

Pain Perception and Response: Central Nervous System Mechanisms

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ABSTRACT: Although several decades of studies have detailed peripheral and ascending nociceptive pathways to the thalamus and cerebral cortex, pain is a symptom that has remained difficult to characterize anatomically and physiologically. Positron emission tomography (PET) and functional magnetic imaging (fMRI) have recently demonstrated a number of cerebral and brain stem loci responding to cutaneous noxious stimuli. However, intersubject variability, both in the frequency and increased or decreased intensity of the responses, has caused uncertainty as to their significance. Nevertheless, the large number of available imaging studies have shown that many areas with recognized functions are frequently affected by painful stimuli. With this evidence and recent developments in tracing central nervous system connections between areas responding to noxious stimuli, it is possible to identify nociceptive pathways that are within, or contribute to, afferent spino-thalamo-cortical sensory and efferent skeletomotor and autonomic motor systems. In this study it is proposed that cortical and nuclear mechanisms for pain perception and response are hierarchically arranged with the prefrontal cortex at its highest level. Nevertheless, all components make particular contributions without which certain nociceptive failures can occur, as in pathological pain arising in some cases of nervous system injury.

RÉSUMÉ: La perception et la réponse à la douleur: mécanismes nerveux centraux. Bien que des études effectuées au cours des dernières décennies aient décrit de façon détaillée les voies nociceptives périphériques et ascendantes vers le thalamus et le cortex cérébral, la douleur est demeurée un symptôme difficile à caractériser au point de vue anatomique et physiologique. La tomographie par l'émission de positons et l'imagerie par résonance magnétique fonctionnelle ont démontré récemment l'existence d'un certain nombre de sites qui répondent à des stimuli cutanés désagréables. Cependant, la variabilité entre les sujets, tant quant à la fréquence qu'à l'augmentation ou la diminution de l'intensité de la réponse, a causé de l'incertitude sur leur signification. Toutefois, les nombreuses études d'imagerie disponibles ont montré que plusieurs zones qui ont des fonctions bien reconnues sont fréquemment touchées par les stimuli douloureux. Avec ces données et les développements récents dans la cartographie des connexions entre les zones répondant aux stimuli désagréables dans le système nerveux central, il est possible d'identifier les voies nociceptives qui sont à l'intérieur ou qui contribuent au système afférent sensitif spino-thalamo-cortical et aux systèmes efférents moteurs squelettique et autonome. Dans cette étude, l'hypothèse proposée est que les mécanismes corticaux et nucléaires de la perception de la douleur et de la réponse à la douleur sont structurés de façon hiérarchique, le cortex préfrontal étant placé au plus haut niveau de la hiérarchie. Cependant, toutes les composantes fournissent une contribution particulière sans laquelle certaines défaillances nociceptives peuvent survenir comme c'est le cas dans la douleur pathologique observée dans certains cas de lésion du système nerveux.

Can. J. Neurol. Sci. 2000;27: 2-16

Since Melzack and Wall¹ proposed a gate control model for pain perception and response 35 years ago, there have been significant advances toward understanding the central nervous system mechanisms subserving pain. However, there is still no general agreement as to its nature nor the manner in which pain is processed within the nervous system.² Speculation as to a "pain centre" has been generally criticized because of the many cortical and subcortical structures that are involved and attempts to elicit pain by electrical stimulation of the human cortex and thalamus has only rarely been successful.^{1,3,4} Also, studies of post-stroke pain or attempts at central nociceptive

deafferentation have not shown localization to a specific part of the nervous system except that damage to the spino-thalamo-cortical pathway is apparently necessary.⁵⁻⁷ Nevertheless, patients experiencing pain show sufficiently reproducible

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RECEIVED JANUARY 12, 1999. ACCEPTED IN FINAL FORM AUGUST 24, 1999

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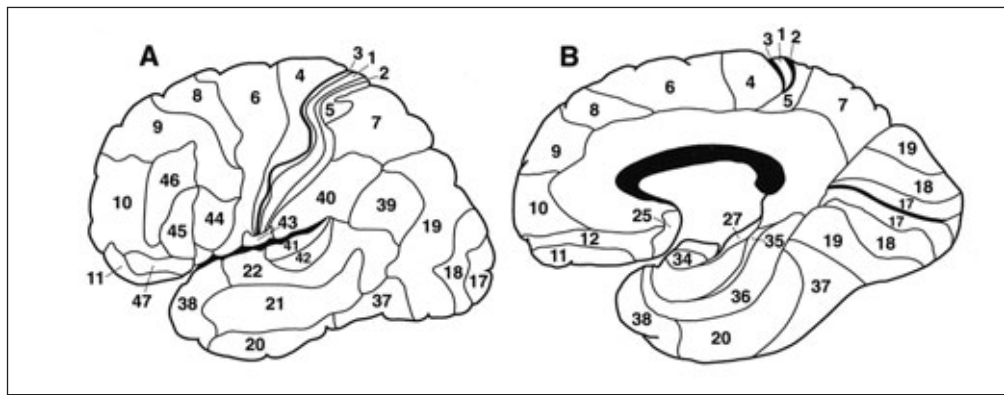


Figure 1. Human cerebral cortex showing cerebral lateral (A) and medial (B) cytoarchitectural areas as described by Brodmann.⁸⁸ The excluded areas on the medial surface are illustrated in Figure 3 (cingulate cortex).

responses when examined by either electrophysiological methods or regional blood flow (rCBF) measurements, using positron emission tomography (PET) and functional magnetic imaging (fMRI), to suggest a nociceptive system consisting of afferent and efferent components.

The ascending nociceptive pathways in the spinal cord and brain stem to the thalamus have been extensively explored since the latter part of the nineteenth century but only very recently have many thalamic and other cerebral connections been identified.^{8,9} Lateral and medial thalamic regions that are involved in processing sensory-discriminative and motivational-affective aspects of pain, respectively, are now recognized through electrophysiological studies.^{10,11,12} Brodmann's area 24 of the anterior cingulate cortex, where a nociceptive area (24c) receiving medial thalamic projections has been identified (see Figure 3), was first recognized as producing complex cardiovascular, respiratory and pupillary autonomic responses and altered emotional expression when electrically stimulated in the monkey by Smith.¹³ Shortly afterward, Ward¹⁴ reported that anterior cingulate ablation in primates produced a state of social indifference and loss of fear (tameness). Foltz and White,¹⁵ noting similar behaviour in the human following frontal lobotomy, postulated "that transection of the cingulum might be of benefit in those clinical cases of intractable pain in which marked emotional factors appeared to contribute to the intolerable situation". When undertaken, they found that the noxious quality of chronic pain was alleviated although pain was still present and, therefore, it remained uncertain whether the emotional reaction to, rather than the pain itself, was relieved. Frontal lobotomy (or leucotomy) is a procedure that often interrupted prefrontal connections between the thalamus and anterior cingulate cortex and similar effective relief of pain has been achieved with lesions involving the midline parafascicular nucleus and intralaminar nuclei of the thalamus.^{16,17} Indeed, Vogt et al.¹⁸ more recently described thalamic afferents from the midline and intralaminar nuclei to the anterior cingulate cortex and suggested that their input, and possibly those from regions such as the amygdala and insula, might be contributors to the noxious aspects of pain.

With the arrival of PET it became possible to explore, by indirect means, cerebral changes occurring in response to painful injury. Jones et al.¹⁹ found that cutaneously applied painful heat produced increased blood flow in area 24 of the contralateral anterior cingulate cortex, the thalamus and lenticular nucleus (Figures 2 and 3). In contrast, activity was not observed in either the primary (S1) or secondary (S2) cortical somatosensory areas, although increased activity has since been described by others in both. This suggested to the authors that pain was a predominantly emotional response to potentially damaging stimuli. Jones et al.²⁰ also found high levels of opioid receptor binding in the projections of the medial thalamic pain system to both the anterior cingulate region and the prefrontal cortex.

Since the report of Jones et al.¹⁹ PET has been used to show that many areas of brain respond to nociceptive stimuli but, more recently, brain imaging has been improved with the introduction of fMRI (Table 1).^{2,4,12,19,21-33} PET and fMRI monitor increases or decreases in rCBF or blood oxygen utilization by different methods. The PET studies employ a radiotracer ($H_2^{15}O$) in the determination of changes in blood flow whereas fMRI measures changes in magnetic fields as a function of blood flow and blood oxygen saturation.^{34,35} PET has been highly useful in locating areas of brain responding to noxious stimuli but, in comparison with fMRI, spatial resolution (measured in mm) is less precise, scan times are longer and results depend upon averaged group data.³⁵ Because of its greater precision and speed and usefulness in studying individual subjects, most studies of nociception using fMRI have tended to focus upon spatial and temporal resolution of pain-related activity in particular regions, such as the anterior cingulate cortex or thalamus, that have been previously identified on PET scans.³⁵⁻⁴² Comparisons of different individuals have shown that fMRI responses to the same stimulus, within a particular area, is variable in location and it can also differ in extent over time depending on pain duration and intensity.^{39,42} Nevertheless, PET provides reproducible data that are comparable to fMRI on the areas of brain responding to painful stimuli. Whereas increased rCBF can be correlated with vasodilatation and increased oxygen utilization, attributable to increased neuronal activity, the significance of a decreased

Table: Human Brain Loci in PET Activated Response to Noxious Stimuli

	Case Studies (References)																		
	1 (21‡)	2 (22‡)	3 (23‡)	4 (24‡)	5 (31‡)	6 (19)	7 (25)	8 (2)	9 (26)	10 (12*)	11 (12*)	12 (27)	13 (28)	14 (29)	15 (30)	16 (4)	17 (32)	18 (33)	
Thalamus	↑ _B	-	-	-	-	↑ _C	↑ _B	-	↑ _C	-	↑ _C	-	↑ _B	-	-	↑ _B	↑ _C	↑ _I	
Anterior cingulate																			
- area 24	↓ _B	↑ _L	-	↑ _R	↑ _B	↑ _C	↑ _C	↑ _C	↑ _C	↑	↑	↑ _C	↑ _C	↕ _L ^R	↑ _B	↑ _I	↓ _I	↑ _B	
- area 25	↑ _L	-	-	-	↑ _C	-	-	-	-	-	-	-	-	-	-	-	-	-	
- area 32	-	↑ _L	↑ _B	↑ _R	↑ _B	-	-	-	-	↑ _I	↓ _I	-	↓ _B	-	↑ _B	↕ _C ^I	↓ _I	↑ _C	
Posterior cingulate																			
- areas 23, 29, 30, 31	↓ _R	-	↓ _B	-	-	-	-	-	↓ _C	-	↓ _C	-	↓ _B	↑ _B	-	-	-	↑	
Somatosensory																			
- S1 areas 3, 1, 2	-	-	↑ _B	-	-	-	↑ _C	↑ _C	↑ _C	-	-	↑ _C	-	-	↑ _B	↑ _C	↑ _C	-	
- S2	-	-	-	-	-	-	↑ _B	↑ _C	↑ _C	-	-	↑ _C	-	-	-	-	↑ _B	↑ _C	
Parietal																			
- areas 7, 39, 40	↓ _L	-	↓ _B	↓ _B	↑ _B	-	-	-	-	↑ _I	↓ _C	-	↓	↑ _B	↕ _B	↑ _B	↑ _B	-	
Insula	-	-	↑ _B	↑ _B	-	-	↑ _C	-	↑ _C	-	↑ _C	↑ _C	↑ _B	↑ _B	↑ _B	↑ _C	↑ _C	↑ _B	
Prefrontal																			
- area 8	-	-	↓ _R	-	-	-	-	-	-	↓ _C	-	↓ _B	-	↓ _C	-	-	-	↓ _C	
- area 9	-	-	↓ _R	↑ _R	-	-	-	-	-	-	-	↑ _C	-	↕ _I ^C	-	-	-	↓ _B	
- area 10	↑ _B	↑ _L	↓ _R	↓ _B	-	-	-	-	↓ _C	↑ _I	↓ _I	-	-	↑ _B	↑ _I	↑ _B	↓ _C	↑ _I	
- area 44	↑ _B	-	↑ _B	↑ _B	-	-	-	-	-	-	-	-	↓ _B	-	↑ _I	↑ _B	-	-	
- area 45	-	-	-	↑ _B	-	-	-	-	-	-	-	-	-	-	-	↑ _B	-	-	
- area 46	-	↑ _L	-	-	-	-	-	-	-	-	-	-	↑ _C	-	-	↑ _B	-	-	
- area 47	↑ _B	-	-	↑ _B	-	-	-	-	-	-	-	-	-	↑ _B	-	-	↑ _C	-	
Basal ganglia †	-	-	-	↑ _B	-	↑ _C	-	-	↑ _I	↑ _C	↑ _C	-	-	-	↑ _C	↑ _B	-	↑ _C	
Supplementary motor	-	-	↑ _B	↑ _R	-	-	-	-	↑ _C	-	-	-	-	-	↑ _B	-	-	-	
Premotor area 6	↑ _B	-	-	↑ _B	-	-	-	-	-	↓ _C	↓ _C	-	↓ _B	-	-	↑ _B	-	-	
Primary motor area 4	-	-	↑ _B	↑ _B	-	-	-	-	-	-	-	-	-	-	↑ _B	↓ _B	-	-	
Periaqueductal gray and brain stem	↑	-	-	-	↑	-	↑	-	-	↑	↑	-	-	-	↑	-	-	-	
Cerebellum	-	-	-	-	-	-	↑	-	-	-	-	-	-	↑	↑ _I	-	-	↕ _B ^I	
Hypothalamus	↑	-	-	-	-	-	-	-	-	-	-	-	-	-	↑ _C	-	-	-	
Occipital																			
- areas 17, 18, 19	-	-	↓ _B	↓ _B	↑ _B	-	-	-	-	↓ _C	↓ _B	-	-	-	-	↕ _I ^C	↓ _B	↓ _B	↓ _B
Temporal lobe																			
- superior - area 22	-	-	-	-	↑ _B	-	-	-	-	-	-	-	↑ _I	-	↓ _C	-	-	-	
- middle - area 21	-	-	-	-	↑ _B	-	-	-	-	-	-	-	↓ _I	-	↓ _C	-	-	-	
- inferior - areas 20, 37	-	-	-	↓ _B	-	-	-	-	-	-	-	-	-	↑ _L	↓ _B	↓ _C	-	-	
- polar - area 38	-	-	-	↑ _R	-	-	-	-	-	-	-	-	-	-	-	↓ _C	-	-	
Hippocamp. formation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	↓ _I	↑ _C	-	-	
Amygdala	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	↓ _B	-	-	
Fusiform gyrus																			
- areas 28, 35	↓ _B	-	-	-	-	-	-	-	-	-	-	-	-	-	↑ _C	-	-	-	

rCBF symbols: ↑ = increased; ↓ = decreased; ↕ = increased and decreased; dash (-) = no response. The side of response is shown in superscript and subscript symbols: C = contralateral; I = ipsilateral; B = bilateral; R = right; L = Left.

‡ The first 5 columns were studies on (1) angina pectoris, (2) intestinal pain, (3) oesophageal pain, (4) cluster headache, (5) migraine.

Lateralization of pain stimulus in some studies varied. Case 17 was diagnosed lateral medullary syndrome.

* Two studies were described in same paper: noxious stimuli (control cases) and atypical facial pain.

† Described as corpus striatum, lentiform nucleus or putamen.

response remains unclear. It may reflect diminution of ongoing neuronal processes as an outcome of increased neuronal activity elsewhere.⁴³ Also, responses are usually lateralized and most often contralateral to a noxious stimulus but the side can be unpredictable.

As stated above, the normal nociceptive pathways, as they extend from the periphery to the thalamus, have been familiar for decades and only recently, have nociceptive projections to other areas of the brain responding to painful stimuli, been recognized.^{8,19} Many of the recent advances can be credited through detailed anatomical tracings and ongoing physiological studies of pathways in the spinal cord and between cortical regions and nuclei. With the introduction of PET and fMRI, many of these regions of brain that were hitherto unappreciated in their significance to pain, were seen to participate in the processing of nociceptive information. The prefrontal cortex, especially in its connections and functions, is now better understood and shows a number of areas responding to painful stimuli, which suggests that it probably has a prominent role in pain awareness and response.⁴⁴⁻⁴⁷ The objective of this review is to attempt to integrate these multiple areas of response into a system of afferent and efferent pathways to enable better understanding of the significance of pain.

DORSAL HORN AND TRIGEMINAL NUCLEUS

Pain is normally experienced when peripheral branches of unmyelinated (group C) and small diameter A δ myelinated axons are activated by noxious chemical, mechanical, electrical or thermal stimuli. Activation produces an electrical discharge that is initiated by nociceptive receptor cation channels and conducted along axons entering the medulla oblongata to the nucleus of the trigeminal spinal tract or, in the case of those entering the spinal cord, to the dorsal horn where processing of nociceptive information begins.⁴⁸ In the trigeminal nucleus and dorsal horn, information on pain is extensively processed, both locally and by descending fibres from higher levels of the nervous system, before contact is made with the cells of origin of the trigeminothalamic and spinothalamic tracts.

Whereas several different neurotransmitters are released in the dorsal horn (and corresponding trigeminal nucleus) during noxious stimulation, pain response is believed to be mediated locally by the release of L-glutamate, the principal transmitter signalling pain at all intensities, and substance P.^{49,50} Substance P does not mediate acute pain but modulates sensitivity to pain and is essential for the "windup" response – a NMDA (*N*-methyl-D-aspartate) mediated augmentation of the response of the dorsal horn nociceptive neurons to a constant repeated stimulus.^{51,52} Substance P and another tachykinin, neurokinin A (and possibly other sensory neuropeptides), can also be released from peripheral sensory nerve terminals in skin and various tissues at higher stimulus intensities producing "neurogenic inflammation" and a state of increased moderate to intense pain.^{50,53} De Felipe et al.⁵² have proposed that substance P also generates stress-induced analgesia by activating central inhibitory pathways from the brain stem, a process that is pharmacologically distinct from the opiate-mediated pathway (see below).

Descending spinal cord pathways also significantly influence nociception. Tract-tracing studies have shown that fibres from

the precentral motor cortex and somatosensory cortex (areas 1, 2, 3, and 5) terminate in the posterior parts of the dorsal horn, although most extensively in laminae VI and VII, where they may have a direct influence on nociceptive responses (Figure 1).⁵⁴⁻⁵⁷ Descending fibres, having an indirect influence on nociceptive thresholds, have been traced from the prefrontal cortex, hypothalamus and amygdala to the periaqueductal gray matter and other brain stem nuclei that project to the trigeminal nucleus and dorsal horn.

Descending fibres can have important inhibitory influences on medullary and spinal nociceptive neurons and are divisible into those which act on either opioid or non-opioid receptors.⁵⁸ Activation of neurons in the periaqueductal gray produces direct antinociception that is μ -opioid receptor-mediated in the dorsal horn.⁵⁹ This may be due to a direct action on either primary afferents or by way of local circuit neurons in the substantia gelatinosa. The periaqueductal gray also projects to the nucleus raphe magnus in the medullary reticular formation where non-opioid effects on the dorsal horn via serotonergic fibres are relayed to the substantia gelatinosa (lamina II).⁶⁰⁻⁶³ Electrical stimulation of either the periaqueductal gray or nucleus raphe magnus produces profound analgesia.^{63,64} Noradrenergic fibres, in a descending pathway from the locus coeruleus, end in the dorsal horn where they also have an inhibitory role on nociceptive responses.⁶⁵ Hitoto et al.⁶⁶ suggest that noradrenergic analgesia is produced by stimulation of A δ afferent fibres which activate descending locus coeruleus neurons causing an increase in noradrenaline level in the dorsal horn. Still other small molecule and peptide neurotransmitters are involved in modulating nociception but their roles have generally been less clearly defined.⁶⁷⁻⁶⁹

Ascending pathways carrying nociceptive information are: (i) the ventral trigeminothalamic tract from the nucleus of the spinal trigeminal tract in the medulla and (ii) the spinothalamic, spinoreticular and spinomesencephalic tracts from the dorsal horn. These terminate in various parts of the brain stem reticular formation and, ultimately, thalamus. Willis,⁴⁹ has suggested that the sensory-discriminative aspects of pain proceed principally by way of the spinothalamic pathway whereas motivational-affective influence requires all three ascending tracts. Most trigeminothalamic and spinothalamic tract fibres terminate in the ventral posterior nucleus of the thalamus whereas some, specifically involved in experiencing pain, end in the intralaminar and, to a lesser extent, in the midline nuclear region of the thalamus and have much larger receptive fields.⁹ Comparisons of PET responses in the thalamus following cranial and spinal nociceptive stimulation, as shown in the Table, are similar.^{31,70,71} A generally unfamiliar pathway is the spinohypothalamic tract that arises in the dorsal horn and carries nociceptive information directly to the limbic system.⁷² Similar to the motivational-affective system, it may be directly involved in emotional and autonomic regulation and might also have nociceptive reflex potential.

THALAMUS

The thalamus is the major sensory relay station where sensory information is sorted for delivery to the cortex and subcortical nuclei. As noted above, nociceptive pathways upon entering the

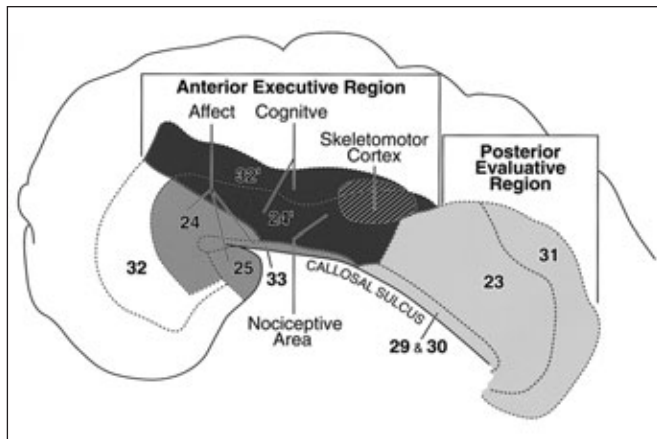


Figure 4. Flat map as in Figure 3 showing functional regions of the human cingulate cortex consisting of anterior executive and posterior evaluative regions.⁹⁵ The area shown as the skeletomotor cortex in cingulate sulcus corresponds to the caudal cingulate zone (gigantopyramidal area) shown in Figure 7. The visceromotor region in areas 24 and 25 is less well defined.

CINGULATE CORTEX

The cingulate cortex is a prominent and functionally complex part of the limbic system which extends the length of the corpus callosum from the genu backward above and adjacent to the corpus callosum (Figure 3). Cytoarchitecturally, it is divided into an anterior part which has an agranular appearance similar to motor cortex with a prominent layer Va, and a posterior part consisting of granular layers II and IV typical of areas receiving primary afferent input.^{88,89} The two parts of the cingulate cortex are further subdivided into specific areas.^{18,77,89} Each of the areas of the anterior part (areas 25, 24, 33, 32) and posterior part (areas 29, 30, 23 and 31) receive and reciprocate very different cortical, thalamic and other subcortical inputs (Figure 3).^{18,90} In general, the anterior cingulate cortex receives a relatively small afferent supply from other cortical areas whereas the posterior cingulate has extensive input from the frontal, parietal, temporal and occipital lobes. Nevertheless, the two cingulate parts are well interconnected. Thalamic projections also differ with the anterior cingulate cortex receiving afferents mainly from the midline and intralaminar thalamic nuclei while the posterior part derives its input particularly from the lateral dorsal and anterior group of thalamic nuclei, all of which are correspondingly reciprocated (Figure 2).⁹¹ Differences in input are especially striking in connections with the amygdala which reciprocally projects to the anterior cingulate areas 33, 25 and the rostral part of 24 but to neither the caudal part of area 24 nor the posterior cingulate cortex.⁹⁰ As discussed below, the major role of the amygdala is the storage of emotional memory, and its connections with the anterior cingulate region, where emotional responses are generated, may be to relate ongoing with past emotional experience. In PET studies of pain the anterior cingulate cortex, and to a lesser degree the posterior part, are highly responsive to noxious stimuli (Table 1).

As differences in cytoarchitecture and connections would suggest, the anterior and posterior cingulate cortices also have

quite different functions.⁹² The anterior part is viewed as having executive responsibility (vis à vis motor function) whereas the posterior part has more of an evaluative role (Figure 4).^{28,77,93-95} Moreover, the anterior cingulate cortex is further subdivided into “affect” and “cognitive” parts. The rostral “affect” subdivision (areas 33, 25 and rostral area 24) is reciprocally connected to the amygdala, hypothalamus and autonomic brain stem motor nuclei, and its function, on the basis of electrical stimulation and surgical ablation studies, is to generate emotional responses.⁹⁵ The caudally located “cognitive” subdivision (areas 24’ and 32’) is considered to be mainly responsible for skeletomotor behaviour and nociception (see also Figure 7).⁹⁵ As discussed above, the midline and intralaminar nuclei of the thalamus (motivational-affective system) project to the anterior cingulate region and those neurons which receive afferents from the spinothalamic tract that originate from cells in the dorsal horn responding to noxious stimuli project to the nociceptive region of the cingulate cortex that is located in the dorsal part of area 24 in the vicinity of 24c.^{18,77} As observed by Rainville et al.⁹⁶ pain affect, i.e. the discomfort of pain, despite evidence in the monkey that somatosensory areas 1 and 2 receive direct nociceptive input, is encoded in the human anterior cingulate and not in the S1 and S2 somatosensory cortices. The latter areas are essential to the location and character of pain for appropriate avoidance responses. The posterior cingulate cortex has widespread input but significant reciprocal connections with the posterior parietal region, visual cortex, striatum and thalamus and, together with the anterior cingulate cortex – particularly the caudal portion of area 24 which receives parietal and the bulk of the posterior parahippocampal projections going to area 24 – may participate in the formation and recall of long-term factual memory and avoidance learning.^{26,29,94,97}

A number of techniques have demonstrated nociceptive responses in the cingulate gyrus accompanying noxious peripheral stimulation. Vaccarino and Melzack⁹⁸ could inhibit peripherally-induced severe pain by the injection of lidocaine into the fasciculus cinguli of rats. Sikes and Vogt⁹⁹ used electrophysiological recording techniques to observe excitatory evoked potentials in area 24b of the anterior cingulate cortex of rabbits in response to noxious transcutaneous electrical, mechanical and thermal stimuli. They concluded that the cingulate nociceptive responses were mediated through the medial and intralaminar nuclei of the thalamus and noted lidocaine injections into the medial thalamus abolished these responses. It is noteworthy in this context that opioid innervation is particularly highly concentrated in the midline and anterior intralaminar regions of the thalamus and there is also an unusually high density of opioid receptors in the anterior cingulate cortex which may have a regulatory function in situations of chronic pain.^{9,77,89,100,101} Vogt et al.⁷⁷ found that nociceptive area of the cingulate cortex in the rhesus monkey brain was, similar to the rabbit, probably located at the dorsal part of area 24. Surgical cingulotomy in man, as noted earlier, has been performed with reported success in the relief of intractable chronic musculoskeletal pain but was unsuccessful with thalamic pain due to old stroke.¹⁰² In PET studies, area 24 of the human anterior cingulate cortex shows the most consistent increase in rCBF in response to noxious stimulation although it is occasionally unresponsive (Table). The location of cognitive

(attention-related) and pain-related activations demonstrated on fMRI correspond to the anterior cingulate areas as described above by others.^{37,95}

SOMATOSENSORY, ASSOCIATION CORTICES AND SUBCORTICAL NUCLEI

In addition to the cingulate cortex, other regions of the brain show significantly increased nociceptive PET responses, notably the somatosensory area S1, thalamus, insula and basal ganglia (Table). Other areas, such as the parietal cortex, show both increased and decreased activity, whereas in the frontal eye field (area 8), posterior cingulate region and occipital cortex almost all activity is significantly decreased. The main connections within and between these regions as they may integrate nociceptive responses are as follows.

Somatosensory (S1 and S2), parietal, occipital and temporal cortices

Somatosensory area S1, visual and auditory cortices in the parietal, occipital and temporal lobes project to their respective adjacent association fields and to the frontal lobe.^{103,104} As described by Jones and Powell,¹⁰³ in primates each of the major sensory areas, through a cascading series of connections, converge at first as unimodal sensory areas and then as polysensory regions (Figure 5). The shift is toward different, more highly advanced sensory association and motor cortices in the parietal and frontal lobes. For example, in the somatosensory system as shown in Figure 5, sensory information from SI is processed in parietal area 5 and then in the posterior parietal area 7 where unimodal topographical boundaries are merged to form a body surface image.¹⁰⁴ From area 7, two or more unimodal “high level” somatosensory association cortices merge to form polysensory zones on the floor of the superior temporal sulcus, cingulate cortex and parahippocampal cortex. Additional recipients of polysensory convergence are located in the lateral aspect of the orbitofrontal cortex, the temporal and frontal poles and amygdala.^{103,104} As stated above, there is a stepwise procession of reciprocal connections from the parietal sensory association areas to the frontal motor and prefrontal regions, toward the frontal pole. Frontal areas are, in effect, reciprocally interlocked with each step of the series of polysensory connections beginning with area 5, the first local projection area of the primary sensory cortex.¹⁰³

Friedman et al.¹⁰⁵ studied area S2 in the monkey and observed that its fibres were interconnected with the postcentral cortex (areas 1, 2, 3), areas 5 and 7 in the parietal lobe and the insula (granular and dysgranular cortex – see below). All of these areas have access to the amygdaloid cortex and hippocampal formation, the latter probably through relays from the perirhinal cortex or parahippocampal gyrus.¹⁰⁴ In a fMRI study of 12 subjects, Davis et al.³⁹ found that responses in S2 to a cutaneous tactile stimulus was 100% whereas responses to noxious heat or cold occurred in only half of the cases. Despite its small area the S2 somatosensory cortex may have an important influence on pain perception although this may be mainly in a tactile component that is distinct from S1.⁷⁰

Insula

The insula is highly active in relation to pain, especially in its affective content, and has a very large spectrum of cortical

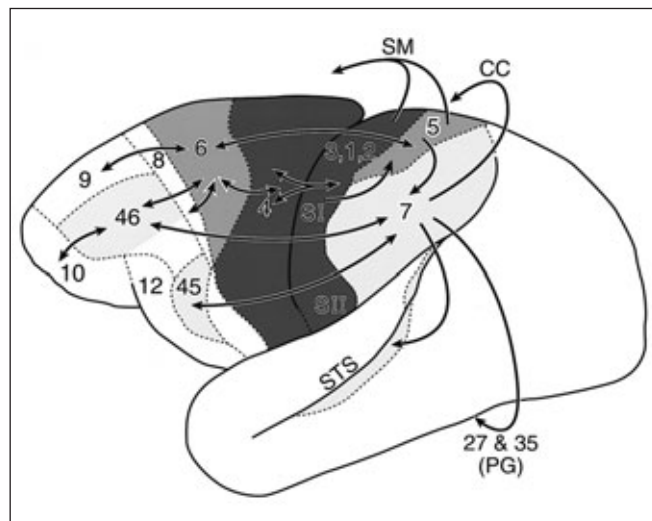


Figure 5. Converging somatosensory and reciprocal motor connections (arrows) in the monkey cerebral cortex are shown as described by Jones and Powell.¹⁰³ Pathways are reciprocal between parietal and the frontal lobes and between frontal areas. However, projections are not returned within the parietotemporal cortex where unimodal sensory input is merged to form increasingly “higher level” polysensory regions. Also, projections from Brodmann areas 5 and 7 to the supplementary motor area (SM) and cingulate cortex (CC) are not reciprocated. STS – superior temporal sulcus, a major high level sensory association area; PG – parahippocampal gyrus that includes area 27 (subiculum) and part of the adjacent area 35 that are involved in processing memory.

connections that can be divided into two groups. The *posterior-dorsal* insula (granular and adjacent dysgranular cortex) has predominantly sensory and motor connections that include the somatosensory cortices S1 and S2, parietal areas 5 and 7b, auditory area, visual area, prefrontal and orbitofrontal cortices, and premotor area 6.¹⁰³ Schneider et al.¹⁰⁶ maintain that the granular field of the posterior dorsal insula is a predominantly modality-specific cortical area for the processing of somatosensory information, rather than visual and auditory inputs, and serves as a high-order link in the somatosensory-limbic pathway. The *anterior-ventral* insula (dysgranular and agranular-periallocortical cortex) is extensively connected with limbic, paralimbic, olfactory, gustatory and autonomic structures. Mesulam and Mufson,¹⁰⁷ noting that the insula has massive connections with the somatosensory areas and amygdala (a limbic structure), suggest that the insula may have a role in motivational-affective valuation of sensory experience. Electrical stimulation of the anterior insula produces autonomic respiratory, cardiovascular and gastric motor responses and, in addition to having access to the amygdaloid complex, receives afferents from the anterior cingulate cortex including area 24 and caudal orbitofrontal cortex, both of which also have autonomic functions.¹⁰⁸⁻¹¹⁰ Coghill et al.²⁶ observed on PET scanning that heat pain did not activate the posterior insula but did activate the anterior insular cortex. As these authors point out, nociceptive activity, *per se*, is not a feature of the insula but “pain-related activation in anterior insula may reflect circuitry involved in affective and reactive components of pain”. Consistent with the

above observations, Davis et al.³⁹ found that the posterior (somatosensory) area of the insula is activated on fMRI by innocuous tactile stimulation and the anterior area by noxious thermal stimuli.

Basal ganglia

The basal ganglia encode and initiate basic movement patterns expressed through the premotor and primary motor areas and show frequent activation to noxious stimuli in PET studies (Table). Although they receive substantial projections from the cerebral cortex these are not reciprocated directly but relayed back through the thalamus.^{111,112} The connections of the basal ganglia can be divided into two groups composed of either input or output nuclei.¹¹² The caudate nucleus, putamen and nucleus accumbens are input nuclei and the globus pallidus and pars reticulata of the substantia nigra are output nuclei. The input nuclei receive a rich input from the prefrontal cortex, motor, sensory and limbic cortices and the output nuclei send axons to the thalamus and from there projections loop back to the cortex (Figure 6).¹¹¹

The nucleus accumbens is a main component of the ventral striatum processing information from affiliated cortical areas, especially the medial prefrontal, insular, entorhinal and hippocampal cortices, and through which most of the limbic cortical areas gain access to the basal ganglia circuitry.¹¹² Deniau et al.¹¹² found that the pars reticulata is a major link between the nucleus accumbens and the prefrontal cortex via the mediodorsal

and ventromedial thalamic nuclei. The nucleus accumbens also projects to the ventral pallidum and input is similarly relayed to the mediodorsal nucleus of the thalamus. Brown and Marsden¹¹³ have recently proposed that the basal ganglia are not structures exclusively linked to motor function but support a basic attentional mechanism in the prefrontal region facilitating the calling up of motor programmes and thoughts.

Amygdala, hypothalamus and periaqueductal gray

Whereas the amygdala has a major role in emotional behaviours and is likely involved in reactions to pain, it has almost consistently failed to show a significant PET response to noxious stimuli, although situations arousing fear alone have produced increased activity.^{4,114,115} Galvez et al.¹¹⁶ observed a release of noradrenaline in the amygdala in response to mildly painful stimuli in rats that was perhaps fear-related. In contrast, the periaqueductal grey to which the amygdala is directly connected shows increased activity in a third of the reported nociceptive PET studies.

The amygdala is located at the tail end of the caudate nucleus in the dorsomedial part of the temporal lobe and contains a dozen or so key nuclei with extensive cortical and subcortical connections.¹¹⁷ Its most prominent cortical sensory projections are from the anterior inferior and superior temporal cortex and posterior insula that are mainly advanced visual, auditory and somatosensory-associated areas.¹¹⁷ Thus, sensory integration in the amygdala is evidently a major part of its function, and from

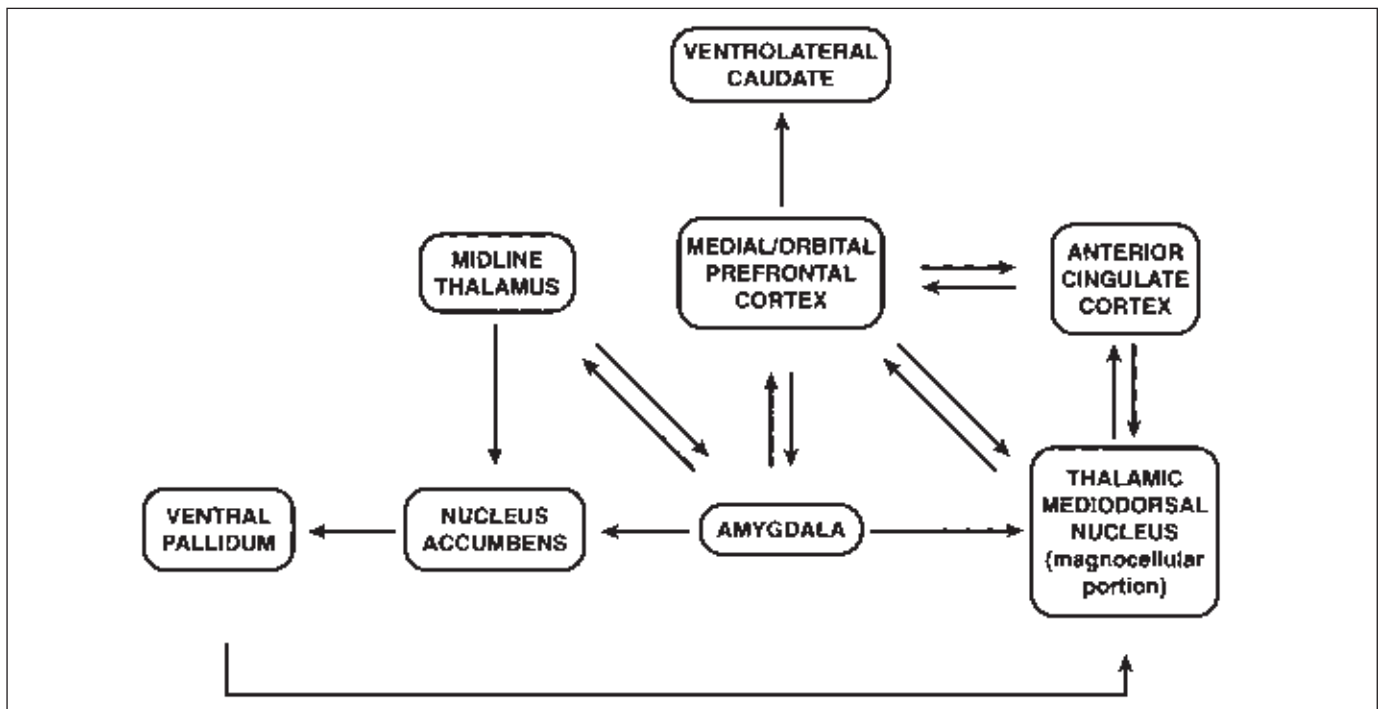


Figure 6. Schematic of some connections of amygdala and medial and orbital prefrontal cortex related to visceromotor functions. As described by Amaral et al.¹¹⁷ the amygdala has extensive reciprocal connections with this region of the prefrontal cortex and also projects to the mediodorsal nucleus of the thalamus that in turn sends fibres to the same frontal region to which the amygdala projects. The amygdala is also connected with the midline thalamic nuclei and nucleus accumbens where its influence is again returned by way of the globus pallidus and mediodorsal nucleus of the thalamus to the prefrontal cortex. Note that cortical and subcortical connections with the basal ganglia are reciprocated indirectly to their source via the thalamus.

the arrangement of the nuclei, it appears to have interfacing sensory and motor systems. There are substantial reciprocal connections between the amygdala and area 24 of the anterior cingulate cortex but the cortical regions receiving the heaviest amygdaloid afferents, with much less in the way of reciprocal projections, are the medial and lateral orbitofrontal cortex, medial wall of the frontal cortex and agranular insular cortex (Figure 6).^{107,118,119} All of these regions, directly and/or by way of the amygdala, have major hypothalamic and autonomic brain stem connections.¹¹⁷ Efferents from the amygdala descend into and through the midbrain, pons and medulla innervating a number of structures implicated in autonomic control, notably the periaqueductal gray, nucleus of the solitary tract, reticular formation and the dorsal nucleus of the vagus.^{117,120,121}

The function of the amygdala has been extensively explored through electrical stimulation and spontaneous or induced ablation. Electrical stimulation of the amygdala elicits extreme emotional behaviour consisting of anger and autonomic responses such as accelerated heart rate, rise in blood pressure and pupillary dilatation.¹²²⁻¹²⁴ Graeff et al.¹²⁵ and others maintain that a longitudinally organized neural system linking the amygdala, medial hypothalamus and periaqueductal gray matter is integral to particular behavioural and physiological manifestations of defensive reactions, such as the fight or flight response, when an individual is subjected to threat of injury or pain.¹²⁶⁻¹³⁰ The amygdala also has a major role in learning and the formation of long-term emotionally influenced memories – referred to as “emotional memory”.¹³¹⁻¹³⁷ The hippocampus is familiar as the main site for neuroplasticity mediating the acquisition and extinction of declarative or factual memory and the amygdala likely has a similar neuroplastic function in relation to conditioned fear.¹³¹ The amygdala and hippocampus are also alike in showing very little response to nociception in the PET studies which may be due to the role of both in memory storage and recall rather than first line defence against injury except, as has been demonstrated with the amygdala, during fearful or threatening situations.^{114,115}

PREFRONTAL CORTEX

Numerous areas in the prefrontal cortex respond to painful stimuli indicating its highly active involvement, especially area 10 which lies at the frontal pole (Table). The prefrontal cortex, including the orbitofrontal region, has inputs from various sectors of the cerebrum which merge into large overlapping areas.¹³⁸ The area of cortex which defines the prefrontal region is actually indefinite because of a lack of reliable cytoarchitectonic boundaries and species variability. However, this difficulty is partly resolved by using afferent connections, especially those relayed through the mediodorsal nucleus of the thalamus, which sends fibres to all areas of the frontal cortex as defined by topography and cytoarchitecture as being likely prefrontal.^{139,140} The mediodorsal nucleus has two major and quite different components, one of which, the magnocellular medial part, is connected mainly to the orbital and medial prefrontal cortex and the other, the parvicellular lateral portion, projects essentially to the dorsolateral prefrontal convexity (see Figure 2).¹⁴⁰ These two well interconnected prefrontal regions also have very different functions and certain selected areas of projection.^{141,142} The prefrontal medial and orbitofrontal areas,

to which functions related to the autonomic state of the organism have been ascribed, project their fibres predominantly to the magnocellular portion of the mediodorsal nucleus, hypothalamus, ventromedial caudate nucleus, amygdala and autonomic brain stem nuclei.¹⁴⁰ The dorsolateral prefrontal area, identified with cognitive and spatial functions, is connected predominantly with the parvicellular part of the mediodorsal nucleus, dorsolateral caudate nucleus, hippocampus and neocortex. The cingulate cortex, which is essential for the perception and response to pain, has abundant and widespread projections to the prefrontal dorsolateral and orbitofrontal cortices.¹⁴³ The prefrontal cortex in turn projects to most or all parts of the cingulate cortex with the dorsomedial and dorsolateral prefrontal cortex projecting preferentially to the anterior cingulate region.^{90,119,144} Almost all connections to the prefrontal cortex are reciprocal, a notable exception being, as discussed above, the basal ganglia which relay feedback by way of the thalamus (Figure 6).^{111,112,145}

The dorsolateral prefrontal cortex (areas 9 and 46) is apparently involved in selecting and maintaining behaviourally relevant information, called “working memory” (see cortical map, Figure 1).^{45,47,146,147} Injury to this region would likely cause impairment in abstract reasoning, complex problem solving and future planning. Access to the hippocampal formation by the dorsolateral prefrontal cortex, as stated by Goldman-Rakic et al.¹⁴⁸ probably provides the means whereby stored memories related to current memories are retrieved. Damasio⁴⁶ also found that patients with lesions in the ventral and medial prefrontal region present with “personal and social impairments of decision-making” without alteration in intellect, attention or working memory. This prefrontal region is related to central autonomic control, suggesting that impairment in these cases may have produced an altered or unaroused “state of mind”.^{149,150} The role of the prefrontal frontopolar region (area 10) has recently been described as mediating a function of holding in mind primary goals while exploring secondary goals as part of the process of planning and reasoning.¹⁵¹

Understanding the functions of the prefrontal cortex has, until very recently, depended upon changes produced by frontal lobe injury or surgical procedures such as prefrontal lobotomy or leucotomy. Certain prefrontal leucotomy procedures were used to provide relief for emotional illness or intractable pain in cases of metastatic carcinoma, causalgia and neuropathy.^{152,153} Depending upon where in the frontal lobe the leucotomy was made, pathways between the prefrontal cortex and the cingulate cortex and/or thalamus (mediodorsal nucleus of the thalamus and midline and intralaminar thalamic nuclei) or between the thalamus and cingulate cortex, were severed.^{16,154-156} It was on the basis of such pathological findings that Foltz and White¹⁵ elected to section the cingulum fasciculus in cases with intractable pain. Because patients subsequently maintained that they still experienced pain but it was no longer unpleasant suggests that the affective component of the nociceptive experience had been removed, comparable to what had been earlier achieved with prefrontal leucotomy.

PREMOTOR, SUPPLEMENTARY AND PRIMARY MOTOR SYSTEMS

The premotor, supplementary motor and primary motor cortices responded to nociceptive stimuli in some PET studies

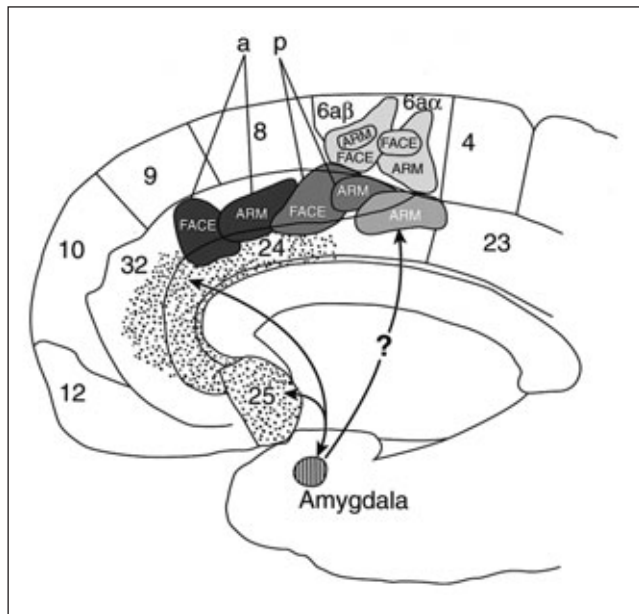


Figure 7. Two premotor regions, the supplementary motor area (SMA) and the cingulate motor area, are located on the medial wall of the human cerebral hemisphere and are well interconnected with one another and also with the premotor area 6 on the lateral hemispheric surface and the primary motor cortex. The SMA (light shade) is divided into (i) a rostral pre-SMA that is located in area 6a β for complex (cognitive-motor) tasks and (ii) the SMA proper in area 6a α for simple (repetitive) tasks.¹⁵⁷ The cingulate motor area has (i) a large rostral cingulate zone (dark shades) consisting of two face and arm areas (a and p) for complex tasks, and (ii) a smaller caudal cingulate zone (lighter shade, shown here as arm area only) for simpler tasks. The caudal site corresponds to Braak's¹⁶⁰ gigantopyramidal area and responds to painful stimuli.¹⁵⁷ The dotted cingulate areas represent the distribution of reciprocal amygdaloid connections (areas 33, 25 and rostral part of 24 with some extension into area 32). A proposed connection of the amygdala with cingulate motor area is shown. (SMA and cingulate motor areas are modified from Figures 4 and 5 in Picard and Strick¹⁵⁷ by permission of Oxford University Press).

(Table) and, whereas a response in the supplementary and primary motor cortices was always increased, it was either increased or decreased in the premotor cortex. Included in the premotor system, but not always seen in the PET studies because it was not readily distinguishable from other parts of area 24 of the anterior cingulate region, was the cingulate motor cortex. All premotor areas project to the primary motor cortex and to the spinal cord.¹⁵⁷ The primary motor area (area 4) projects to the spinal cord but is programmed for only simple actions and therefore the premotor cortices are required to direct the primary motor neurons in the execution of particular, more complicated, movements (Figures 5 and 7).¹⁵⁸ The purpose, initiative and facilitation of movements depends on the prefrontal cortex but this does not project to the primary motor cortex nor to the spinal cord and therefore is dependent upon its abundant connections with premotor areas.^{158,159}

Although it has received very little attention the cingulate motor cortex may have major importance in the motor responses to pain. In the anterior cingulate region, there are two distinctive motor areas, a *skeletomotor* (premotor) area 24c' in the lower

bank of the cingulate sulcus and an *autonomic motor* (visceromotor) region located in the ventral part of the gyrus (Figures 4 and 7).¹¹⁹ The cingulate *skeletomotor* cortex in man was described by Braak¹⁶⁰ as a primordial limbic motor area. It actually consists of probably three closely related and interconnected premotor areas projecting abundantly, somatotopically and reciprocally to the frontal premotor area 6 on the lateral surface of the hemisphere, supplementary motor area on the medial surface and the primary motor cortex (Figures 1 and 7).^{119,157,161-163} The cingulate skeletomotor areas are also heavily connected with the dorsolateral prefrontal cortex, similar to the other premotor areas, and it has, as well, modest input from the orbitofrontal cortex and parietal lobe.^{119,163} Also, the cingulate motor cortex, again similar to other premotor regions, is the target for efferents from the basal ganglia and cerebellum, with additional afferents from the temporal pole, entorhinal and perirhinal cortices and posterior parahippocampal cortex. The cingulate *autonomic* motor cortex in areas 24 and 25 project to the amygdala, hypothalamus, periaqueductal gray, brain stem reticular formation, dorsal motor nucleus of the vagus and nucleus of the solitary tract.¹⁶⁴

The anterior cingulate cortex in man has remarkably little if any significant connection with the cingulate skeletomotor cortex in the cingulate sulcus, frontal premotor areas, primary motor cortex or spinal cord.^{163,165} As raised by Dum and Strick¹⁶³ the lack of evidence for the cingulate skeletomotor areas having substantial interconnections with the cingulate gyrus would indicate that motor expression must occur, directly or indirectly, by other known projections from area 24. A most likely route would be indirect, such as via the prefrontal cortex or amygdala. The amygdala has abundant connections with the anterior cingulate cortex but does not project to the primary motor cortex nor substantially to other skeletomotor areas.¹⁶⁶ Nevertheless, an amygdaloid connection with the cingulate motor cortex, which is well connected with the frontal premotor, supplementary and primary motor areas, might provide a route for skeletomotor response to pain and fear for both the amygdala and the anterior cingulate cortex (Figure 7). Van Hoesen et al.¹¹⁹ suggest "that the cortex along the lower bank of the cingulate (where the cingulate motor cortex is located) provides a pivotal anatomical interface between the traditional (premotor and primary motor) isocortical motor areas and traditional limbic and multimodal association areas of the primate cerebral cortex". It is possible, therefore, that the cingulate cortex and amygdala, as high order limbic structures, may have at some time (phylogenetically) depended almost entirely upon the cingulate motor cortex for their expression, including responses to pain.

CONCLUDING REMARKS

Pain is a signal of bodily injury that is normally generated in peripheral nerve nociceptors but also occurs pathologically within the nervous system in association with peripheral, spinal or cerebral disorders such as with neuromas, amputation, strokes, etc.^{5,6,167} In this review, the objective was to integrate current understanding of cerebral connections between cortical regions and nuclei with multiple areas of response in PET and fMRI studies to noxious stimuli in an attempt to define a system of nociceptive afferent and efferent pathways. The proposed nociceptive system, as shown schematically in Figure 8,

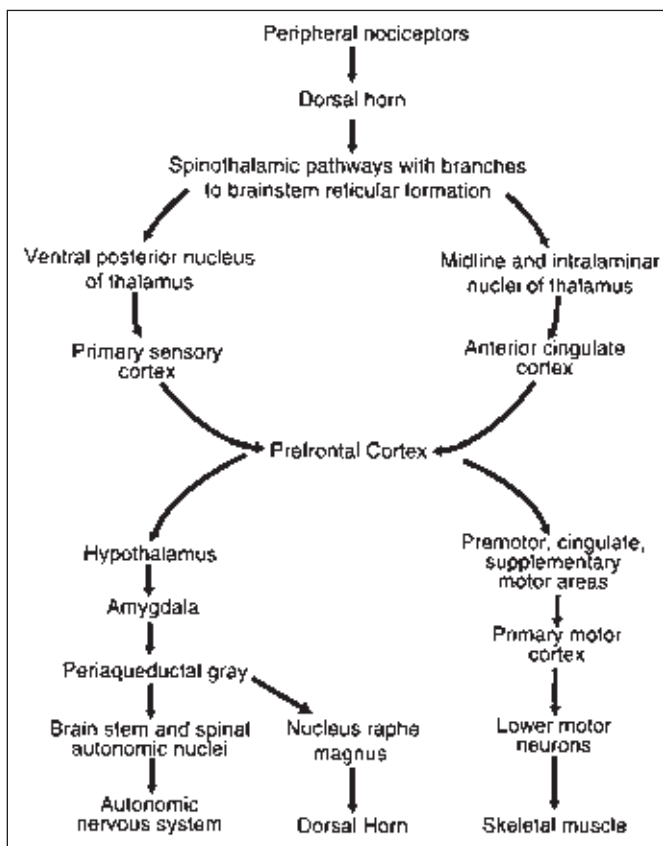


Figure 8. Schematic version of a proposed afferent and efferent nociceptive pathway. Only certain key components and not contributing inputs from other areas of brain are shown. In the efferent pathway the projection of the periaqueductal gray to the nucleus raphe magnus represents part of an inhibitory system acting upon the dorsal horn (see text).

demonstrates only the principal structures as derived from the studies excluding contributing inputs from other loci or connections that may act as possible lower level nociceptive “short circuits”.

The response of the various cerebral loci in PET to noxious peripheral stimulation is quite variable in activity (increased and/or decreased) and frequency. This could have many causes including differences in experimental technique and, as has been recently demonstrated with fMRI, intersubject variability.³⁹ Also, as shown in a fMRI study by Ploghaus et al.¹⁶⁸ the anticipation of pain and the experience of pain activate different regions although these were in close proximity to one another. Nevertheless, some structures have shown a high incidence of increased and very little or no decreased rCBF activity with PET, such as the anterior cingulate region, suggesting a high state of neuronal activity. Decreased responses (most consistently the posterior cingulate region, frontal eye field area 8 and occipital cortex) have been difficult to explain although they would seem to represent a relatively passive state of neuronal activity. This is supported in the highly variable (increased and decreased) responses in the parietal lobe and prefrontal frontopolar area 10,

both high order association cortices where, as described by Koechlin et al.¹⁵¹ functions may at times be in a relatively passive state, as when listening and reading, versus periods of active exploration and processing as required during planning and reasoning. As commented upon earlier, the amygdala rarely reacted to pain during PET studies in contrast to the effect of fear or anxiety that may have been due to precautionary efforts to avoid fear as an experimental condition.^{114,115} It is likely, nonetheless, that the amygdala is active, if not visibly, in retrieving emotionally based memory during painful experiences. The experience of pain, therefore, is accompanied by changes in rCBF in many areas of the nervous system and whether these represent increased or decreased neuronal activity, it is assumed they are structures that are among the most affected during pain. Accordingly, in this context, they can be viewed as significant components of a nociceptive system.

The proposed nociceptive afferent pathway as shown in Figure 8 extends from the peripheral nerves to the thalamus, anterior cingulate and somatosensory cortices to the prefrontal cortex. Many cerebral structures during this phase contribute to the interpretation and the integration of information such as the posterior parietal cortex, posterior cingulate cortex, insula, amygdala and hippocampal formation, all of which are interconnected with the prefrontal cortex. The assembly of information and response to a painful experience may depend largely upon the prefrontal cortex because of its large, advanced sensory and motor input and capacity to provide such functions as sustained attention, spatial working memory, capacity for decision-making, holding information and the programming of skeletomotor and autonomic behavioural responses. Thus, the prefrontal region is provided with comprehensive and evaluated information, both current and past, the latter through the hippocampus (factual memory) and amygdala (emotional memory). In the efferent pathway a conscious behavioural response to pain is initiated in the prefrontal cortex, notably in its frontopolar and dorsolateral aspects, which provide direction to the adjacent premotor areas. The latter are then programmed to orchestrate the primary motor cortex and lower motor neurons to execute the appropriate skeletomotor responses to either limit or avoid painful threat or injury. Simultaneously autonomic efferent responses to the same threat or injury are initiated in the prefrontal medial and orbitofrontal cortex to the hypothalamus, amygdala, periaqueductal gray, nucleus raphe magnus, brain stem and spinal autonomic neurons.

Why is the cingulate cortex so significantly involved in pain perception? It is possible that nociceptive integration and the recognition and evaluation of pain was at one time, prior to neocortical development, limited to the limbic nervous system, notably the hippocampus, cingulate cortex, cingulate skeletomotor and autonomic motor areas and amygdala, that represented the highest order cognitive, afferent and efferent levels. Accordingly, the prefrontal cortex and other parts of the neocortex may represent additions to an otherwise primordial limbic pain system which might still be capable of functioning autonomously but with prior aversive conditioning involving prefrontal and other neocortical input.^{169,170} Indeed, direct nociceptive spinal pathways extending from the dorsal horn to the limbic system, especially to various nuclei in the thalamus and hypothalamus bilaterally, have been described that may still

function in a nociceptive reflex capacity, i.e. rapid withdrawal from painful stimuli.⁷²

In summary, there have been recent major developments in neuroimaging of areas of brain predominantly responding to painful stimuli and in the tracing of central nervous system connections between these areas. A process for pain perception and response has been proposed in which central nervous system afferent and efferent components are arranged in a hierarchical manner from the dorsal horn and trigeminal nucleus to the prefrontal cortex, the latter representing the highest level of nociceptive response.⁴⁴

ACKNOWLEDGMENT

The author is grateful to Professor John A. Kiernan, Dept. of Anatomy, University of Western Ontario, for his helpful advice in the preparation of the manuscript.

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