechanism involving descending circuits was proposed. Electrical stimulation of the medial prefrontal cortex resulted in analgesia when tested on the hot plate, and tail flick [63] and further experiments recording from the midbrain [64] led to the proposal that these effects were mediated by the descending inhibitory system. It should be noted that the stimulation sites in the medial prefrontal cortex [63] are immediately rostral to those of the ACC [61], yet the effects on nociceptive behavior are opposite.

One issue arising from many of the animal experiments noted above is that it is usual to measure the nociceptive response by measuring changes in the threshold to withdrawal from a stimulus. Such measures do not address the affective-emotional aspect of the nociceptive stimulus. Recent studies [65, 66] approached such issues by pairing a nociceptive stimulus with a place preference test as a measure of the non-discriminatory-based effects of the stimulus. These studies showed that destruction of the anterior cingulate gyrus in the rat did not alter the acute response to a formalin stimulus but did reduce the avoidance that rats normally showed towards the chamber in which the stimulus was received [66]. More recently the same group has shown that the ACC is involved in a 'teaching signal' that results in avoidance learning [65] and that the ACC is able to activate another (as yet undefined) site to cause place avoidance. Such results are supported by other studies showing that scopolamine, a cholinergic antagonist, injected into the ACC before nociceptive stimulus results in reduction of pain later on. Scopolamine after pain stimulus does not reduce pain score, so it seems that ACC is involved in the memory of pain [67]. Presently there is no evidence that activation of the descending inhibitory system is involved in the pain avoidance mechanism described above. Thus, this effect is probably mediated entirely at the cortical level.

In our study of the rostral part of the insular cortex (RAIC) we found that nociceptive thresholds could be increased or decreased depending on how the cortex was manipulated. When the levels of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) were raised, nociceptive thresholds were increased, and this antinociception could be reversed by blocking the descending inhibitory system. This concept that the cortex is able to activate the descending inhibitory system is the same as proposed for other cortical sites such as the VLO mentioned previously. More intriguing, however, was the observation that if we raised GABA levels in the RAIC but then blocked one of the GABA receptor subtypes (the $GABA_B$ receptor), the nociceptive threshold was lowered. In this case, blocking the activity of the amygdala reversed the effect, and the nociceptive threshold was raised as the $GABA_A$ receptor activation of the descending inhibitory system remained. There are many components of this circuit that remain to be understood, but the results support the idea that responses to nociceptive input can be altered entirely at the forebrain level by means other than interrupting the nociceptive input somewhere between the periphery and the cortex.

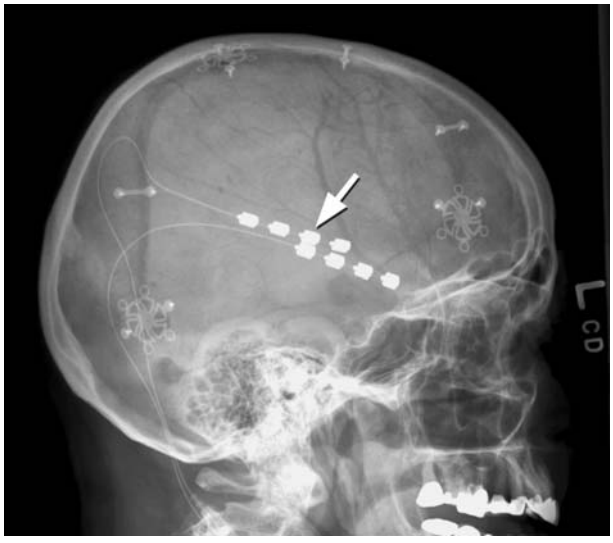

Figure 3. Electrical stimulation of the motor cortex provides significant pain relief in patients with intractable chronic pain. This figure is a cranial X-ray showing a lateral view of a patient with stimulating electrodes (arrow) centered over the face and arm region of the primary motor cortex. The wires from the stimulating electrodes are attached to a power source (not shown) located subcutaneously that is used to deliver the stimulating current to the electrodes.

**Other sites for cortical modulation of pain**

One advantage of human functional imaging studies is that the entire cortex can be surveyed for the response to a single stimulus. Thus, a number of cortical regions have been identified in humans that are activated by nociceptive stimuli but for which there is not much additional data and few animal studies. One such area is the posterior parietal cortex [68], although it has recently been shown that a region designated parietal 2 (called somatosensory cortex 2 in the Paxinos atlas [69]) is activated when a rat is placed in conditioning chamber where it received a nociceptive formalin stimulus two days previously [70]. The SII occupying the superior bank of the lateral fissure and the adjacent insular cortex are also both consistently activated in human imaging studies following nociceptive stimulation. However, these regions do not seem to be specific to pain, and responses to innocuous sensation [71–73] and olfactory/gustatory [74, 75] stimulus have been recorded in this region. In addition, the activity of this area changes with the intensity of the nociceptive stimulus [49, 76, 77]. These observations suggest that in humans the SII/insular cortex is more involved in the discriminatory aspects of nociception and general somatosensory integration. There is some evidence, however, that the insular cortex does play a role in generating the fearful aspects of pain. Berthier and colleagues have reported on six cases where lesions that involved the insular cortex led to pain where the patients no longer reacted to physical nociceptive stimuli or to verbal menaces [78].

**Electrical stimulation of the cerebral cortex** (fig. 3)

The idea that pain can be changed by cortical modulation is supported by several clinical observations and procedures. One of the most compelling pieces of evidence that the cerebral cortex can change responses to pain is the demonstration that electrical stimulation of the human primary motor cortex reduces pain in a number of conditions where other methods are ineffective at relieving pain. Since the initial report of Tsubokawa and colleagues [79], a number of independent groups have shown the reliability of this therapy for various pain syndromes [80, 81]. The rationale that guided surgeons to attempt cortical stimulation was based on the results of decades of experimentation showing that electrical stimulation of the cortex changes the transmission of information from both the spinal cord and the trigeminal system supplying sensation to the face [82–84]. The analgesic effect is, in part, mediated by presynaptic modulation of somatic afferents [85, 86–88], including nociceptive afferents [89, 90], that results in changes to the neural activity of ascending spino- and trigeminothalamic tracts [91, 92]. Interestingly, stimulation of the cerebral cortex can be either inhibitory, excitatory or both on spinothalamic neurons [91–94], and so it is not yet clear what neural mechanisms are involved in reducing pain. It is important to note that the most effective region for stimulation is the motor, rather than somatosensory, cortex and that stimulation does not appear to affect the sensory threshold or the discriminative component of pain. Thus, despite the fact that cortical stimulation has some effect on the ascending transmission of information, it also appears that much of the effect is at the supraspinal level [95].

There is another set of data from human studies that are most intriguing and are often cited when discussing affective-motivational versus sensory-discriminative issues. There are numerous anecdotal reports and a scattering of case reports (see [96]) that certain frontal cortical lesions result in a decreased pain response without a decrease in pain sensation. In other words, patients still feel the pain but find it less bothersome. In fact, Talbot and colleagues [96] report a case where bilateral lesions of the anterior-internal capsule resulted in the subject reporting increased sensitivity to nociceptive stimuli (they withdrew from a noxious stimulus sooner than pre-lesion) but rated the sensation as less unpleasant than pre-lesion. The opposite situation has also been reported. Ploner and colleagues [97] describe a case of a subject who suffered a stroke of the right sensory cortex that involved the hand area of SI and SII. Thermal laser stimulation of the left (contralateral to the stroke) hand could not be localized or described (e.g. hot, cold pinprick-like etc.) but was reported as 'clearly unpleasant' and caused the subject distress.

## Summary

It seems quite clear that processing of the sensation referred to as 'pain' is not confined to a single cortical region. The ability to locate and describe a painful stimulus resides in the primary somatosensory cortex, while the unpleasant and aversive aspects involve other cortical areas, notably the frontal, opercular and cingulate cortices. Just as lesions of SI makes us anesthetic and unable to locate or describe cutaneous input, lesions of the other named cortical areas reduce the unpleasantness of the stimulus. There are still many issues concerning these two components of pain that are open to question and interpretation, but enough solid information is now available to construct, meaningful, defensible and sometime provocative hypotheses on what pain is [12, 98].

It has also become clear that there are mechanisms for a 'top down' control of pain. The first mechanism involves the cortical activation of descending pathways involving brainstem sites that interrupt the flow of nociceptive information from the periphery. However, it should be noted that in animal experiments, when cortical manipulation results in changes in nociceptive threshold, an obvious follow-up is to see if descending pain modulatory pathways are involved. Very often other possibilities are not investigated, and thus the involvement of sites such as the amygdala or other forebrain areas might be overlooked.

A second, not well understood or as yet fully characterized pain modulatory system, involves interactions between different cortical regions and between the cortex and other telencephalic structures. This system allows nociceptive information to reach consciousness but prevents it from being perceived as 'painful.' Being able to alter cortical processes so that nociceptive stimuli are felt but 'don't hurt' may have advantages in some clinical situations. It should not be forgotten that pain is necessarily such a focusing sensation because it draws attention to stimuli that are potentially life threatening. Thus it might be preferable to retain the ability to recognize these stimuli but be able to prevent the attendant debilitating emotional effects [99]. Examples where cortical control of pain affect would be useful are in the treatment of chronic pain, particularly when there is no apparent physical cause of the pain, and the alleviation of terminal cancer pain that is presently treated with powerful medications that bring relief but cloud the intellectual faculties.

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