

The Human Pain System

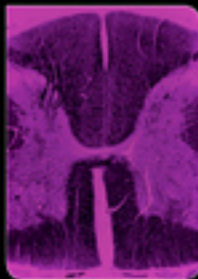
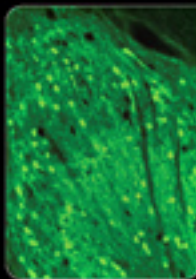
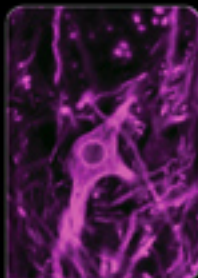
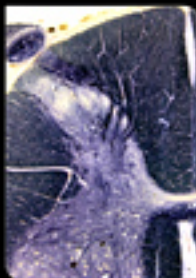
Experimental and Clinical Perspectives

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The Human Pain System

Pain is a subject of increasing scientific and clinical interest. Studies of non-primate animal models have contributed greatly to our knowledge of pain. Nonetheless, investigators often refer to basic neuroscientific and behavioral studies of humans and non-human primates to emphasize the relevance of their results to human pain. Likewise, the interpretation of human pain studies and clinical observations relies upon understanding the relevant anatomy and physiology as gleaned from animal, and especially primate, research. Here, Lenz, Casey, Jones and Willis review the neurobiology of nociception in monkeys and pain in humans, to provide a firm basis for understanding the mechanisms of normal and pathological human pain. This book is essential reading for anyone interested in pain research.

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UPPER RIGHT IMAGES

Top image: Activation (PET rCBF) of the mid-anterior and rostral cingulate cortex, thalamus, and cerebellum of 11 subjects during immersion of the left hand in painfully cold water. *Lower image:* Activation of the far rostral anterior cingulate cortex in the same subjects following the injection of an opioid analgesic. Images from Figure 1 of Casey *et al.* (2000).

LOWER RIGHT IMAGE

Autocorrelations (fMRI BOLD fluctuations) in the resting brain of 10 subjects. Regions typically activated during task performance are correlated (red-yellow) but are anti-correlated with typically deactivated regions (green-blue). Image taken from Figure 11 of Chapter 5 as adapted from Fox *et al.* (2005).

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Preface

Unless suffering from one of those rare forms of hereditary indifference to pain, no human is without the experience of pain. Yet humans have always had difficulty in conveying a unified concept of pain since it can include subjective states ranging from mere unpleasantness to extreme physical agony, or to the feeling of sadness and desolation accompanying an episode of major depression. Plato and Aristotle did not regard pain as an elemental sensation like touch or vision but rather saw pain and pleasure as contrasting elements vying with one another for the maintenance of internal wellbeing of the individual by operating on the soul, which was thought to be located in the liver or heart. For Aristotle, pain arose from ripples in the heart and blood vessels, not from the activity of the reasoning brain. Perhaps we can still see crude echoes of the Aristotelian position in modern suggestions that pain is no more than a disruption of bodily homeostasis, akin to that associated with dysautonomia and other visceral disturbances.

It is to Galen, writing more than 450 years after Aristotle, that we owe the recognition that sensory impressions, including those leading to pain, are carried by nerves to the brain and Galen described carrying out cordotomies in animals in order to demonstrate the key role of the spinal cord in the conduction of painful impressions to the brain. Galen, however, had no concept of specific nerves for pain and to him intense irritation of any nerve or of a sensory organ such as the eye would lead to pain. A reader interested in ancient and early modern theories of pain can find them summarized in Keele (1957) and Finger (1994).

Our more recent forebears had considerable difficulty in defining pain in clinical or scientific terms. Their difficulty can, perhaps, be summed up in the words of Thomas Lewis, whose once popular little book *Pain*, was first published in 1942. In this, he says: "Pain, like similar subjective things, is known to us by experience and described by illustration." Moreover: "We have no

knowledge of pain beyond that derived from human experience.” In these words there is not only a kind of hopelessness that pain could ever be analyzed in mechanistic terms but also an implicit rejection of the idea that investigations in animals could be of any use in advancing the understanding of fundamental pain mechanisms.

Even before Lewis’ pronouncements, however, Gasser and his colleagues (Gasser and Erlanger, 1929) had begun to make the correlations between nerve fiber diameter and conduction velocity that represented the beginning of a new era in studies of peripheral sensory mechanisms, including pain. By the 1930s, thanks to experiments of various kinds in humans and animals carried out by numerous investigators, including Lewis himself, the correlation of A δ and C fibers with pain had been established (summarized in Sweet, 1959). Even earlier, Ranson and Billingsley (1916) had reported that division of the thin fibers entering the spinal cord in the lateral divisions of the dorsal roots led to a loss of pain reflexes, and in recognition of the importance of the fibers ascending in the anterolateral funiculus of the spinal cord, the first spinal cordotomies began to be performed for the alleviation of pain (Spiller and Martin, 1912).

But it was the difficulty of delineating how pain was processed at higher levels of the central nervous system that most exercised our predecessors and it was from this that Lewis’ negativism undoubtedly arose. It is with these higher levels that the current volume is primarily concerned.

We are in a better position today to grapple with central mechanisms of pain. With the recognition, stemming from the fundamentally important observations of Burgess and Perl (1967), that A δ and C fibers entering the spinal cord and terminating in the superficial dorsal horn are thermo- or nociceptor-specific and the more recent cloning of the vanilloid receptors (Caterina *et al.*, 1997) which confer this physiological specificity upon the fibers expressing them, the peripheral nociceptive system has become far better understood and has given us points of entrée into the central nervous system from which to mount investigations of the central pain system itself. They also tell us that, contra Lewis, it is entirely possible to carry out meaningful studies of pain in laboratory animals.

Modern investigations of pain and the central pain system have been facilitated by better and universally agreed definitions than existed in the past and by advances in experimental and clinical techniques. In the present work, we have adopted the definition of pain proposed by the International Association for the Study of Pain (IASP): *An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage* (Merskey, 1986). In adopting this definition, we have also adopted the now universal acceptance that pain as an experience has sensory (discriminative), hedonic (affective) and cognitive (contextually dependent) components (Melzack and Casey, 1968;

Merskey and Bogduk, 1994; Fields, 1999; Price, 2000). How the peripheral, spinal and brainstem levels of the nociceptive system engage regions of the forebrain whose activity gives expression to these different components of pain is a challenge that we have attempted to rise to. In doing so, we present to the reader what we believe to be the most up to date information, as derived from the newest anatomical, physiological and functional imaging techniques, as well as that derived from modern neurosurgical approaches.

The emphasis in the present work is on the human brain and spinal cord and the pathways leading from the spinal dorsal roots to the forebrain centers and mechanisms for the perception and experience of pain. Where, as is often the case, details of the organization of the human nervous system are lacking, we have turned to experimental work in other primates, notably Old World monkeys, for relevant information. Important as they may be, observations on non-primates will receive little attention unless necessary to fill in gaps in the primate evidence.

The work commences in [Chapter 1](#) with a historical overview of investigations of the spinal cord and central pathways critical for pain, leading from the early years of the nineteenth century to about the middle 1980s when, as the result of the perfection of neuroanatomical and neurophysiological techniques, the anatomy of these pathways and the stimulus-response properties of their constituent neurons in primates had been analyzed at a level of detail not previously possible. Later chapters take the reader through the anatomy and chemistry of the spinal cord and the central nociceptive pathways up to the thalamus and cerebral cortex ([Chapter 2](#)), the physiological properties of the cells of origin of the spinal and brainstem pathways ([Chapter 3](#)), the physiology of supraspinal pain-related structures ([Chapter 4](#)), the imaging of sensory and affective components of acute pain ([Chapter 5](#)), ascending and descending pain modulatory systems ([Chapter 6](#)), peripheral and central mechanisms of chronic pain and sensitization ([Chapter 7](#)), imaging of sensory and affective components of chronic pain ([Chapter 8](#)), and spinal and forebrain procedures for the treatment of chronic pain ([Chapter 9](#)). Individual authors took responsibility for the initial preparation of one or more chapters but the final work is a joint effort.

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Discovery of the anterolateral system and its role as a pain pathway

Introduction

On January 19 1911, persuaded by his colleague, the neurologist William Spiller, a Philadelphia surgeon named Edward Martin made a small transverse cut in the spinal cord of a patient suffering from severe pain caused by a tumor affecting the lower end of the spinal column. The cut, made with a thin cataract knife, was no more than 2 mm deep or wide and entered the cord some 3 mm ventral to the entry of a dorsal root in the middle thoracic region. The patient experienced much relief from what had until then been intractable pain (Spiller and Martin, 1912). The operation of “chordotomie” or section of the anterolateral tracts of the spinal cord had been introduced in 1910 by Schüller in work on monkeys in which he was exploring the possibility of using the operation for the alleviation of spastic paralysis and tabetic crises in humans. Spiller argued for the procedure on the basis of clinico-pathological observations that appeared to implicate the anterolateral tracts as pathways for conduction of impulses related to pain and temperature through the spinal cord (Müller, 1871; Gowers, 1879; Spiller, 1905; Petrén, 1910). Reports of other successful cases quickly followed (Beer, 1913; Foerster, 1913) and soon, at the hands of Foerster (1913, 1927; Foerster and Gagel, 1932) in Germany and Frazier (1920) in the United States, cordotomy was to become for a time the surgical method of choice in dealing with intractable pain. With it came renewed interest in the anatomy of the spinothalamic tract, its localization in the spinal cord and its site of termination in the thalamus.

Dorsal roots, somatic sensation and lateralization in the spinal cord

The background to the localization of the pain pathways in the anterolateral columns of the spinal cord is an extensive one and knowledge accrued

2 Discovery of the anterolateral system and its role as a pain pathway

slowly as ideas developed about the role of the spinal nerve roots and the spinal cord tracts in somatic sensation. Magendie clearly delineated the dorsal roots of the spinal cord as sensory and the ventral as motor in 1822. Although his claims to priority were questioned by Charles Bell, it is clear from reading Bell's 1811 pamphlet, *Idea of a New Anatomy of the Brain*, that Bell at that time had little idea of the sensory role of the dorsal roots, conceiving of them as being connected with the dorsal white columns of the cord which he saw as conveying some vaguely described efferent integrative influence from the cerebellum to the body. The ventral roots he saw as conveying a more definite motor influence from the cerebrum via the pyramidal tracts to the muscles. Where he speaks of sensation at all, he implies that sensory impressions may be carried up to the brain via the spinal gray matter. Bell has been found guilty of modifying his later texts to create an impression that he had arrived at conclusions similar to Magendie's many years before (Bell, 1837, 1845). If he had some inkling of the sensory and motor roles of the dorsal and ventral roots he did not reveal it in his pamphlet. Nevertheless, the law of differential polarization of the roots became known as the Bell-Magendie Law. Detailed accounts of this episode in the history of neuroscience can be found in Cranefield (1974) and in Clark and Jacyna (1987).

By the time of Longet (1841, 1842) and Stilling (1842) it was accepted by many that the dorsal roots became continuous with the posterior columns of the cord and that the latter were in some way connected with sensation, but not by all. Brown-Séquard (1849, 1850, 1860), for example, saw the posterior columns as being continuous with the inferior cerebellar peduncle and believed that it was the spinal gray matter that was essential for sensory transmission to higher centers. In a variant of this view, Schiff (1858) thought that while tactile sensation was conveyed via the posterior columns, pain might be transmitted through the gray matter. This is perhaps the first time that a distinction was drawn between the two components of the somatosensory system. Brown-Séquard and Schiff based their interpretations on experimental work in animals in which the spinal cord was fully or partially transected at different levels, the animal then being tested for sensory loss. For Brown-Séquard, section of the dorsal columns led to no loss of sensation below the level of the lesion, while a hemisection led to loss of sensation in the limb or limbs (depending on the level of the hemisection) *contralateral* to the lesion. A second hemisection made below the first on the opposite side would lead to bilateral sensory loss. From this he concluded that ascending sensory fibers must decussate in the spinal cord. He went on to show in many experiments that anesthesia did not occur unless the gray matter itself was injured. Even with multiple cuts at different levels affecting virtually all white matter tracts there was little diminution of sensation in the lower limbs.

Thus, to Brown-Séquard, sensory transmission occurred via the gray matter of the spinal cord and if a longitudinal cut was made down the center of the cord in the lumbosacral or cervical enlargements, there was a bilateral loss of sensation in the lower or upper limbs.

Schiff's conclusions from his experiments were similar but only in relation to pain. He felt that his experiments revealed that tactile and muscular sense impressions were conveyed by the dorsal columns while impressions of pain, cold and heat were conveyed via the gray matter. In these experiments, we are perhaps seeing the first glimmerings of understanding of the decussation of the pain and temperature-related fibers through the anterior commissure of the spinal cord. Had Brown-Séquard's testing for sensory loss gone beyond merely observing if an animal withdrew its limb from a severe pinch, he too may have been able to make the distinction that Schiff made between low-threshold sensory impressions ascending in the dorsal columns and those for pain ascending in the anterolateral columns after decussation in the anterior white commissure. Nevertheless, Brown-Séquard's influence remained strong and in 1876 Ferrier could still maintain that all sensory messages from one side of the body were conveyed up to the brain chiefly on the side opposite the entry of the dorsal roots from that side. Long after it was admitted that the dorsal columns were continuations of the dorsal roots and sensory in character, many neurologists continued to believe that the dorsal root fibers decussated in the gray matter on entering the cord and ascended on the contralateral side (Bramwell, 1884; Ferrier, 1886). For these authors, many dorsal root fibers also decussated via the anterior commissure and ascended through the lateral columns.

The anterolateral funiculus and Gowers' tract

Bastian (1867) had been first to describe ascending degeneration in the ventrolateral aspect of the spinal cord in a case of paraplegia but following Flechsig's (1876) description of the dorsal or, as it was then called, the "direct" spinocerebellar tract it was generally thought that the degenerated fibers Bastian had described were part of this tract. In 1879 Gowers also described ascending degeneration consequent upon a crush lesion at the first lumbar segment in the anterolateral columns of the spinal cord but considered it independent of the dorsal spinocerebellar tracts (Fig. 1.1). He called the tract so delineated the *anterolateral ascending tract* and thought that it might be concerned with the transmission of painful influences from the opposite side of the body, largely on the basis of observations made earlier on the same patient (Gowers, 1878). In his description, the tract "occupies an irregular area in front of the pyramidal and cerebellar tracts, and degenerates upwards throughout

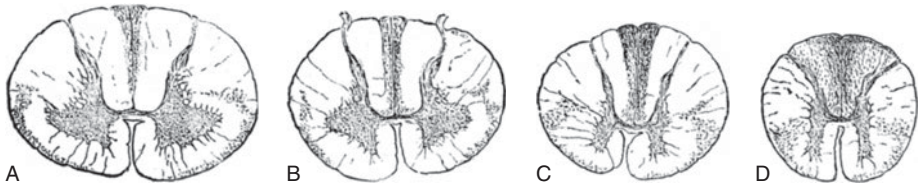


Fig. 1.1. Gowers' figure showing the location of ascending degeneration, as visualized by loss of myelin staining, in the gracile and anterolateral fasciculi of the spinal cord following a crush injury at the level of the first lumbar segment. The drawings have been rotated 180° from the original. From Gowers (1879).

the cord. It extends across the lateral column, as a band which fills up the angle between the pyramidal and cerebellar tracts, and it reaches the surface of the cord in front of the latter tract, nearly on a level with the anterior commissure; it then extends forward in the periphery of the anterior column, almost to the anterior median fissure, and up to the direct pyramidal tract when this exists." He was able to follow the degeneration in this tract into the brainstem and as far rostrally as the midbrain. Although initially influenced by Brown-Séquard and convinced that the anterolateral tract might be a continuation of decussating dorsal root fibers, by 1886 (Gowers, 1886a, 1886b) and having had access to preparations of Mott in which, after dorsal root damage, the ascending degeneration was confined to the dorsal columns, Gowers was able to make the assumption that the cells of origin of the anterolateral tract were located in the contralateral dorsal horn and innervated by dorsal root fibers that ended there.

Flechsig, in myelogenetic studies in 1876, had differentiated the direct spinocerebellar tract as a tract whose axons myelinated earlier than those of the adjacent pyramidal tract and he had followed it into the inferior cerebellar peduncle. In 1885 Bechterew identified two additional ascending tracts lying ventral and medial to the dorsal spinocerebellar tract that myelinated one or two months later than that tract. These he referred to as the *lateral* and *anterior ground bundles* and traced them into the reticular formation of the medulla oblongata. It was within these ground bundles that Gowers' anterolateral tract lay. At about the same time, Löwenthal (1885) in experimental studies in animals made the first clear distinction between the dorsal spinocerebellar tract which he followed into the inferior cerebellar peduncle, and a cerebellar component of Gowers' tract which he followed into the superior cerebellar peduncle. Later, Edinger (1889, 1890) in further myelogenetic studies in cats was able to identify fibers crossing in the anterior commissure, ascending in the anterior and lateral ground bundles, and eventually reaching as far as the diencephalon. Edinger was confident that these fibers arose from cells located in the base of the dorsal horn

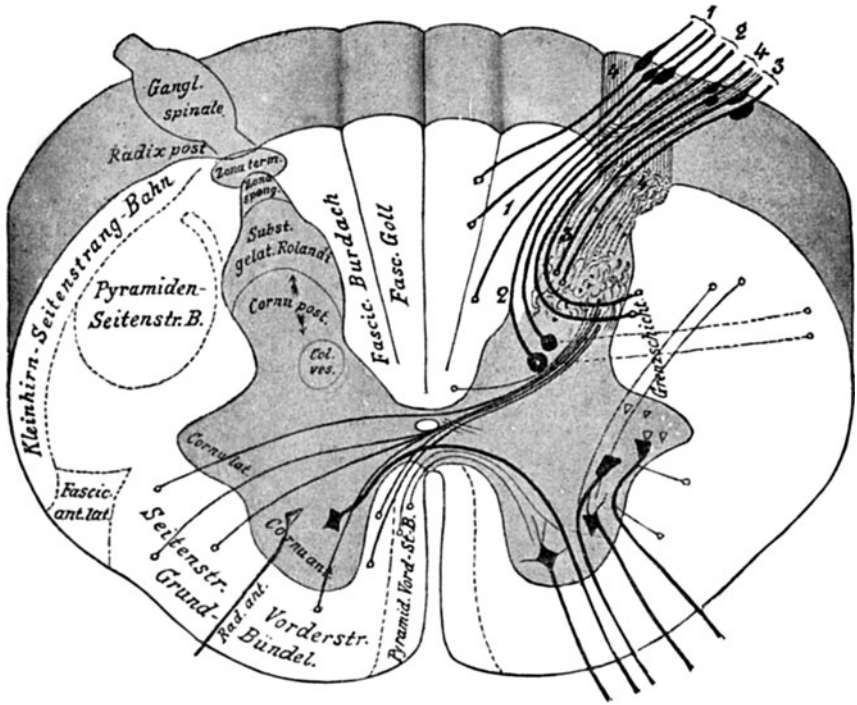


Fig. 1.2. Edinger's scheme of a cross section of the human spinal cord demonstrating the organization of the central gray matter and the cellular origins of ascending and efferent fiber pathways. Fibers arising from cells in the base of the dorsal horn decussate in the anterior commissure and ascend in the anterolateral tract of the opposite side. From Edinger (1889).

that were innervated by incoming dorsal root fibers (Fig. 1.2), although his evidence came mostly from his studies of fish and amphibians.

Tract tracing by the Marchi method

The next advances came from the use of the Marchi technique to trace degenerating fibers in the spinal cords of humans suffering from spinal lesions or in those of monkeys subjected to experimental lesions. In this technique, introduced by Marchi and Algeri in 1886, the fragmentation of the myelin sheaths of axons undergoing Wallerian (anterograde) degeneration can be selectively impregnated with osmic acid and stand out against a clear background. The first successful use of the technique of relevance to the afferent pathways of the spinal cord came in the study of Mott made in 1895 on monkeys (Fig. 1.3). It was a landmark study that served to resolve many of the inconsistencies in the manner in which contemporary neurologists viewed the sensory pathways

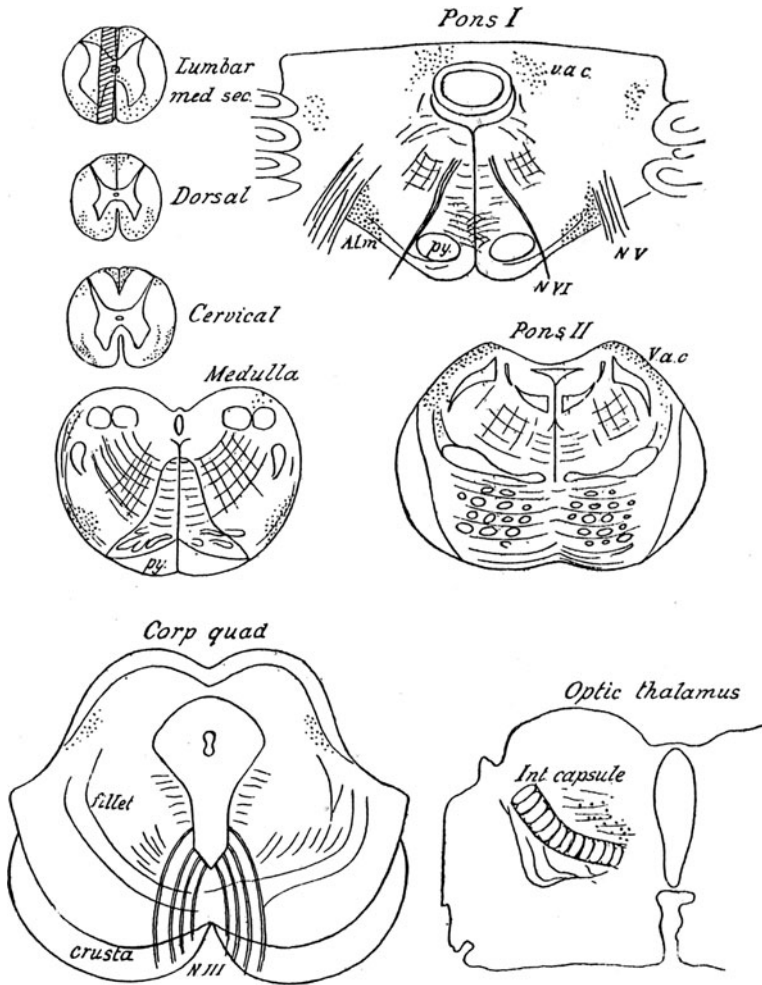


Fig. 1.3. Location of Marchi-stained degenerating fibers in the spinal cord, brainstem and diencephalon of a monkey following a median longitudinal section of the spinal cord in the lumbar region. From Mott (1895).

of the spinal cord. In the first part of his investigation, Mott sectioned the dorsal roots of several spinal nerves in the lumbosacral region, observing that all degeneration of fibers above the level of the lesion was confined to the gracile fasciculus of the same side, an observation that served to end the debate about laterality in the dorsal columns and whether dorsal root fibers decussated on entry into the cord. He was also able to note the topography in the gracile fasciculus, with lower-entering fibers being pushed into the dorsomedial aspect of the fasciculus by higher-entering fibers.

In a second set of experiments, Mott made a median section of the cord in the region of the last thoracic and first three lumbar segments. In these cases he observed symmetrical degeneration in the anterolateral columns of both sides. He was able to distinguish degeneration in the dorsal spinocerebellar tract from that in the other tracts by reason of the size of its fibers and the fact that degeneration in it was more severe on the side of the cord in which more gray matter and thus more of Clarke's column was damaged. Ventral to this he observed a superficially placed ventral spinocerebellar tract, a tract that he had earlier traced to the superior cerebellar peduncle (Mott, 1892; Tooth, 1892); separated from this by normal fibers was a more deeply located tract whose fibers could be traced to the level of the superior colliculus and some of them beyond to the level of the thalamus. These fibers, he said, form "in all probability the crossed sensory tract of Edinger." He was, however, unwilling to ascribe a precise function to the tract and he did not identify it as a pathway uniquely concerned with pain.

In his third set of experiments, Mott undercut the dorsal column nuclei in order to sever the arcuate fibers leaving the ventral aspects of these nuclei. He traced the ensuing degeneration across the decussation of the medial lemniscus, saw it ascending in the medial lemniscus and traced it into the posterolateral aspect of the contralateral thalamus. In this, he was confirming experimentally the deductions of Mahaim (1893) who argued that since only modest degeneration occurred in the lemniscus following complete retrograde degeneration of the lateral thalamus due to cortical lesions, the lemniscus must terminate in that part of the thalamus and not continue, as some had suggested, directly to the cerebral cortex.

The results of Mott's study, although by no means directly implicating the anterolateral pathway in central pain mechanisms, were sufficiently clear-cut to resolve all preexisting controversies about the lateralization of the ascending pathways associated with the sensory nerve roots of the spinal cord. Gowers immediately accepted the new findings and his description of the spinal sensory pathways in the third edition (1899) of his textbook on *Diseases of the Nervous System*, unlike its predecessors, reads like any early modern textbook of neuroanatomy (Gowers and Taylor, 1899). In reviewing his clinical experience at this point, Gowers was ready to conclude that following a unilateral cord lesion pain is always lost on the contralateral side of the body below the lesion. But he was not prepared to concede that anything other than muscular sense (that is proprioception) was conveyed by the dorsal columns. He still considered that touch, along with pain and temperature, were conveyed via the contralateral anterolateral columns. And because loss of pain or temperature can be dissociated after cord lesions, he felt that they could be conveyed by paths that did not run together.

In the years following Mott's work, the application of the Marchi technique to the spinal cords and brains of patients who had died within a few weeks of sustaining spinal cord injuries served to confirm the observations of Mott and to show the comparable organization of the various tracts of the anterolateral white matter in the human spinal cord. A number of these revealed degeneration of anterolateral fibers that ascended as far as the midbrain and thalamus, separating them from fibers ascending only as far as the superior cerebellar peduncle (Patrick, 1893, 1896; Hoche, 1896; Sölder, 1897; Worotynski, 1897; Quensel, 1898; Rossolimo, 1898; Tschermak, 1898; Amabilino, 1901; Henneberg, 1901; Thiele and Horsley, 1901; Collier and Buzzard, 1903; Dydyński, 1903; Marburg, 1903; Petrén, 1901, 1910; Rothmann, 1903; Bruce, 1910; Goldstein, 1910). It was largely the reports of Petrén and Goldstein, along with his own case report of 1905, that influenced Spiller in determining to pursue anterolateral cordotomy as a treatment for alleviating pain in his patient. Although some of the reports listed are brief and relatively superficial, others are quite extensive and very comprehensively illustrated, often with high quality photomicrographs that clearly reveal the capacity of the Marchi technique to demonstrate degenerating fiber tracts against a clear background. It is from these studies that detailed knowledge of the organization of ascending tracts in the lateral white matter of the spinal cord and their central courses and terminations was built up. In 1901, for example, Thiele and Horsley could delineate four tracts: the direct cerebellar tract of Flechsig, renamed the fasciculus spino-cerebellaris dorsolateralis by Barker (1899); Gowers' tract or the fasciculus spino-cerebellaris ventralis, as renamed by Barker; the fasciculus spino-tectalis, originally called the spino-quadrigeminal system by Mott; the fasciculus spino-thalamicus, as named by Mott. They were also able to identify spino-vestibular fibers which Collier and Buzzard (1903) were later to call a tract in its own right. As Barker (1899) put it in his extensive and influential review, the original tract of Gowers had become revealed as a combination of several independent fiber systems. It was largely at his suggestion that the name, Gowers' tract, became restricted to the ventral spinocerebellar tract.

Mott's study had clearly delineated the course of the ascending components of the old Gowers' anterolateral system, tracing the ventral spinocerebellar, spinotectal and spinothalamic fibers through the medulla oblongata in a position lateral to the inferior olivary nucleus, then ventrolateral to the superior olivary nucleus and so up to the level of the entering trigeminal nerve, at which point the ventral spinocerebellar fibers passed up lateral to the spinal tract of the trigeminal nerve to gain the brachium conjunctivum and entry into the anterior medullary velum of the cerebellum. The spinotectal and spinothalamic fibers continued ventromedial to the spinal tract before joining the fibers of the

lateral lemniscus with which they ascended to a more dorsal position. The spino-tectal fibers turned medially to end in the deep layers of the superior colliculus while the spinothalamic fibers continued on past the inferior colliculus to enter the posteroventral aspect of the thalamus, passing medial to the medial geniculate body in association with fibers of the medial lemniscus. In Mott's (1895) view, the spinothalamic fibers ended in the same part of the ventral nucleus of the thalamus as the fibers of the medial lemniscus but he had little detailed information and it remained for Quensel (1898) to demonstrate this conclusively in the brain of a human patient who had suffered from a spinal cord lesion.

The status of the ascending afferent pathways of the spinal cord was summed up in an extensive review in *Brain* in 1906 by May. In this, he examined the peripheral afferent fibers, dorsal root ganglion cells, the primary and secondary afferent pathways to which they contributed, and the thalamo-cortical projections to the postcentral gyrus, in the light of the recent division of common sensation by Head and his colleagues into three forms: deep or pressure sensibility; epicritic or discriminative cutaneous sensibility; and protopathic or pain and intense thermal sensibility (Head and Sherren, 1905; Head *et al.*, 1905). After a lengthy consideration of the recent histological work of Cajal (1894a, 1894b, 1900, 1902), the tract tracing experiments described above, and a detailed consideration of the clinical literature, he concluded that "the different factors underlying muscular sensibility ... pass ... along the [homolateral] posterior columns," that "the impulses that underlie the sensation of touch ascend in the same paths as those for pressure, viz., in the uncrossed posterior column, and later in the crossed anterior column," and that "the conduction of painful impulses ... occurs ... chiefly in the lateral and slightly in the anterior column, and is almost entirely crossed" He went on to say, however, that "the corresponding homolateral path may assume a more important role during the process of compensation in disease" and "the conduction of impulses of heat and cold, occurs in separate paths [from those concerned with pain], chiefly in the lateral column, and is almost entirely, if not entirely, crossed" Here is a summing up of the position adopted by clinical neurologists at that time. By 1914 and the publication of Dejerine's *Sémiologie des affections du système nerveux* (Dejerine, 1914), the anatomy of the pathway leading from dorsal root fibers through dorsal horn cells to the contralateral anterolateral quadrant and the ascent to and termination of many of these secondary fibers in the thalamus was firmly established.

Unmyelinated fibers and pain

It was a new histological technique that permitted a new step to be taken towards understanding the pain pathways. Ranson's discovery of the

pyridine silver method permitted him to reveal the presence of unmyelinated fibers in peripheral nerves and in the dorsal spinal roots in numbers that often exceeded those of the myelinated fibers (Ranson, 1911, 1912, 1913, 1914). Impressed with Head's ideas of protopathic and epicritic sensibility, Ranson (1914) suggested that the fine unmyelinated fibers might be concerned with pain and temperature sensation. He discovered that the fine fibers were peripheral processes of small dorsal root ganglion cells and found that as their central processes approached the spinal cord they became concentrated in the fascicles making up the lateral divisions of each root. Entering the cord lateral to the apex of the dorsal horn, they branched within Lissauer's tract (Lissauer, 1886), the branches extending over no more than one or two segments. He thought that they terminated in the substantia gelatinosa which he therefore saw as a "mechanism for the reception and conduction of pain and temperature sensations." In experiments in which he made knife cuts of the medial or lateral divisions of the entering dorsal roots in cats, he was able to demonstrate that the fine fibered lateral divisions undoubtedly were important for mediating the transmission of painful stimuli (Ranson and Billingsley, 1916). His experiments attempting to demonstrate the central pathways conveying painful impressions centrally in the spinal cord were less successful, although he was able to show that the vasomotor reflexes that often accompany a painful experience could be altered following interruption of the anterolateral funiculus (Ranson and Von Hess, 1915).

Foerster and the cellular origins of the anterolateral system

In subsequent years, the anatomy of the pain system was perhaps dominated by the name of Otfried Foerster, the German neurologist turned neurosurgeon, who not only performed numerous surgical interruptions of the anterolateral pathways at all levels for the relief of pain but also published a series of exhaustive clinical investigations of the sensory deficits accompanying pathological lesions affecting the pathway. His account in Bumke and Foerster's *Handbuch der Neurologie* (Foerster, 1936), summarizing some 20 years of clinical research, has never been surpassed. It was from Foerster's analyses that neurologists came to believe in the differential localization of pain, touch and temperature fibers in the anterolateral funiculus: tactile-related fibers located ventrally in what was to become known for a time as the ventral spinothalamic tract and pain- and temperature-related fibers more dorsolaterally in what was to become known as the lateral spinothalamic tract. In this, Foerster believed temperature-related fibers were located dorsal to the pain-related fibers (Fig. 1.4). Another of Foerster's contributions that came from close clinical observation was that

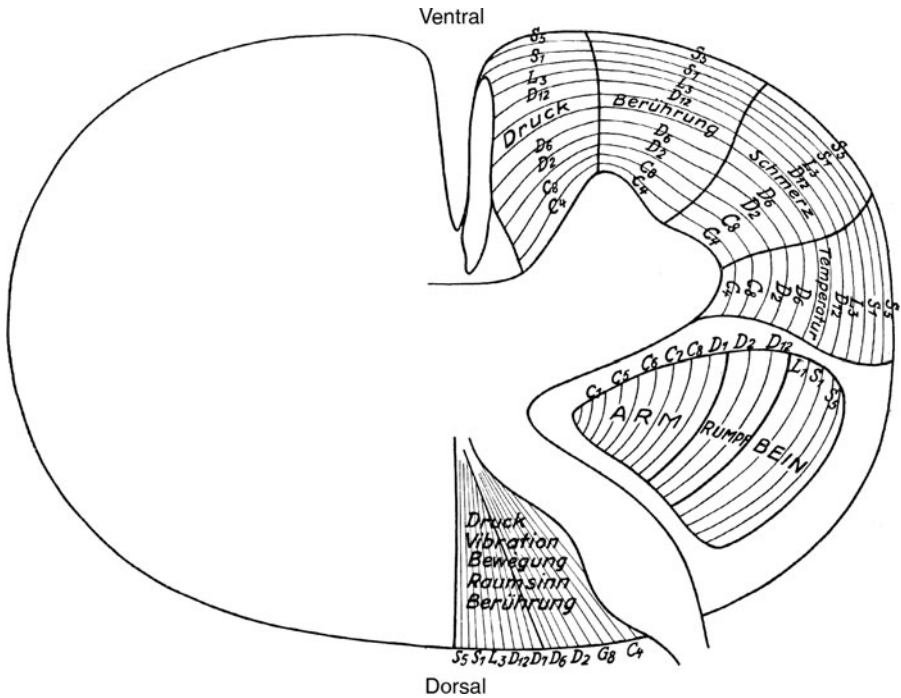


Fig. 1.4. Schematic diagram of the functional and segmental lamella-like organization of the anterolateral and posterior funiculi and corticospinal tract, as deduced from clinical signs in patients sustaining accidental or surgical lesions of the spinal cord. *Berührung*: touch; *Bewegung*: movement; *Druck*: pressure; *Raumsinn*: spatial sense; *Schmerz*: pain; *Temperatur*: temperature; *Vibration*: vibration. Dorsal is towards the bottom of the figure. From Foerster (1927).

pain- and temperature-related fibers entering the anterolateral funiculus must cross within no more than one or two segments of the level of entry of the dorsal root fibers that provided the input to their cells of origin in the contralateral dorsal horn.

Edinger's demonstration that decussating fibers contributing to the anterolateral tract arose from neurons located in the base of the dorsal horn had by now been accepted for many years, although neither Cajal (1899) nor Lenhossék (1895) had been able to show this; to them, all dorsal horn cells projected their axons into the ipsilateral Lissauer's tract or lateral funiculus (Fig. 1.5). Gagel and Sheehan had traced silver-stained dorsal root axons to dorsal horn cells and Gagel (1928) in monkeys and humans had observed transneuronal degeneration of these cells after section of the dorsal roots. Foerster and Gagel (1932) in a number of human cases with surgical lesions of the contralateral anterolateral funiculus also detected retrograde degeneration in the large cells surrounding

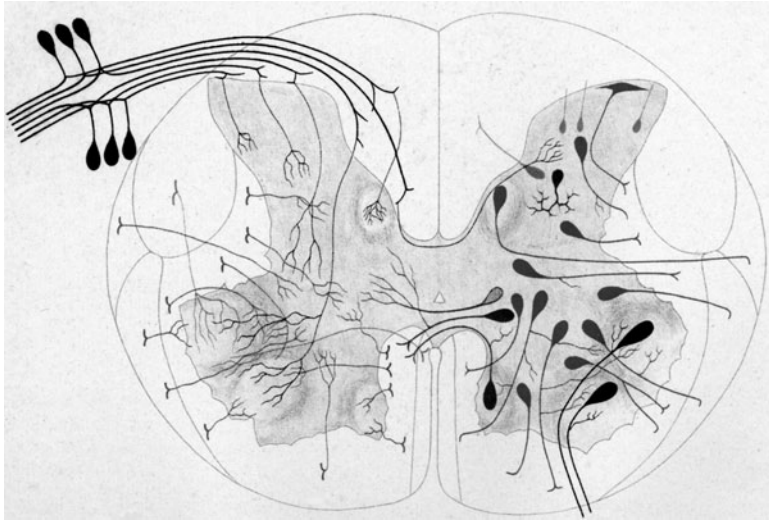


Fig. 1.5. Lenhossék's schematic representation of the structure of the spinal cord, showing the arrangement of collateral fibers on the left and of the neurons on the right. Note that there is no indication of decussating fibers entering the contralateral anterolateral column. From Lenhossék (1895).

the substantia gelatinosa and forming layers I and IV of the dorsal horn in modern terminology (see below) (Fig. 1.6). Earlier attempts at identifying the cells of origin of Gowers' tract by this method, for example those of Schäfer (1899) and Bruce (1910), had been unsuccessful or had related the origin of the fibers to cells in the caudal end of Clarke's column. Foerster and Gagel stressed that "the fibers of the anterolateral tract arise only from the large cells of the dorsal horn" and that there is "no relationship between the substantia gelatinosa and the anterolateral tract." The marginal cells of the dorsal horn were to Foerster and Gagel an apical component of a more extensive group of large dorsal horn cells surrounding the substantia gelatinosa (Fig. 1.6; see below). Later, Kuru (1938, 1949) and Morin *et al.* (1951) were to confirm the findings of Foerster and Gagel. Kuru divided the large cells into a marginal group that underwent retrograde degeneration after more dorsally placed lesions of the contralateral lateral funiculus which resulted in relief from pain, and a deep group in the nucleus proprius that underwent retrograde degeneration after more ventrally placed lesions of the contralateral lateral funiculus that resulted in a loss of tactile sensation only. Modern evaluations of the size and location of lesions effective in producing complete analgesia (and thermoanesthesia) after cordotomies in humans indicate that a far more substantial lesion than the dorsal lesion described by Kuru and involving the ventral half of the

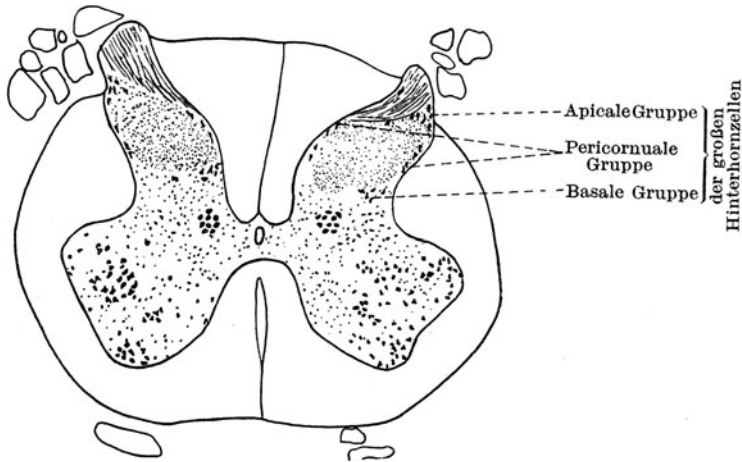


Fig. 1.6. Representation of the giant cells of the marginal zone and head and neck of the dorsal horn as a continuous population made up of apical, pericornual and basal groups. Adapted from Foerster and Gagel (1932).

lateral funiculus and adjacent parts of the ventral funiculus is necessary (Nathan *et al.*, 2001).

Thalamic terminations of spinothalamic fibers

As mentioned earlier, there was a general consensus from the experimental work on tract tracing with the Marchi technique in monkeys, supported by similar observations in human post-mortem material, that spinothalamic fibers terminated in close association with those of the medial lemniscus within the posterior and lateral division of the ventral nuclear complex of the thalamus. Further confirmation came from comparable work in rabbits (Wallenberg, 1899; Quensel and Kohnstamm, 1907), dogs (Rothmann, 1903) and cats (Probst, 1902a, 1902b). However, few details of the exact level of termination were provided and in many instances the degenerating spinothalamic fibers could not be traced much further than the external medullary lamina, probably because their thin myelin sheaths proved difficult to impregnate.

Between 1936 and 1940 five papers appeared that provided more extensive details of the thalamic terminations of the spinothalamic fibers. Le Gros Clark (Clark, 1936) in a Marchi-based investigation of the terminations of the medial lemniscus, spinothalamic tract and trigeminothalamic pathway and of the brachium conjunctivum in monkeys gave a detailed account of the

course of degenerating ascending fibers after hemisections of the spinal cord, tracing them through the brainstem and describing their entry into the thalamus between the parafascicular and medial geniculate nuclei at a level dorsal to the medial lemniscus; he showed them ending as terminal ramifications in the “lateral part of the pars externa of the ventral nucleus” (the ventral posterior lateral nucleus, VPL, of modern terminology), and throughout the caudal part of the internal medullary lamina around but not in the centre médian nucleus and concentrated in the central lateral nucleus. In VPL he described their terminations as coinciding with those of the medial lemniscal fibers but at times he seemed to suggest that they might have extended a little more anteriorly than the latter. His lesions of the spinal nucleus of the trigeminal nerve gave a similar result but with the degenerating fibers being concentrated medially and invading the pars arcuata of the ventral posterior nucleus (the VPM nucleus). His lesions were, however, incomplete and contaminated by interruption of internal arcuate fibers leaving the cuneate nucleus.

The Marchi-based studies of Walker in the monkey (1936, 1938a), chimpanzee (1938b) and human (1940) gave results that were substantially the same as those of Le Gros Clark, confirming that spinothalamic fibers entered the thalamus anterodorsal to those of the medial lemniscus and terminated in overlapping fashion with those of the medial lemniscus within the VPL nucleus (Fig. 1.7). Walker thought that in the chimpanzee, in particular, the terminations were concentrated in the most “posterior and basal part” of the VPL nucleus. Like Le Gros Clark, however, he also felt that some of the spinothalamic fiber terminations might have extended somewhat anterior to those of the medial lemniscus in the ventral nuclear complex.

In another Marchi study, Weaver and Walker (1941) used midline myelotomies rather than anterolateral cordotomies in monkeys to demonstrate a relatively crude topography of the ascending degenerating fibers in the spinal cord and brainstem, with fibers from the lumbar region located lateral to those ascending from the cervical region.

In what were to be the last Marchi-based studies of the spinothalamic projection, Gardner and Cuneo (1945), looking at the brain of a patient who had had an anterolateral cordotomy 21 days previously, were puzzled by seeing so little degeneration in the thalamus, but Chang and Ruch (1947) in the spider monkey utilized hemisections or transections of the cord at various levels in order to demonstrate the topography of the spinothalamic terminations on the ventral posterior nucleus of the thalamus. They described the projection as distinctly bilateral and equally heavy on both sides, with a mediolateral topography matching that of the medial lemniscal terminations in the VPL

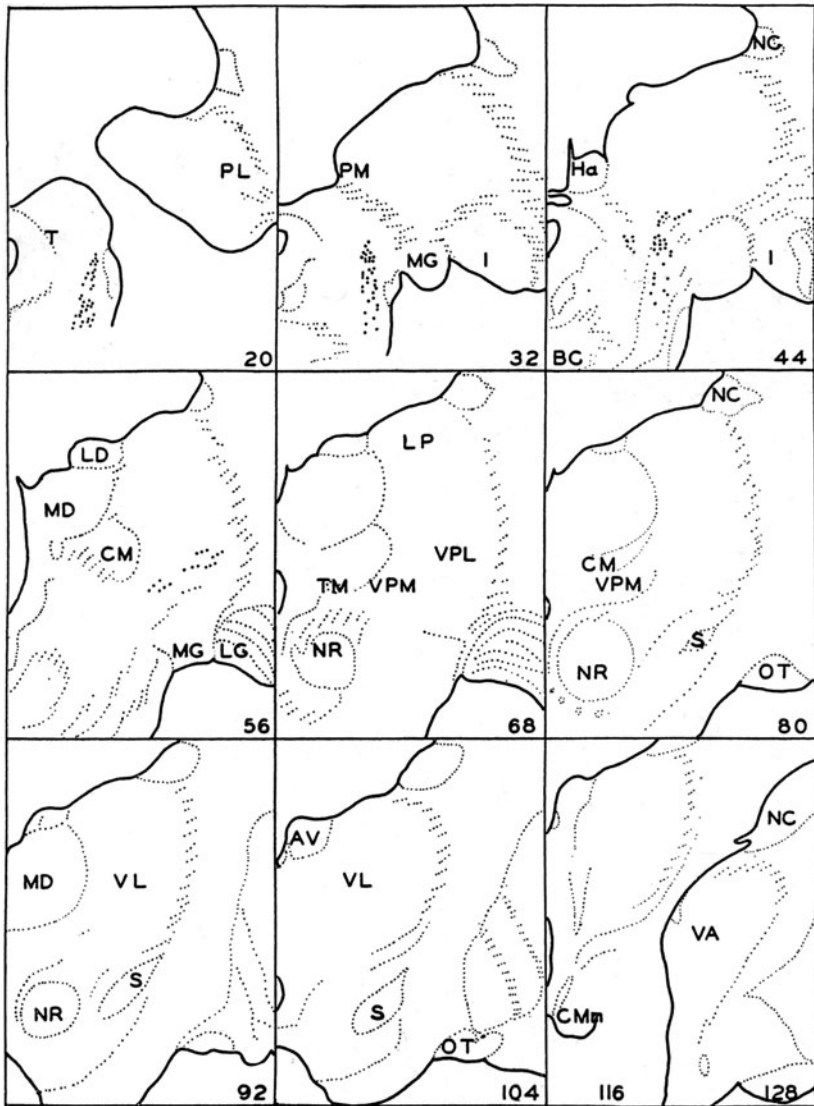


Fig. 1.7. Localization of Marchi-stained degenerating fibers in the midbrain and thalamus of a chimpanzee following anterolateral cordotomy in the mid cervical region 14 days previously. From Walker (1940). AV, anteroventral nucleus; BC, brachium conjunctivum; CM, centre médian nucleus; CMm, mamillary body; Ha, habenular nuclei; I, inferior pulvinar nucleus; LD, lateral dorsal nucleus; LG, lateral geniculate nucleus; LP, lateral posterior nucleus; MD, mediodorsal nucleus; MG, medial geniculate body; NC, caudate nucleus; NR, red nucleus; OT, optic tract; PL, lateral pulvinar nucleus; PM, medial pulvinar nucleus; S, subthalamic nucleus; T, tectum; TM, habenulo-peduncular tract; VA, ventral anterior nucleus; VL, ventral lateral nucleus; VPL, ventral posterior lateral nucleus; VPM, ventral posterior medial nucleus.

nucleus, fibers from lower cord segments terminating lateral to those from higher cord segments.

Trigeminothalamic projections

The projection of the principal trigeminal nucleus to the arcuate nucleus (VPM) of the thalamus had been identified quite early in Marchi-stained material from human pathological cases (Hösel, 1892; Spitzer, 1899; Probst, 1902a, 1902b; Lewandowsky, 1904; Wallenberg, 1904; Economo, 1911). Other studies were also carried out on experimental animals (Wallenberg, 1896, 1900, 1905; Van Gehuchten, 1901). Two ascending pathways came to be recognized, a crossed one that joined the medial lemniscus and ascended with it to the VPM nucleus, and an uncrossed dorsal pathway that ascended along the lateral edge of the medial longitudinal bundle and ended in the most medial part of the VPM nucleus (Fig. 1.8). Economo thought that the uncrossed dorsal pathway was a taste pathway and it was only much later revealed to make up the substantial uncrossed trigeminal input to the ipsilateral body representation in the VPM nucleus of monkeys (Jones *et al.*, 1986).

Fibers destined for the thalamus but arising from the spinal nucleus of the trigeminal nerve were first identified by Spitzer (1899) and Wallenberg (1901, 1904) in cases with pontine lesions affecting the spinal tract of the trigeminal nerve. In the brains from these cases, they could trace Marchi-stained degeneration along a pathway closely associated with the spinothalamic tract to the vicinity of the posterior part of the internal medullary lamina of the thalamus.

Le Gros Clark's (1936) Marchi-based experiments on the central projections of the principal and spinal nuclei of the trigeminal nerve in monkeys were inconclusive, mainly on account of incomplete lesions or lesions that involved other pathways such as the internal arcuate fibers leaving the dorsal column nuclei. Papez and Rundles (1937), in similar experiments, identified the crossed and uncrossed tracts ascending from the principal sensory nucleus and what they called a ventral tract arising from the spinal nucleus, its fibers crossing the midline and reaching the lateral aspect of the contralateral medulla by passing between the inferior olivary nucleus and the pyramid. The fibers then ascended with the spinothalamic fibers to the thalamus. Kuru (1938, 1949) was later able to demonstrate this pathway in brains from human cases with pathology or surgical lesions affecting the spinal nucleus.

Walker did not carry out any experiments on the trigeminal system in his early investigations on monkeys. Later (Walker, 1939a), he confirmed the findings of Papez and Rundles, tracing the fibers from the spinal nucleus to the

The structure of the dorsal horn

Before Cajal

Early investigations of the structure of the spinal cord were carried out on thin slices of the cord, either fresh or after hardening in alcohol and sometimes after further clearing in turpentine. Such unstained preparations permitted Rolando in 1824 to identify the substantia gelatinosa as a part of the gray matter that had a more translucent appearance than the remainder, although in stating that it occupied as much as two-thirds of the gray matter he was undoubtedly viewing something far greater than the substantia gelatinosa as recognized today. The technique, by means of which myelinated axon bundles are rendered visible by their refringency and neuronal somata and sometimes their proximal processes are visualized as vesicular bodies, permitted Lockhart Clarke (1851) in his initial investigations to outline in more detail the structure of the dorsal horn; in these he identified the column of cells at the base of the thoracic dorsal horn that later came to bear his name, and he identified the lateral horn, or as he called it the *intermediolateral tract*. With the introduction of chromic acid as a fixative, further advances were possible and Clarke (1859) and Stilling (1842) were able to make further contributions on the structure of the gray matter, including identifying nerve cells of different sizes in the dorsal horn and the orientations of the bundles of nerve fibers that traversed it (Fig. 1.9). Stilling's measurements of the relative proportions of gray and white matter at different segmental levels of the spinal cord continued to be reproduced in textbooks for most of the next half century. Stilling stressed that the majority of nerve fibers entering the cord in the dorsal roots ascended in the dorsal funiculi and that all the ventral root fibers arose from ventral horn cells, features that had not always been widely accepted. Clarke even considered, as did many others at that time, that the dorsal and ventral roots might be continuous with one another. In the dorsal horn, Clarke was able to identify larger fusiform cells around the perimeter of the substantia gelatinosa, later called the marginal cells or zonal layer by Waldeyer (1888); Clarke also identified many small cells within the substantia gelatinosa itself, the longitudinal bundles of nerve fibers that dominated the head of the dorsal horn, and some larger cells in the neck of the dorsal horn, as well as the nerve cells that made up the column that came to bear his name. Stilling's results were similar, as were the later ones of Deiters (1865) (Fig. 1.10), who in some of his preparations had the added benefit of staining neurons with carmine, a dye introduced into histology by Gerlach in 1858. Deiters was of the opinion that entering dorsal root fibers traversed the dorsal horn rather than terminating in it. Further contributions by Kölliker (1867), Gierke (1885, 1886), Lissauer (1886), Virchow (1887) and Waldeyer (1888) made

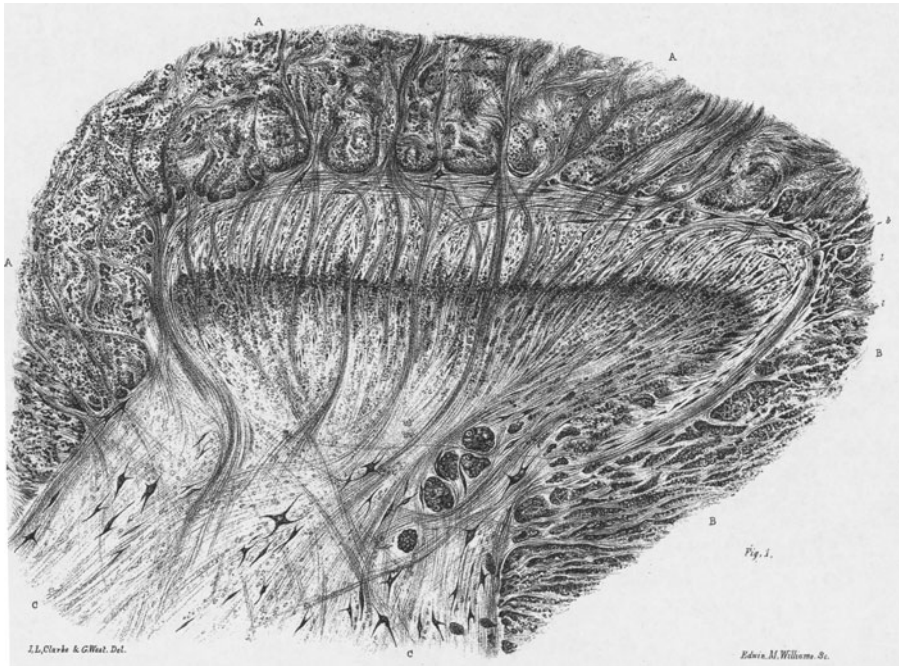


Fig. 1.9. Structure of the dorsal horn of the cervical spinal cord of an ox, as visualized in a fresh cut preparation hardened in alcohol. From Clarke (1859). (A) Posterior white column; (B) lateral white column; (C) cervix of the dorsal horn with large cells and crossed by bundles of dorsal root fibers; b, caput of the dorsal horn with deep zone made up of bundles of longitudinal fibers and superficial substantia gelatinosa.

it clear that the substantia gelatinosa was made up of nerve cells, although Gerlach (1872) and Bechterew (1886) were more inclined to think that it consisted of neuroglial cells. Around this time, as the result of the application of the myelogenetic technique, the order of myelination in the white matter tracts came to be worked out (Flechsig, 1876; Kahler, 1888). It was at about this time also that it became recognized that the smaller fibers that constitute the lateral division of the entering dorsal root myelinated later than the larger fibers entering in the medial division and that many of them left Lissauer's tract for the substantia gelatinosa.

At the end of this period, before the successful introduction of the Golgi technique into neurohistology by Cajal, a standard textbook of the day would have divided the gray matter of the dorsal horn into an *apex* covered by the *marginal bundle* or *spongiform zone* lying just deep to the tract of Lissauer; beneath this was the *substantia gelatinosa* forming a cap to the underlying *head* or *caput* of the dorsal horn which was delineated from the substantia gelatinosa by a substantial bundle of longitudinally oriented fibers that Clarke had called

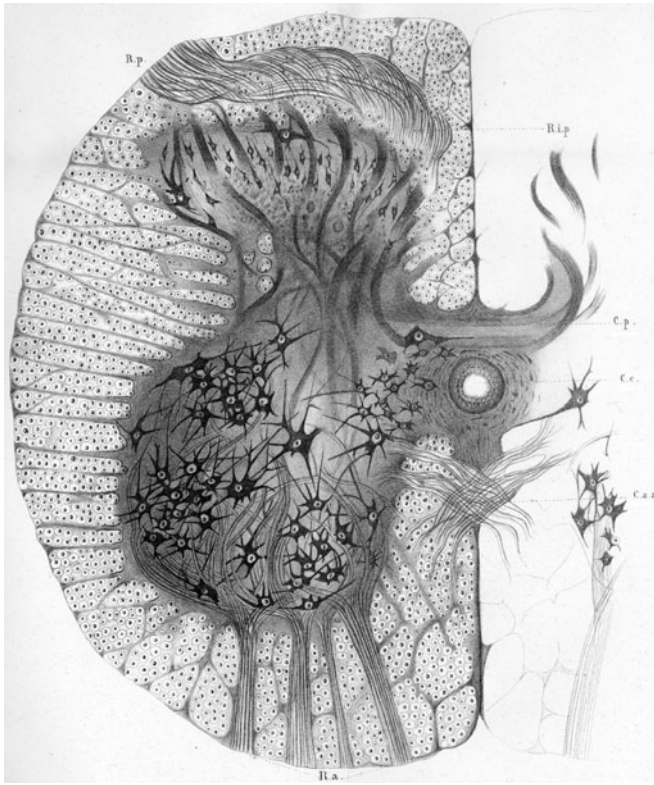


Fig. 1.10. Structure of the gray and white matter of the human lumbar spinal cord. Adapted from Deiters (1865). C.a.a., anterior white commissure; C.c., central canal; C.p., posterior gray commissure; R.a., ventral root fibers; R.i.p., internal division of posterior root; R.p., dorsal root.

the “opaque portion of the caput cornu.” The head was joined to the *base* of the dorsal horn by a narrow *neck* (*cervix cornu*). The base sat on the intermediate gray zone and the two intermediate zones were joined across the midline. Dorsally, lateral to the head and neck of the dorsal horn and most marked in the cervical region was the *processus reticularis* of Stilling (Fig. 1.11). Ventral to the intermediate zone was the ventral horn whose large motoneurons had been identified from earliest times (e.g. Lenhossék, 1855).

Cajal

The contributions of Santiago Ramón y Cajal to knowledge of spinal cord structure cannot be overestimated. In applying the Golgi technique for the first time in a concerted manner to the spinal cord he was able to reveal its cellular and axonal architecture at a level of resolution hitherto unimagined.

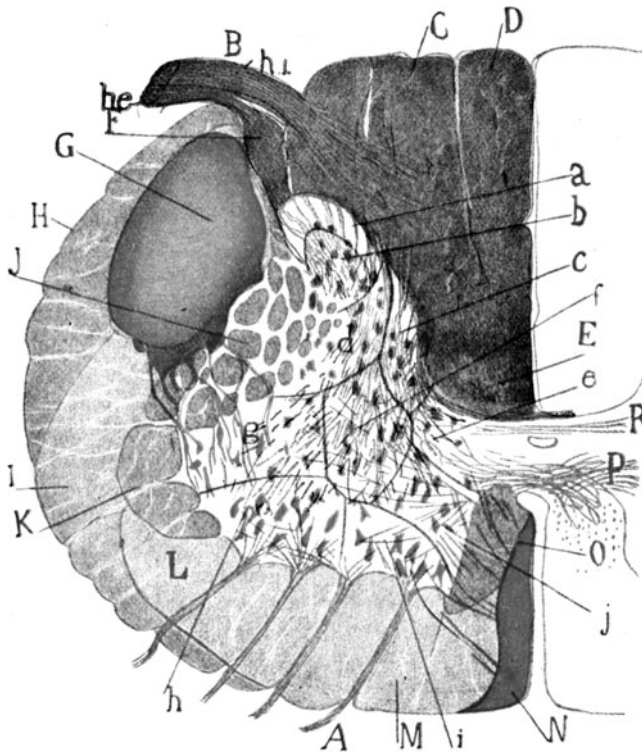


Fig. 1.11. Cajal's divisions of the gray and white matter of the human spinal cord. A, anterior root; B, posterior root; C, fasciculus of Burdach; D, fasciculus of Goll; E, ventral part of posterior funiculus; F, marginal zone of Lissauer; G, crossed pyramidal tract; H, cerebellar bundle of Flechsig; I, tract of Gowers; J, system of bundles of the posterior horn; K, system of the intermediate gray nucleus; L, intermediate column; M, short pathways of the anterior horn; N, direct pyramidal tract of bundle of Türck; O, commissural bundle; P, white or anterior commissure; R, gray or posterior commissure; a, substance of Rolando; b, vertex or head of the posterior horn; c, internal basal nucleus; d, external basal nucleus; e, central gray or central substantia gelatinosa; f, intermediate gray nucleus; g, nucleus of the anterolateral column; h, external motor nucleus; he, external division of posterior root; hi, internal division of posterior root; i, internal motor nucleus; j, gray commissural nucleus. From Cajal (1899).

His spinal cord studies were among the first that he carried out with the Golgi technique between 1888 and 1890. Spinal cord preparations were among those that he presented at the 1889 Congress of the German Anatomical Society in Berlin and it was the unique quality of these that helped bring his name to the attention of the scientific world. In a series of papers published between 1890

and 1895 Cajal reported the results of his investigations with the Golgi technique as applied by him primarily to the spinal cords of embryonic and newborn chicks and small mammals (Cajal, 1890a, 1890b, 1890c, 1891, 1893, 1895). Parallel studies carried out with the same technique by Kölliker (1890, 1891) and Lenhossék (1895) on the human spinal cord served to confirm Cajal's findings for the primate spinal cord and there were many other confirmatory studies in fish, reptiles, birds and other mammals as well (Retzius, 1891; Van Gehuchten, 1891; Lenhossék, 1895). Cajal's summing up of his spinal cord work in Volume 1 of the 1899 Spanish and 1909 French editions of his *Histology of the Nervous System of Man and Vertebrates* served to bring his descriptions of the cells and axons of the central gray matter of the spinal cord to a wide readership. His organizational plan was perhaps less widely used, although echoes of Cajal's nomenclature for the divisions of the dorsal horn can still be found in modern writings.

Cajal's division of the spinal gray matter was into three major territories, each with further subdivisions (Fig. 1.11). The dorsal horn consisted of four parts: the *substantia gelatinosa*, itself divided into the *substantia gelatinosa proper* and the *superficial marginal zone of Waldeyer*; the *head of the dorsal horn*; the *base of the dorsal horn*, a poorly delineated region divided into a *medial basal* and a *lateral basal nucleus*; *Clarke's column*, replacing the medial basal nucleus in the thoracic and upper lumbar regions. The ventral horn consisted of three nuclei: the *ventromedial* or *commissural nucleus* located near the central canal; the *ventrolateral nucleus* that contained the motoneurons and could be double; a dorsolateral zone or *nucleus of the ventrolateral funiculus*. Between the dorsal and ventral horns was the *intermediate gray zone* divided into a *medial central gray zone* or central *substantia gelatinosa* that contained the central canal, and an *intermediate nucleus* distinguished mainly as the region through which bundles of myelinated dorsal root fibers destined for the ventral motor nuclei passed. A further region, designated the *interstitial nucleus* by Cajal, was made up of nerve cells that lay among the bundles of myelinated fibers of the lateral funiculus that invade the base of the dorsal horn and which are especially prominent in the cervical region. This region was what Stilling had called the reticular process or zone. The bundles of fibers delimiting the interstitial nucleus were important to Cajal (see below) and he named them the *dorsal horn bundle*.

Among Cajal's most important contributions, as recognized at the time, was his identification and tracing to their terminations of the extensive systems of collateral branches given off by the entering dorsal root fibers. Kölliker, according to Cajal, regarded the discovery of the collaterals as "the most transcendental advance of recent times in the knowledge of the structure of the spinal cord". It is perhaps difficult to conceive now how fundamental an observation was the demonstration of axonal collaterals in the nervous system.

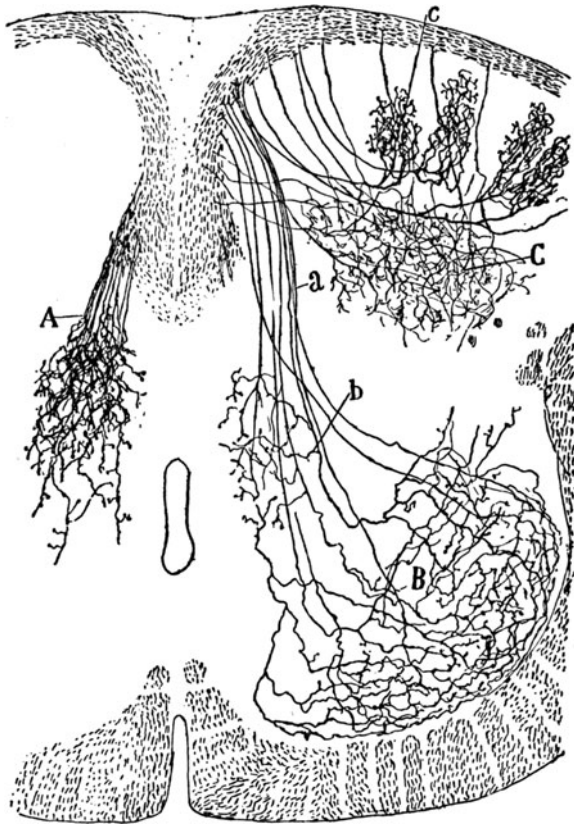


Fig. 1.12. Cajal's demonstration of the different sets of collaterals given off by entering dorsal root afferent fibers and terminating in the central gray matter. Golgi staining of a newborn rat spinal cord. (A) Collaterals for the intermediate gray nucleus; (B) arborizations for the motor nuclei; (C) ramifications for the head of the posterior horn; a, sensory-motor bundle; b, collateral of one of the fibers for the intermediate gray nucleus; c, deep collaterals in the substantia gelatinosa of Rolando. From Cajal (1899).

Their visualization had only become possible by the introduction of the Golgi technique and although Golgi himself had recognized their presence in the spinal cord (1886, 1890a, 1890b), it was left to Cajal to demonstrate their extent and their organization into what he called different systems. Those entering and terminating in the gray matter are particularly well illustrated in Fig. 1.12. Missing from the figure are the collaterals destined for Clarke's column and the branching of the entering dorsal root fibers into ascending and descending branches that ran in the dorsal columns, giving off the collaterals shown in the figure over a number of segments and continuing on to the gracile and cuneate

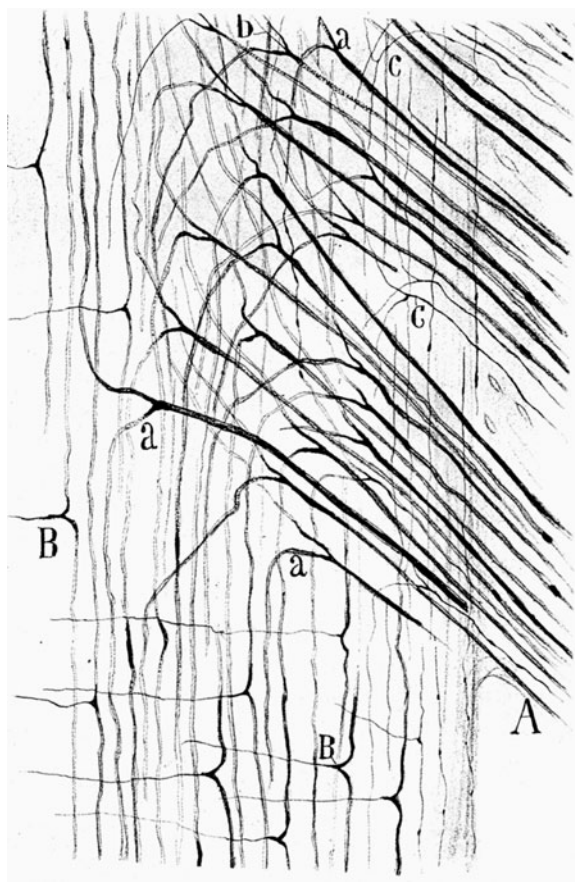


Fig. 1.13. The initial collaterals of both thick and thin afferent fibers on entering the spinal cord of a 15-day-old cat. Methylene blue stain. (A) posterior root; (B) posterior column with collaterals; a, b, bifurcation and trifurcation of sensory roots; c, fine fibers which bifurcate in the zone of Lissauer. From Cajal (1909).

nucleus (Fig. 1.13). It is noteworthy that Cajal observed branching at root entry of both thin fibers destined for Lissauer's tract as well as of the larger myelinated fibers that entered in the medial bundle of the dorsal root. It was only these larger fibers, he stressed, that gave off the collaterals forming his "sensory-motor bundle" to the ventral horn, and only from the fibers at the point of entry of these nerves into the cord, never from the ascending fibers in the gracile or cuneate fasciculi.

Of relevance to the present account is Cajal's description of the collaterals of dorsal root afferent fibers that terminated in the dorsal horn. He described collaterals destined for the head and center of the dorsal horn (Fig. 1.14) and

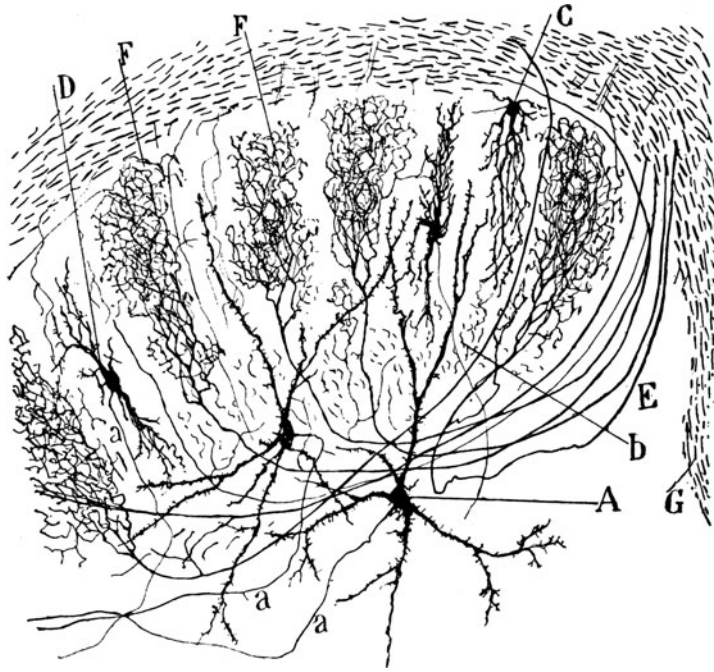


Fig. 1.14. Golgi-stained cells and axons in the substantia gelatinosa and underlying parts of the dorsal horn of the cervical spinal cord in a newborn cat. (A) cells of the head of the dorsal horn; (C, D) cells of the substantia gelatinosa of Rolando; (E) thick or deep collaterals; (F) terminal nervous arborizations continuous with the thick or deep collaterals; (G) ventral part of the posterior column; a, axons; b, longitudinal nervous arborizations of the head of the posterior horn. From Cajal (1899).

another set destined for the substantia gelatinosa (Fig. 1.15). Collateral fibers destined for the head and center of the dorsal horn were very numerous and derived from the “less robust” fibers ascending or descending in the dorsal funiculi or in Lissauer’s tract. They penetrated the substantia gelatinosa vertically in bundles of five or six fibers, dividing the substantia gelatinosa into a series of lobules. They formed a rich plexus around the cells in the center of the dorsal horn, some ascending into the deeper aspect of the substantia gelatinosa (Fig. 1.14). Overall, they formed a dense mass of longitudinally running fibers at the junction of the substantia gelatinosa and the head of the dorsal horn.

Collaterals destined for the substantia gelatinosa appear late in development and they were at first missed by Cajal but soon identified by Kölliker (1890). In the substantia gelatinosa proper Cajal later characterized the collateral fibers as forming two layers in the substantia gelatinosa: a thinner superficial layer formed by unmyelinated fibers emanating from Lissauer’s tract and the cuneate



Fig. 1.15. (Left) Golgi-stained longitudinal section of the dorsal horn of a newborn dog, dorsal to the right, showing the large marginal cells, the linear arrangement of neurons in the substantia gelatinosa, and the underlying plexus of axons in the head of the dorsal horn. (A) Fibers of the posterior column; (B) marginal cells of the substantia gelatinosa; (C) cells of the substantia gelatinosa; (D) longitudinal plexus of collaterals of the head of the posterior horn; (E) longitudinal fibers, probably sensory collaterals of the head of the posterior horn. From Cajal (1899). (Right) Methylene blue stained preparation from the spinal cord of an 8-day-old cat, showing the pericellular nests formed by afferent fibers around the giant cells in the marginal zone of the dorsal horn. (A) unmyelinated fibers; (B) short collaterals; (C, D) large marginal cells of the substantia gelatinosa; (E) strongly varicose terminal arborization. From Cajal (1909).

fasciculus, and a deeper layer formed by thicker myelinated fibers emanating from the cuneate fasciculus. These are the fibers seen ascending into the substantia gelatinosa in Fig. 1.14. They formed extensive, anteroposteriorly oriented arborizations in the substantia gelatinosa. Subsequent work has confirmed that the deeper plexus is formed by collaterals of afferent fibers and that the superficial plexus is probably formed mainly by axons of substantia gelatinosa cells that leave and re-enter the substantia gelatinosa via Lissauer's tract (Szentágothai, 1964).

At the surface of the substantia gelatinosa, Cajal observed what he regarded as a special category of sensory collaterals. Given off by certain large fibers of the dorsal funiculus where it lies close to the substantia gelatinosa these collaterals

wrapped the giant fusiform cells that characterize the marginal zone in a loose plexus (Fig. 1.15).

In describing the cells of the dorsal horn, Cajal described the head and lateral basal nucleus as being made up of similar populations of giant or medium-sized cells and distinguished by their possession of notably spiny dendrites (Fig. 1.14). The dorsal dendrites of these cells dichotomized and penetrated the substantia gelatinosa, ending in longitudinally elongated arborizations within one or more of the lobules defined by the afferent fiber bundles that vertically traversed the substantia gelatinosa. Ventral dendrites descended into the intermediate zone of the central gray matter. Cajal thought that the bitufted nature of the cells could be important in permitting the cells to receive input from one type of sensory fiber in the deeper aspects of the dorsal horn and from a second kind in the substantia gelatinosa. Cajal followed the axons of the large cells into his dorsal horn bundle, ipsilaterally; he did not describe any of the axons crossing to the contralateral lateral funiculus.

In the substantia gelatinosa proper, Cajal, whose preparations came mostly from chicks, described the neurons as being the smallest in the spinal cord and very densely packed. A thin outer layer of cells adjacent to the marginal zone was made up of ovoid cells with vertical dendrites. A thicker, deeper layer of cells exhibited a radial arrangement of dendritic fascicles and tended to form vertical clusters separated by the vertically traversing afferent fibers. The cells were primarily oriented in a longitudinal direction within the lobules formed by the traversing fibers. They gave off very thin axons; these, after a tortuous course during which they emitted numerous collaterals, entered the dorsal horn bundle. Lenhossék (1895) also observed this and, later, Szentágothai was to show that these fibers re-entered the substantia gelatinosa.

On the surface of the substantia gelatinosa proper, Cajal gave good descriptions of the large marginal cells, embedded in the plexus of afferent collaterals (Fig. 1.16). He thought that they were displaced cells of the head of the dorsal horn, a view that was to persist for many years. And he stressed that all of these giant cells sent their axons, like the cells of the head of the dorsal horn, into the dorsal horn bundle *ipsilaterally*.

It is noteworthy that Cajal never described axons of dorsal horn or intermediate zone cells crossing in the anterior commissure to the contralateral anterolateral funiculus. He located all cells with axons in the anterior commissure within the commissural nucleus of the ventral horn. He was ready to conclude that thermal and pain sensations were likely mediated by fine peripheral nerve fibers that ended freely in the skin, although largely by exclusion of the specialized endings associated with the larger fibers. And he was ready to quote current belief in a pain and temperature pathway in the spinal cord that commenced in

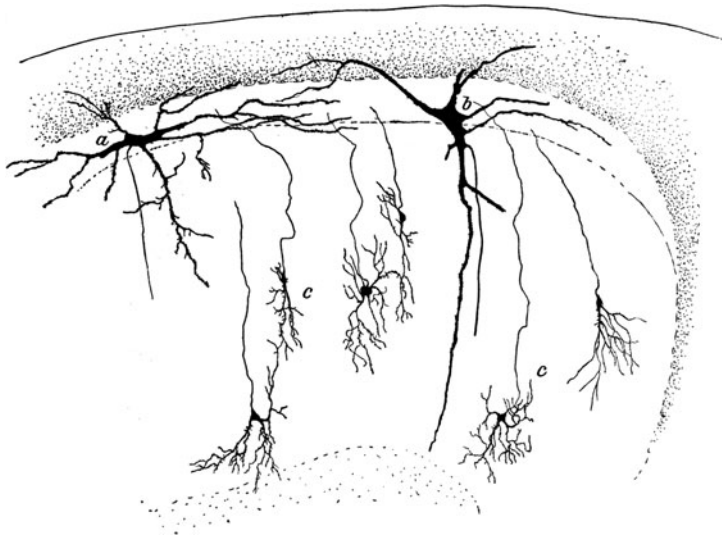


Fig. 1.16. Golgi-stained preparation from the dorsal horn of a human infant showing spindle (a) and pyramidal (b) forms of the giant marginal cells and cells of the underlying substantia gelatinosa (c) with axons entering the marginal zone. Adapted from Lenhossék (1895).

the dorsal horn and was mediated by fibers crossing in the anterior commissure and ascending in the anterolateral funiculus; but he clearly found the literature on the effects of lesions of the spinal cord on pain sensation rather confusing. He did not describe the elements of this pathway and did not refer to Edinger.

After Cajal

Although the branching afferent fibers and the nerve cells that Cajal illustrated in the various divisions of the dorsal horn attracted wide attention and were repeatedly reproduced, his divisions of the gray matter never really caught on. Of greater influence were the delineations of the human spinal gray matter made on cytoarchitectonic grounds by Jacobsohn (1908), Massazza (1922, 1923, 1924) and Bok (1928) (Figs 1.17–1.19). From these studies emerged the major names for the divisions of the gray matter that were in use until Rexed's re-evaluation of 1952 (see below). Jacobsohn's drawing of the cellular masses in the fifth lumbar segment of the human spinal cord is shown in Fig. 1.17. Like Cajal, he regarded the large cells located in the marginal zone and deeper within the head of the dorsal horn as part of a common magnocellular group. The substantia gelatinosa and the longitudinally running fibers beneath it he labeled the *nucleus sensibilis proprius*. Massazza called it the posterior sensory zone. The longitudinally running fibers, along with Jacobsohn's central group

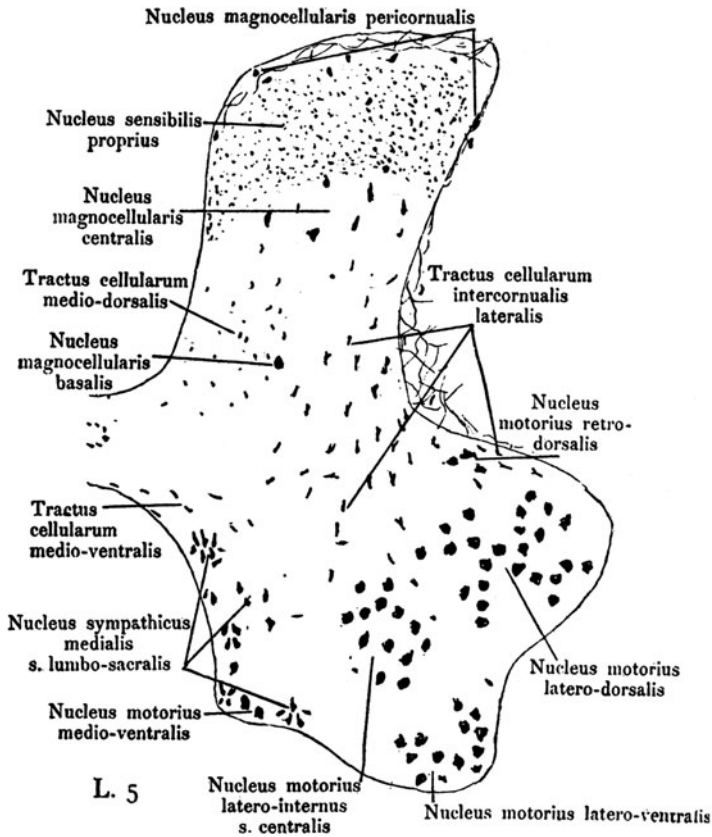


Fig. 1.17. Cell populations of the human spinal gray matter. From Jacobsohn (1908).

of magnocellular cells, became labeled the *nucleus proprius cornu dorsalis* by Bok (Fig. 1.19). The nucleus proprius always remained an ill-defined nucleus and Bok seems to have seen it as a kind of background matrix into which other more circumscribed groups of cells were inserted. He recognized a similar nucleus proprius of the ventral horn into which the groups of motoneurons were inserted. As used after Bok, the dimensions of the nucleus proprius of the dorsal horn varied with different investigators, some commonly showing it extending into the mediodorsal and lateral intercornual tracts of cells that Jacobsohn described. The lateral of these tracts of cells seems to have been the region of the dorsal horn bundle of Cajal or the reticular process of Stilling. Bok called it the reticular region. The medial tract of Jacobsohn was called the *nucleus cornu-commissuralis posterior* by Bok. It was compressed medially by Clarke's column in the thoracic region. Between the two tracts of neurons in the base of the dorsal horn Jacobsohn saw some giant cells which he called *nucleus magnocellularis*

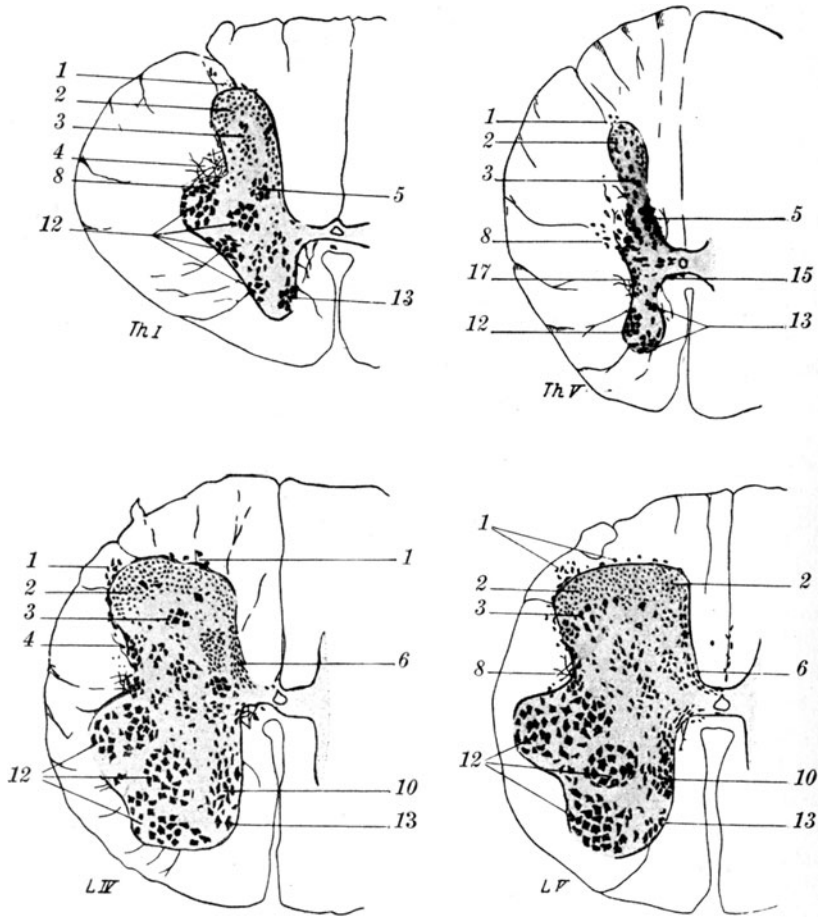


Fig. 1.18. Cell populations at levels of the human spinal gray matter similar to those illustrated in Fig. 1.17. From Massazza (1922–1924). 1: pericornual group of the lateral column; 2: posterior sensory zone; 3: centro-dorsal spino-thalamic group; 4: intercornual zone of the lateral column; 5: dorsal spino-cerebellar group; 6: mediodorsal zone of the posterior column; 8: lateral myoleiotic groups; 10: medial myoleiotic zone; 12: lateral groups of myorabdotic cells; 13: medial group of myorabdotic-commissural cells; 15: medioventral commissural zone; 16: sparse cell column of the anterior horn; 17: commissural cells.

basalis; to him, these cells belonged to the same group as those forming the pericornual and central groups of giant cells. The intermediate zone of Cajal in Jacobsohn’s eyes, was part of his lateral intercornual cell tract. Massazza and Bok divided the region into intermediolateral and intermediomedial divisions. Medially in the ventral horn all three recognized the group of commissural cells identified by Cajal, Jacobsohn calling it the medial sympathetic nucleus,

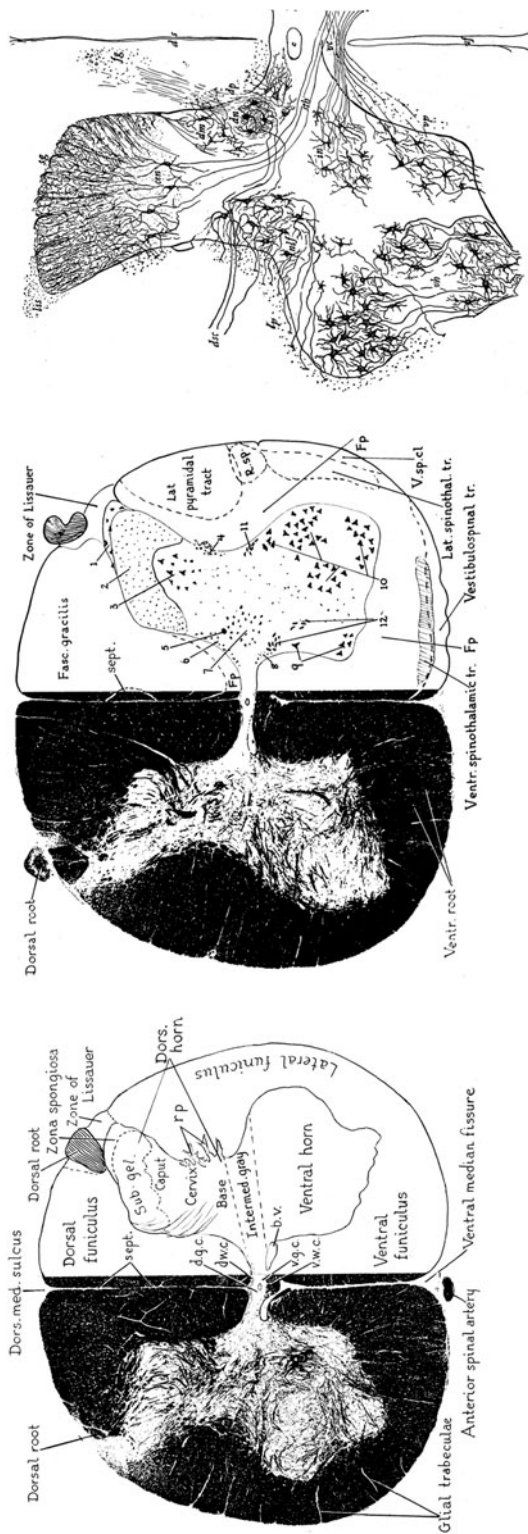


Fig. 1.20. Divisions of the human spinal central gray matter, as typically represented in textbooks prior to 1952. (Above) Myelin-stained preparations from Strong and Elwyn (1943) b.v., blood vessel; d.g.c., dorsal gray commissure; d.w.c., dorsal white commissure; Fp, fasciculus proprius; r.p., reticular process; R.sp., rubrospinal and reticulospinal tracts; sept. (above), dorsal median septum; sept. (below), septomarginal fasciculus; sub. gel., substantia gelatinosa; v.g.c., ventral gray commissure; V.sp.cl., ventral spinocerebellar tract; v.w.c., ventral white commissure. 1, nucleus posteromarginalis; 2, substantia gelatinosa; 3, nucleus proprius cornu dorsalis; 4, nucleus reticularis; 5, cell from Clarke's column; 6, nucleus cornucommissuralis posterior; 7, nucleus intermediomedialis; 8, nucleus proprius cornu dorsalis; 9, nucleus reticularis anterior; 10, nucleus motorius lateralis; 11, nucleus sympathicus lateralis; 12, nucleus sympathicus medialis. (Below) Reduced silver stained preparation from Papez (1929). c, central canal; cen, central nucleus; dn, dorsal nucleus or Clarke's column; dp, dorsal fasciculus proprius; ds, dorsal median septum; dsc, dorsal spinocerebellar tract; fg, gracile fasciculus; in, intermediate nucleus of Cajal; lis, Lissauer's tract; lp, lateral fasciculus proprius; nlf, nucleus of the lateral column of Cajal; sg, substantia gelatinosa; sth, spinothalamic tract fibers; vc, ventral commissure; vf, ventral median fissure; vh, ventral horn; vp, ventral fasciculus proprius.

Massazza the medioventral commissural zone and Bok the nucleus cornu-commissuralis anterior.

It was to Jacobsohn that Foerster and Gagel (1932) and Kuru (1938, 1949) turned when they located the neurons that they observed undergoing retrograde degeneration following anterolateral cordotomies in their human cases. Both sets of authors identified retrograde changes in the pericornual and central giant cells of Jacobsohn but not in his deeper basal magnocellular nucleus.

Rexed

Textbooks published in the years following Bok's 1928 account were content to use his or Jacobsohn's delineations of the dorsal horn or some variant of them (Fig. 1.20). In 1952, however, came the first of two papers by Bror Rexed (1952, 1954) that were to transform the way in which subsequent generations visualized and named the cellular regions of the dorsal horn and the rest of the spinal central gray matter. Starting from a position that the finer histology of the spinal cord as then known was inadequate for relating spinal cord structure to the exquisite details of spinal cord physiology that were then emerging, and from a viewpoint that the cytoarchitecture of the spinal gray matter would be similar in all mammals, Rexed undertook an exhaustive cytoarchitectonic re-evaluation in the cat. From it emerged what he called a new principle of the cytoarchitectonic structure of the spinal central gray matter. In this, the spinal gray matter is built up of nine laminae, most of which extend from one end of the spinal cord to the other (Figs 1.21–1.23). *Lamina I* is Waldeyer's thin zonal cell layer and contains the giant marginal cells originally named by Waldeyer (1888) and observed subsequently by many authors, as described above. *Lamina II* is the substantia gelatinosa. *Laminae III* and *IV* make up the greater part of the head of the dorsal horn. *Lamina III* still follows the curve of the substantia gelatinosa but in the deeper aspect of lamina *IV* the curve is flattened out. Together, they include the nucleus proprius cornu dorsalis of Bok and the central magnocellular nucleus of Jacobsohn but are probably more extensive than the two nuclei together. *Lamina III* is made up of small neurons and *Lamina IV* of large neurons. *Lamina V* includes most of what used to be called the neck of the dorsal horn, has only a few widely scattered neurons and is dominated by nerve fibers passing through it. It includes the medially located mediodorsal tract of cells of Jacobsohn as well as the larger lateral reticular process (Cajal's bundle of the dorsal horn) which Rexed brought into the spinal gray matter instead of leaving it as an appendage; he also regarded it as being present at all levels of the cord, not just a feature of the cervical segments. *Lamina VI* forms the base of the dorsal horn and is greatly expanded in the cervical and lumbosacral enlargements. It is made up of small, tightly packed nerve cells medially and larger, more

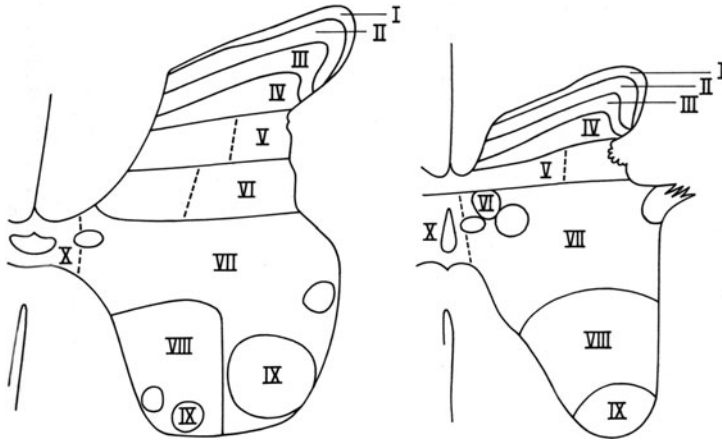


Fig. 1.21. Rexed's (1952) laminar divisions of the central gray matter of the spinal cord at the fifth lumbar (left) and third thoracic (right) segments in a cat. From Rexed (1964). See text for details.

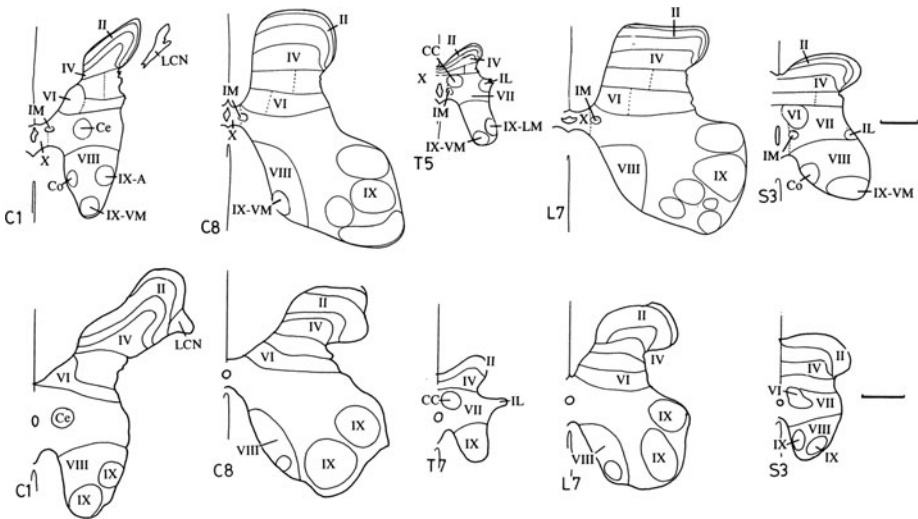


Fig. 1.22. Comparison of the laminar divisions of the central gray matter at different segmental levels in the cat as made by Rexed (1954) (upper) and in the monkey as made by Shriver *et al.* (1968) (lower). Modified from Voogd (1998).

diffusely arranged nerve cells laterally. *Lamina VII* is the greater part of the old intermediate zone and includes the old nuclei intermedio-medialis and intermedio-lateralis but continues down into the ventral horn between the groups of motoneurons. Mediolaterally, it extends from the area around the central canal to the lateral edge of the gray matter in the thoracic and upper

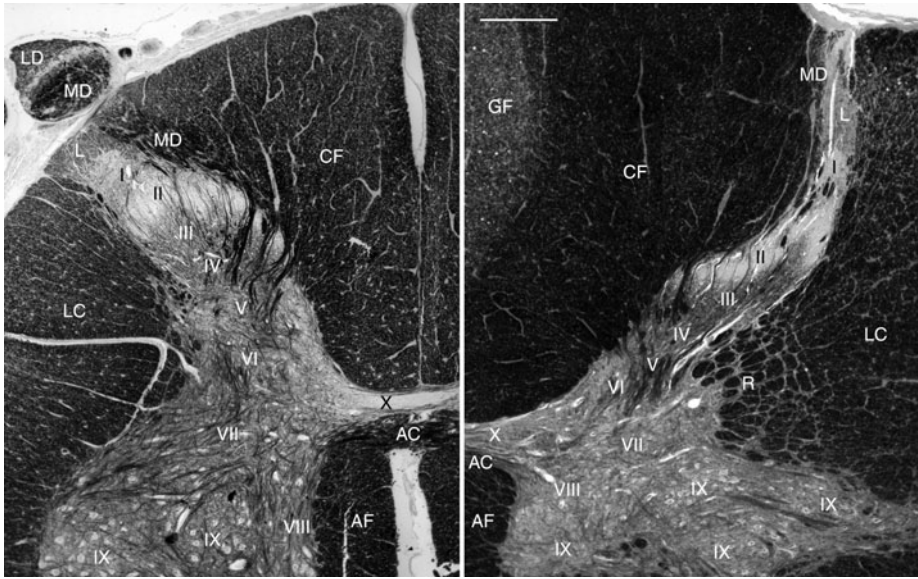


Fig. 1.23. Photomicrographs of myelin-stained preparations from human spinal cords at upper lumbar (left) and upper cervical (right) levels, with the approximate locations of the laminae (I–X) of the central gray matter indicated. AC, anterior commissure; AF, anterior column; CF, cuneate fasciculus; GF, gracile fasciculus; I–X, laminae of central gray; L, Lissauer's tract; LC, lateral column; LD, lateral division of dorsal root filament; MD, medial division of dorsal root filament; R, reticular zone (part of lamina V). Bar 500 μ m.

lumbar and sacral regions incorporating the lateral horn, but in the enlargements it is pushed upwards by the dorsolaterally expanded groups of motoneurons. It is made up of nerve cells that are uniform in size and appearance and evenly distributed. In the thoracic region, Clarke's column is inserted into its medial part. *Lamina VIII* extends right across the base and center of the ventral horn in the thoracic region but in the cervical and lumbosacral enlargements it is restricted to the medial half of the ventral horn in the position of Cajal's commissural nucleus. Its cells range in size from small to large and are all heavily stained. *Lamina IX* is made up of the columns of motoneurons. *Lamina X* is the small-celled region around the central canal.

Rexed's 1952 paper was focused on the laminar structure of the spinal gray matter and with relating what he observed to the older traditional parcellations going back to Clarke. His 1954 paper was an atlas, with extensive accompanying descriptive text in which he exhaustively described the laminar structure and its variations in the different segments throughout the length of the cat spinal cord, remarking in the upper part of the cord on the lateral cervical nucleus whose cells he saw as being very similar to those in Clarke's column, the transition from

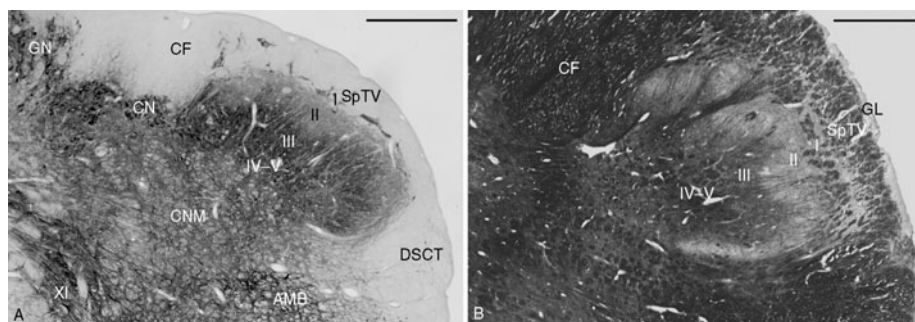


Fig. 1.24. Photomicrographs of cross sections through the lower part of the medulla oblongata, stained for cytochrome oxidase activity in a monkey (A) or for myelin in a human (B), showing the laminar organization of the caudal spinal trigeminal nucleus. Abbreviations as in Fig. 1.23 plus AMB, nucleus ambiguus; CN, cuneate nucleus; CNM, central nucleus of medulla oblongata; DSCT, dorsal spinocerebellar tract; GL, glia limitans; GN, gracile nucleus; SpTV, spinal tract of the trigeminal nerve. Bar 500 μ m.

the first cervical segment to the medulla oblongata in which he identified a central cervical nucleus located within the medial aspect of lamina VII, and the continuity of the spinal and medullary dorsal horns. In the medullary dorsal horn or caudal spinal trigeminal nucleus, he considered that laminae I–IV had exactly the same appearance as their counterparts in the spinal cord, whereas lamina V had become continuous with the underlying reticular formation (Fig. 1.24).

Rexed's laminar scheme became widely popular, perhaps because of the high degree of activity in the field of spinal cord physiology at the time and because of the widespread use of the cat as the experimental animal of choice in these investigations. It has stood the test of time and remains the standard to this day, its forerunners having been forgotten. The scheme, as Rexed predicted, has been applied successfully to many other mammalian species, including monkeys (Shriver *et al.*, 1968) and humans (Schoenen and Faull, 2004) (Figs 1.22 and 1.23). If it has been questioned at all it is in the extent to which the substantia gelatinosa should be regarded as only lamina II or whether the adjacent part of lamina III, containing the cells and collaterals that Cajal described as peculiar to the transition zone, should be included in it (Szentágothai, 1964; Réthelyi and Szentágothai, 1973).

The caudal spinal trigeminal nucleus

Lockhart Clarke had recognized as early as 1859 that the dorsal horn of the spinal cord continued without interruption and for a considerable distance

into the medulla oblongata, becoming separated from the remainder of the central gray matter there by the decussation of the pyramids. He was also able to track what he considered to be its continuity with the principal sensory nucleus of the trigeminal nerve. The continuity of the spinal and medullary dorsal horns became widely accepted and it was generally agreed that the latter should form a component of the ascending pain pathway representing the face (e.g. Gowers and Taylor, 1899). By 1919 Fuse, in myeloarchitectonic studies, had divided the human spinal nucleus into spinal, medullary and pontine divisions that largely correspond to the caudal, interpolar and oral divisions recognized today (see also Winkler, 1921). These were given their current names by Olszewski in his cytoarchitectonic study of the human and monkey brainstem in 1950. Prior to that, Meesen and Olszewski (1949) in the rabbit had recognized a caudal division with characteristics identical to those of the spinal dorsal horn and an oral division whose structure was quite different. Olszewski found that the caudal nucleus continued the spinal dorsal horn to the level at which the rootlets of the glossopharyngeal nerve leave the brain, at which level it transitioned into the interpolar nucleus whose architecture was much more homogeneous. The interpolar nucleus was succeeded in turn by the also homogeneous oral division which ended rostrally at the level of the root of the facial nerve. Olszewski renamed the components of the medullary dorsal horn as represented in the caudal division or *nucleus tractus spinalis trigemini caudalis* (Fig. 1.24): the *subnucleus marginalis*, equivalent to the marginal zone of Waldeyer, was located immediately deep to the descending spinal tract of the trigeminal nerve and capped the *subnucleus gelatinosus*, equivalent to the substantia gelatinosa, deep to which and bordering on the reticular formation of the medulla, was the *subnucleus magnocellularis*, equivalent to the head or nucleus proprius of the dorsal horn. Deep to this was the reticular formation of the medulla. These terms remained in use to the present day but have gradually been replaced by Rexed's laminar names, as an indication of the essential continuity of the spinal and medullary dorsal horns.

Cellular origins of spinothalamic tract fibers

Massazza (1924) was not in any doubt as to the cellular origins of the spinothalamic fibers when he labeled the nucleus proprius region of the dorsal horn the "centro-dorsal group of spinothalamic cells" but he seems to have been adopting Edinger's view that it was from these cells that the ascending tract of the anterolateral column arose. There was no definitive evidence other than the older studies of Edinger, which depended to a large extent upon observations in fish and amphibia, for the presence of dorsal horn neurons whose axons crossed in the anterior commissure and ascended in the anterolateral tract of the

opposite side to the thalamus. Neither Cajal (1899) nor Lenhossék (1895) in their extensive Golgi-based studies of the spinal cord had identified such cells (Fig. 1.5); all of the commissural cells that they described were located in the ventral horn or commissural nucleus (Fig. 1.11). The first direct evidence for the presence of dorsal horn cells with decussating axons that contributed to the spinothalamic tract came in the studies of Foerster and Gagel (1932) on the spinal cords of patients who had undergone anterolateral cordotomies for the relief of pain. In these, they were able to detect retrograde chromatolysis in the large cells of the marginal zone and head of the contralateral dorsal horn. Using Jacobsohn's terminology, they specifically referred to the affected cells as belonging to the apical, pericornual and central magnocellular groups. They did not observe retrograde changes in the deepest magnocellular cells, in what Jacobsohn had referred to as the nucleus basalis magnocellularis. Kuru's (1938, 1949) and Morin *et al.*'s (1951) observations, made in similar material, were essentially identical to those of Foerster and Gagel. Retrograde changes in the parent neurons of spinothalamic fibers after anterolateral cordotomies in humans have been described in more recent times by Smith (1976) and Schoenen (1981). In both studies the cells showing the retrograde reaction to severing of their axons were concentrated in regions of the central gray matter corresponding to Rexed's laminae I and IV, that is, in locations identical to those occupied by the spinothalamic tract cells identified by Foerster and Gagel and by Kuru. A smaller number of retrogradely affected cells were also described in regions corresponding to laminae VII and VIII. In Chapter 2 we shall describe the findings made in monkeys with more sensitive experimental tract tracing techniques. These suggest a somewhat wider distribution of spinothalamic tract cells although the principal concentrations of such cells remain located in laminae I and IV.

Early modern studies of spinothalamic and spinoreticular projections

Many of the older Marchi-based studies outlined above had mentioned not only that some fibers of the ascending anterolateral system were given off to various parts of the brainstem that Gowers had called "the reticular formation," but also that the number of fibers reaching the thalamus appeared significantly less than the number found within the tract at spinal and medullary levels. Spino-tectal fibers, both crossed and uncrossed, were the most consistently reported in the earlier studies (Sölder, 1897; Bruce, 1898; Russell, 1898; Thiele and Horsley, 1901; Walker, 1940); and reports of fibers to what is now called the lateral reticular nucleus of the medulla oblongata were also fairly consistent

(Tooth, 1892; Petrén, 1901; Collier and Buzzard, 1903; May, 1906; Kohnstamm and Quensel, 1908a, 1908b). Terminations at other levels of the reticular formation of the brainstem were less consistently reported (Bruce, 1898; Kohnstamm, 1900; Collier and Buzzard, 1903; May, 1906; Petrén, 1910; Walker, 1940). As early as 1908, Kohnstamm and Quensel postulated the existence of a reticulothalamic connection that would be necessary for bringing spinal influences upon the reticular formation to the thalamus and cerebral cortex.

The introduction of the Nauta technique, by means of which both unmyelinated and myelinated axons degenerating in anterograde fashion could be impregnated against a clear background from which staining of normal fibers was suppressed (Nauta and Gyax, 1954), provided an unparalleled opportunity for reinvestigation of the spinothalamic tract and its terminations at all levels of the neuraxis. The first studies on monkeys, apes and humans, along with a number of other species, were carried out by William Mehler in Nauta's laboratory at the Walter Reed Army Medical Center in Washington, DC but were initially reported only in abstract form (Mehler *et al.*, 1956; Mehler, 1957). The first full length account, of the study on monkeys, appeared in 1960 (Mehler *et al.*, 1960) and Mehler was to publish a series of papers on his findings in humans, monkeys, chimpanzees and other species in subsequent years (Mehler, 1962, 1965, 1966a, 1966b, 1969, 1971, 1974). Before publication of Mehler *et al.*'s first full length account, Bowsher (1957) was able to report on his findings in four human cases of anterolateral cordotomies. In these cases, he briefly described degeneration of terminal fibers of the anterolateral system in the VPL and centre médian (CM) thalamic nuclei and in numerous brainstem sites that included the central raphe at various levels, the parvo- and gigantocellular reticular formation, the oral and caudal pontine reticular nuclei, the subcoeruleus nucleus, the pedunculo-pontine tegmental nucleus, the paralemniscal nucleus of the midbrain, the interstitial nucleus of Cajal, the periaqueductal gray matter and the inferior and superior colliculi.

The study of Mehler *et al.* (1956, 1960), on the brains of macaque monkeys subjected to hemisections of the spinal cord at cervical or thoracic levels, was reported in more comprehensive terms and served as the standard reference work for many years. The brains were sectioned in the frontal, sagittal or horizontal planes in order to provide clear views of the location and orientation of the ascending degenerating fibers at all levels of the neuraxis (Fig. 1.25). The authors felt that they could discern two principal ascending systems of fibers within the anterolateral column; a more deeply situated group corresponding more or less to the two "groundbundles" of Bechterew (1894) that distributed fibers massively throughout many nuclei of the medullary and pontine reticular formation; a more superficially located group that accompanied the ventral

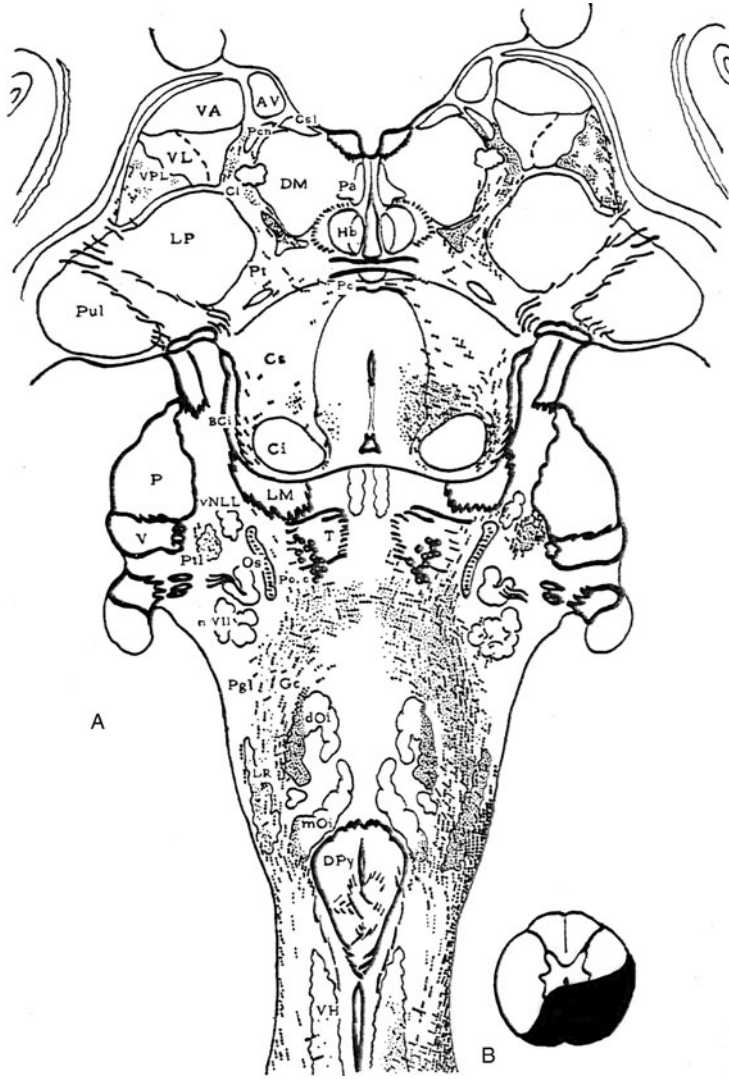


Fig. 1.25. (A) Drawing of an oblique horizontal section through the spinal cord, brainstem and thalamus of a rhesus monkey showing (dots) the locations of degenerating axons and terminals, stained by the Nauta technique following an anterolateral cordotomy at the sixth thoracic segment (B). From Mehler *et al.* (1960). AV, anteroventral nucleus of thalamus; BC, brachium conjunctivum; BCI, brachium of inferior colliculus; Ci, inferior colliculus; Cl, central lateral nucleus of thalamus; CM, centre médian nucleus; Cs, superior colliculus; Csl, superior central lateral nucleus of thalamus; DM, mediodorsal nucleus of thalamus; dOi, dorsal accessory olivary nucleus; DPy, pyramidal decussation; Gc, nucleus gigantocellularis; Hb, habenular nuclei; LM, medial lemniscus; LP, lateral posterior nucleus of thalamus; LR, lateral reticular nucleus; mOi, medial accessory olivary nucleus; nVII, facial nucleus;

spinocerebellar tract and then at the junction of the pons and midbrain ascended along the medial margin of the lateral lemniscus to terminate in the lateral aspect of the mesencephalic central gray matter and deeper layers of the superior colliculus; fibers continuing anteriorly from this system formed loose fascicles running medial to the brachium of the inferior colliculus and capping the medial lemniscus near the caudal pole of the medial geniculate complex of the thalamus. Fibers given off at right angles from this level and having the appearance of collaterals turned dorsomedially and, running through the pretectum, entered the caudal part of the internal medullary lamina of the thalamus (Fig. 1.26). The parent fibers, continuing the course of the classical spinothalamic tract, gave off terminations in the magnocellular nucleus of the medial geniculate complex and then broke up into smaller fascicles that entered the “pars caudalis” of the VPL nucleus where they ended in dense “bursts” of pericellular degeneration throughout the full extent of the VPL nucleus. These bursts of degeneration were separated by gaps, contrasting with the more homogeneous distribution of degenerating medial lemniscal fibers that they had seen in VPL following lesions of the dorsal column nuclei. The archipelago-like distribution of spinothalamic terminations in the VPL nucleus and its environs has been a consistently reported feature in all later investigations of the spinothalamic projection.

The terminal spinothalamic degeneration was located laterally in cases of thoracic hemisections and throughout the mediolateral extent of the VPL nucleus in cases of cervical hemisections. The fibers given off at upper mesencephalic levels and extending through the pretectum towards the internal medullary lamina of the thalamus ended in the dorsal aspect of the parafascicular nucleus, central lateral nucleus and in the paralaminae divisions (pars densocellularis and pars multiformis) of the mediodorsal (MD) nucleus. Contrary to Bowsher (1961), no degeneration was observed in the centre médian nucleus and this has been a consistent finding in all subsequent studies.

In the brainstem, below the level of the rostral pole of the inferior olivary complex, the spino-bulbar terminations were concentrated ipsilaterally; above it, some crossed the midline through the gigantocellular reticular nucleus to

Caption for Fig. 1.25. (cont.)

Os, superior olivary nucleus; P, brachium pontis; Pa, paraventricular nuclei of thalamus; Pc, posterior commissure; Pcn, paracentral nucleus of thalamus; Pgl, lateral paragigantocellular nucleus; Po.c., caudal central pontine nucleus; Pt, pretectal region; Pul, pulvinar; vNLL, ventral nucleus of lateral lemniscus; T, trapezoid body; V, trigeminal nucleus; VA, ventral anterior nucleus of thalamus; VH, ventral horn; VL, ventral lateral nucleus of thalamus; VPL, ventral posterior lateral nucleus of thalamus.

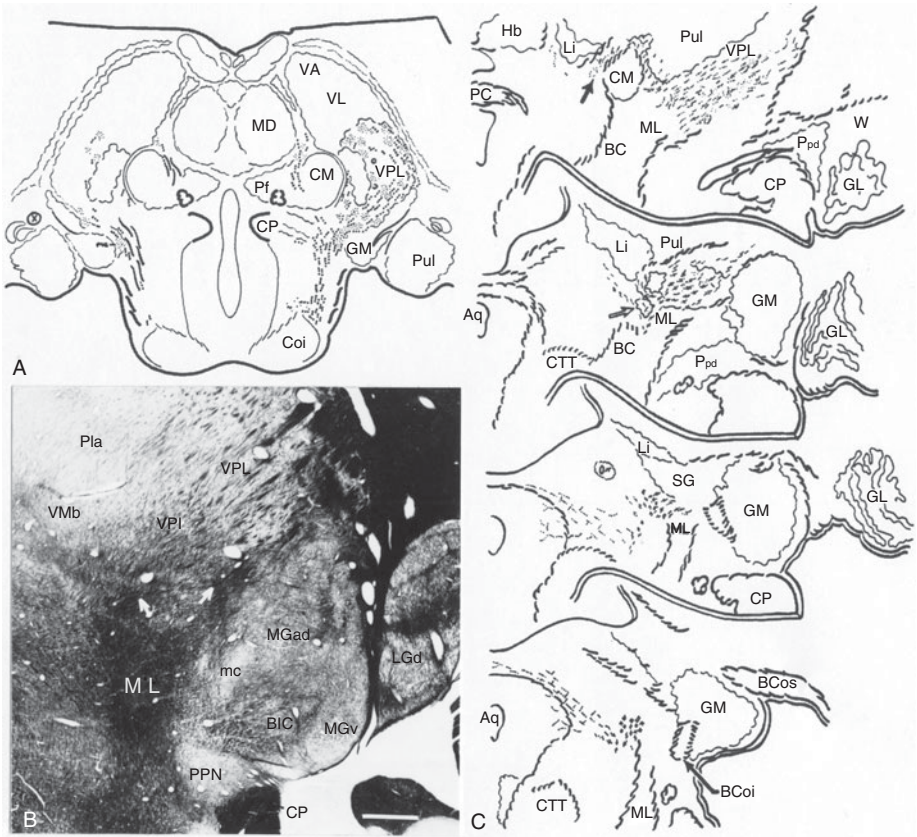


Fig. 1.26. (A) Drawing of an oblique frontal section through the thalamus of a macaque monkey showing the distribution of degenerating fibers and terminals in the posterior and ventral posterior nucleus consequent upon a lesion that severed the spinothalamic tract in the ipsilateral anterolateral quadrant of the spinal cord. (B) Photomicrograph of a hematoxylin-stained frontal section through the posterior nucleus and posterior pole of the ventral posterior nucleus of a cebus monkey showing the fibers of the medial lemniscus (ML) and the region of entry of spinothalamic tract fibers (arrows) shown in A. Bar: 1 mm. (C) Drawings of sections in anterior (upper) to posterior (lower) order through the thalamus shown in A, revealing at higher magnification the terminations of degenerating spinothalamic fibers in the region posterior to the ventral posterior complex and medial to the medial geniculate complex. A, C from Mehler (1966b) with modern labeling; B from Jones (2007). For abbreviations see Fig. 1.25 and Table 1.1.

terminate contralaterally in the same regions as the heavier ipsilateral system of fibers; at the level of the superior colliculus, others crossed in the tectal commissure. The thalamic terminations were bilateral and symmetrically located. In the intralaminar and paralaminar nuclei the ipsi- and contralateral terminations

were of equal density but in the VPL nucleus they were far heavier ipsilateral to the spinal hemisection. From comparative studies in many other mammalian species, Mehler (1957, 1966a, 1966b) was led to believe that the medially directed intra- and paralamina projection represented a phylogenetically “older” “palaeo-spinothalamic” system and the laterally directed VPL projection a later evolved “neo-spinothalamic” system.

Mehler *et al.* (1960) were struck by the enormous extent of the ascending spinal fiber terminations in the brainstem. The number of medullary, pontine and midbrain nuclei that received spinal fibers was considerable and the density of terminations far exceeded those formed by fibers continuing on to the thalamus. Many earlier reports of studies conducted with the Marchi technique and even before had indicated that fibers ascending in the anterolateral columns were distributed to various reticular nuclei but it is doubtful that the full extent of the spinoreticular projections had been fully realized before the study of Mehler *et al.* The following is a list of the principal brainstem nuclei in which Mehler *et al.* reported finding terminal degeneration of spinal fibers in their hemisection cases. Some of the names have been converted to their modern forms.

- Central nucleus of the medulla oblongata
- Lateral reticular nucleus
- Paramedian reticular nucleus
- Nucleus of Roller
- Raphe pallidus
- Gigantocellular reticular nucleus
- Paragigantocellular reticular nucleus
- Pontine reticular nucleus
- Nucleus subcoeruleus
- Pontine tegmental nucleus
- Subtrigeminal nucleus
- Facial nucleus
- Nucleus of solitary tract
- Dorsal and medial accessory olivary nuclei
- Intercollicular nucleus
- Periaqueductal gray matter
- Vestibular nuclei
- Deep layers of superior colliculus
- Preectum

As an overall description of the extent and general pattern of terminations of the ascending anterolateral fiber system, that of Mehler *et al.* stands out as a

landmark. Subsequent studies, carried out with the same and later with more refined tracing techniques, have mainly served to fill in the finer details of the pattern of fiber terminations. We shall examine these in detail below. One area of immediate concern to Mehler and to others at the time was to examine in more detail the spinothalamic terminations in the caudal aspect of the thalamus, for it was here, in humans, that Hassler (Hassler and Riechert, 1959; Hassler, 1961) had located the effective site for eliciting severe localized pain by electrical stimulation and for the elimination of pain by stereotaxic lesions. Moreover, Poggio and Mountcastle (1960) in their contemporaneous investigations on cats had located seemingly nociceptive-related thalamic neurons not in the VPL nucleus but in a more caudal region then called the posterior group of thalamic nuclei. Whitlock and Perl (1961) in parallel studies in monkeys had localized a similar region to the magnocellular nucleus of the medial geniculate complex, a part of the posterior group. For a history of the posterior group and its short-lived role as a thalamic pain nucleus see Jones (2007).

There can be little doubt that the early investigators observed the greatest concentration of spinothalamic terminations in the basal region of the thalamus where the ventral posterior, limitans-suprageniculate and medial geniculate nuclear complexes come together and through which spinal and lemniscal fibers enter the thalamus. As the entry portal for these massive fiber systems, it warrants the name given to it by Hassler (1959), *porta thalami* (Fig. 1.26). The problem for the early investigators was that they found it difficult to make a definitive cytoarchitectonic parcellation of the region of their own or to relate their findings to the parcellations of others, which some of them clearly misunderstood.

A revised view of the *porta thalami* region will be presented in Chapter 2. For the present it is sufficient to state that it commences posteriorly along the medial border of the medial geniculate complex in the region of the magnocellular nucleus of the latter complex, then it expands dorsally, embracing the posterior pole of the ventral posterior complex in the region where the limitans-suprageniculate nucleus joins the medial geniculate complex, and ends ventral to the posterior pole of the ventral posterior complex (Fig. 1.26). The early investigators clearly saw degenerating spinothalamic fibers in this region. Mehler (1966a, 1966b), however, was inclined to see most of these as terminating in relation to large cells of the VPL nucleus that clearly invade the region and felt that these were cells that other investigators were referring to when they related degeneration to the magnocellular medial geniculate nucleus (Fig. 1.27). In a later study, Boivie (1979) was to re-echo this point of view. Boivie also described degeneration encompassing the posterior pole of the VPM nucleus and invading

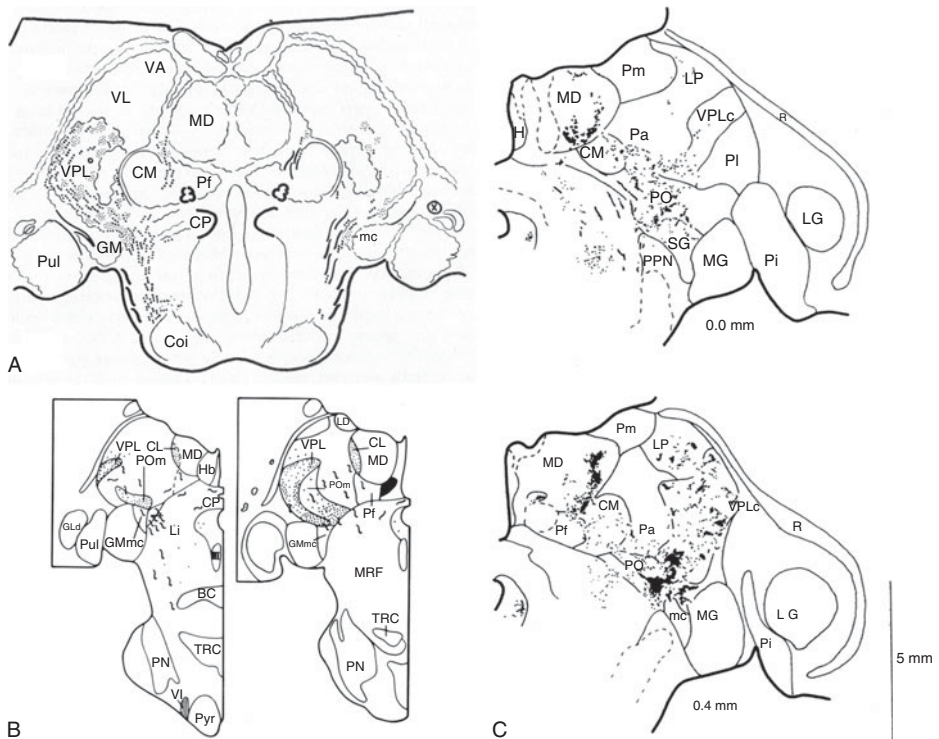


Fig. 1.27. Different representations of the locations of spinothalamic fiber terminations around the posterior pole of the VPL nucleus of the thalamus in monkeys. (A) from Mehler (1966a), horizontal section; (B) from Boivie (1979), frontal sections; (C) from Burton and Craig (1983), frontal sections. Modern labeling has replaced the original labeling. Abbreviations in A: CM, centre médian nucleus; Coi, inferior colliculus; CP, posterior commissure; GM, medial geniculate nuclei; MD, mediodorsal nucleus; Pul, pulvinar; VA, ventral anterior nucleus; VL, ventral lateral nucleus; VPL, ventral posterior lateral nucleus. Abbreviations in B: BC, brachium conjunctivum; CL, central lateral nucleus; CP, posterior commissure; Gld, dorsal lateral geniculate nucleus; GMmc, magnocellular medial geniculate nucleus; Hb, habenular nuclei; III, oculomotor nucleus; LD, lateral dorsal nucleus; Li, nucleus limitans; MD, mediodorsal nucleus; MRF, medullary reticular formation; Pf, parafascicular nucleus; PN, pontine nuclei; POM, posteromedial nucleus; Pul, pulvinar; Pyr, pyramid; VI, abducens nerve; VPL, ventral posterior lateral nucleus. Abbreviations in C: CM, centre médian nucleus; H, habenular nuclei; LG, dorsal lateral geniculate nucleus; LP, lateral posterior nucleus; mc, magnocellular medial geniculate nucleus; MD, mediodorsal nucleus; MG, medial geniculate nuclei; Pa, anterior pulvinar nucleus; Pf, parafascicular nucleus; Pi, inferior pulvinar nucleus; Pl, lateral pulvinar nucleus; Pm, medial pulvinar nucleus; PO, posterior nucleus; PPN, peripeduncular nucleus; R, reticular nucleus; VPLc, ventral posterior lateral nucleus.

the anterior pulvinar nucleus and called this region the medial division of the posterior group, by analogy with the organization of the cat thalamus (Fig. 1.27). Others, at the time, simply saw this degeneration as being within the confines of VPL.

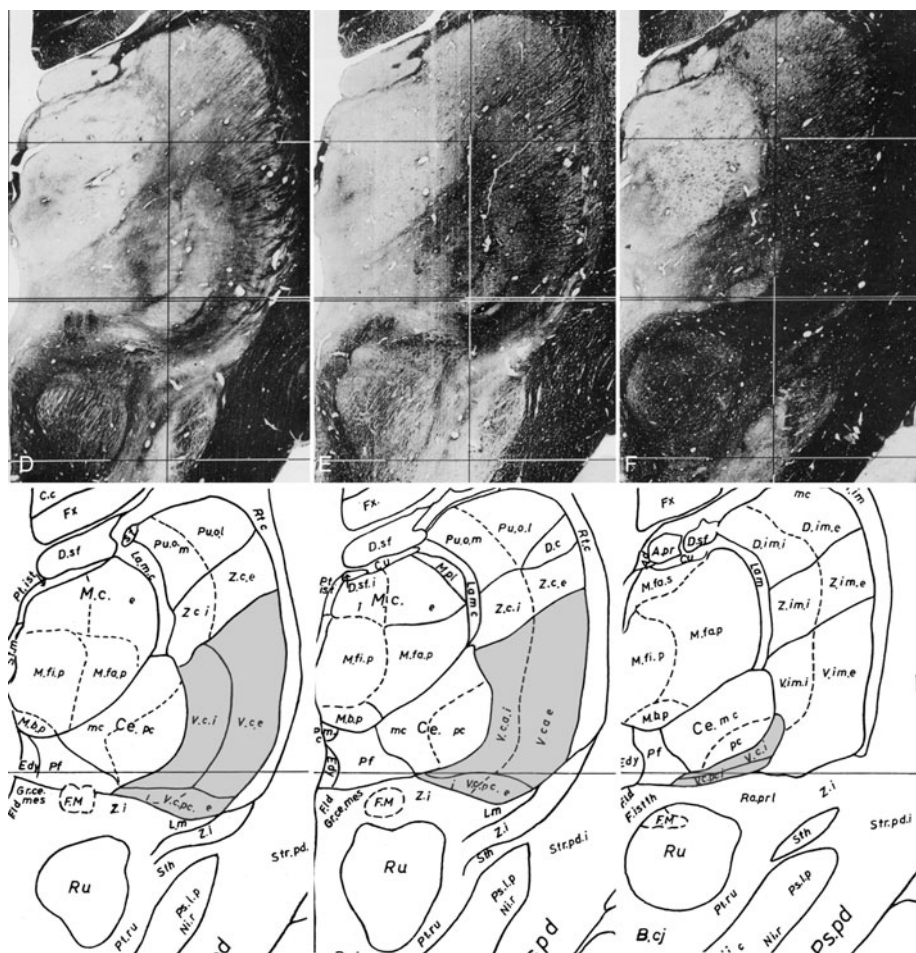
Hassler both in his studies of Marchi-stained degeneration in humans (Hassler, 1948) and of Nauta-stained degeneration in macaques and baboons (Hassler, 1970) adopted the parcellation scheme that he finalized in the *Schaltenbrand and Bailey atlas of the human forebrain* (Hassler, 1959). In this, he divided the ventral posterior complex into two dorsal and two ventral nuclei (Fig. 1.28). Dorsally were the external ventrocaudal nucleus (V.c.e) and the internal ventrocaudal nucleus (V.c.i), approximately equivalent to the dorsal two-thirds of the VPL and VPM nuclei respectively of modern terminology. Ventrally were parvocellular divisions of these nuclei, the external (V.c.pc.e) and internal (V.c.pc.i) parvocellular nuclei, approximately equivalent to the ventral posterior inferior (VPI) and basal ventral medial (VMB or parvocellular VPM) nuclei of modern terminology but incorporating the larger outlier cells of VPL and VPM, as well as the uncertain porta thalami region extending back along the medial border of the medial geniculate complex. Hassler located the densest focus of spinothalamic terminations in V.c.pc.e, although, like the other authors, he saw these terminations extending into VPL (V.c.e) as well (Fig. 1.29). It was the combined V.c.pc.e and V.c.pc.i region that Hassler saw as the critical site at which electrical stimulation elicited pain in humans.

Other early modern investigations, carried out with the older fiber tracing techniques, adopted a position somewhat between the extremes of Hassler and Mehler and located a dense zone of spinothalamic terminations in a region embracing the caudal pole of the ventral posterior nucleus but separate from the magnocellular medial geniculate nucleus and variously called the posterior nucleus (Po) or the suprageniculate nucleus (SG) (Berkeley, 1980; Asanuma *et al.*, 1983). Clearly, all investigators were in agreement that there was a dense zone of spinothalamic terminations at or just outside the caudal pole of the ventral posterior complex but, as Mehler put it, “atlas semantics” got in the way of their agreeing about what to call the relevant region and gave an impression of disagreement that was more apparent than real.

Atlas semantics also got in the way of an agreement about the rostral extent of spinothalamic terminations within the ventral posterior complex itself. All were agreed that spinothalamic fiber terminations extended throughout the VPL nucleus, ending there in the characteristic bursts or archipelagoes described first by Mehler *et al.* (1960). But there was little early agreement about the rostral extent of these terminations. In one of the atlases commonly used at the time, Olszewski (1952) in the monkey had divided the ventral nuclear complex into a



Fig. 1.28. Hassler's delineations of the nuclei in the caudal regions of the human thalamus. (A–F) Myelin-stained frontal sections in posterior (A) to anterior (F) order. Below are outline drawings of the nuclei and fiber tracts in the sections, as identified by Hassler. Nuclei of relevance to the present chapter have been shaded. Adapted from Hassler (1959). Abbreviations of relevant nuclei and tracts: B.co.i, brachium of inferior colliculus; Ce.mc, nucleus centralis magnocellularis; Ce.pc, nucleus centralis parvocellularis; G.m.fa, nucleus geniculatus medialis fasciculosus; G.m.fi, nucleus geniculatus medialis fibrosus; G.m.li, nucleus geniculatus medialis limitans; G.m.mc, nucleus geniculatus medialis magnocellularis; Li., nucleus limitans thalami; Li.opt, nucleus limitans opticus; Li.por, nucleus limitans portae; Li.m, nucleus limitans medialis; L.l, lateral lemniscus; L.m, medial lemniscus; La.m.c, lamina medialis caudalis; Pf, nucleus parafascicularis; Ppd, nucleus peripeduncularis; Pu.sf, nucleus pulvinaris superficialis; V.c.a.e, nucleus ventrocaudalis anterior externus; V.c.a.i, nucleus ventrocaudalis anterior internus; V.c.i, nucleus ventrocaudalis internus; V.c.e, nucleus ventrocaudalis externus; V.c.pc.e, nucleus ventrocaudalis parvocellularis



Caption for Fig. 1.28. (cont.)

externus; V.c.pc.i, nucleus ventrocaudalis parvocellularis internus; V.c.p.e., nucleus ventrocaudalis posterior externus; V.c.p.or, nucleus ventrocaudalis portae; V.im.e, nucleus ventrointermedius externus; V.im.i, nucleus ventrointermedius internus; Z.i, zona incerta. For a conversion of these to modern terminology, see [Table 1.1](#) and [Fig. 2.18](#).

posteriorly located nucleus ventralis posterior pars caudalis (VPLc) followed in caudal to rostral order by a nucleus ventralis posterior pars oralis (VPLo), a nucleus ventralis lateralis pars oralis, and a nucleus ventralis anterior (Fig. 1.30). Hassler (1959) in the human had, in posterior to anterior order, a nucleus ventralis caudalis (V.c.) divided into posterior (V.c.p.) and anterior (V.c.a) parts, a nucleus ventrointermedius (V.im.), a nucleus ventralis oralis (V.o.) also divided into posterior (V.o.p.) and anterior (V.o.a.) parts, and a nucleus

Table 1.1. *Past and present terminology and abbreviations.*

Abbreviation in Fig. 1.28	Name	Modern name	Modern abbreviation
B.co.i	Brachium colliculi inferioris	Brachium of inferior colliculus	BCI
Ce.mc	Nucleus centralis magnocellularis	Centre médian nucleus, large cells	CM
Ce.pc	Nucleus centralis parvocellularis	Centre médian nucleus, small cells	CM
G.m.fa	Nucleus geniculatus medialis fasciculosus	Posterodorsal medial geniculate nucleus	MGpd
G.m.fi	Nucleus geniculatus medialis fibrosus	Ventral and anterodorsal medial geniculate nuclei	MGv and MGad
G.m.li	Nucleus geniculatus medialis limitans	Small cells usually included in magnocellular medial geniculate nucleus	MGmc
G.m.mc	Nucleus geniculatus medialis magnocellularis	Magnocellular medial geniculate nucleus	MGmc
La.m.c	Lamina medialis caudalis	Internal medullary lamina	IML
Li.	Nucleus limitans thalami	Nucleus limitans	LI
Li.m	Nucleus limitans medialis	Nucleus limitans	LI
Li.opt	Nucleus limitans opticus	Nucleus limitans	LI
Li.por	Nucleus limitans portae	Suprageniculate and posterior nuclei	SG and Po
L.l	Lemniscus lateralis	Lateral lemniscus	LL
L.m	Lemniscus medialis	Medial lemniscus	LM
Pf	Nucleus parafascicularis	Parafascicular nucleus	Pf
Ppd	Nucleus peripeduncularis	Peripeduncular nucleus	PPN
Pu.sf	Nucleus pulvinaris superficialis	Medial division of inferior pulvinar nucleus	Plim
V.c.a.e	Nucleus ventrocaudalis anterior externus	Anterior division of ventral posterior lateral nucleus	VPLa
V.c.a.i	Nucleus ventrocaudalis anterior internus	Anterior part of ventral posterior medial nucleus	VPM
V.c.e	Nucleus ventrocaudalis externus	Ventral posterior lateral nucleus	VPL
V.c.i	Nucleus ventrocaudalis internus	Ventral posterior medial nucleus	VPM

Table 1.1. (*cont.*)

Abbreviation in Fig. 1.28	Name	Modern name	Modern abbreviation
V.c.p.e	Nucleus ventrocaudalis posterior externus	Posterior division of ventral posterior lateral nucleus	VPLp
V.c.pc.e	Nucleus ventrocaudalis parvocellularis externus	Ventral posterior inferior nucleus	VPI
V.c.pc.i	Nucleus ventrocaudalis parvocellularis internus	Basal ventral medial nucleus or parvocellular division of ventral posterior medial nucleus	VMb or VPMpc
V.c.por	Nucleus ventrocaudalis portae	Anterior pulvinar nucleus	Pla
V.im.e	Nucleus ventrointermedius externus	Ventral lateral posterior nucleus, ventral part	VLp
V.im.i	Nucleus ventrointermedius internus	Continuation of ventral lateral posterior nucleus, ventral part	VLp
Z.i	Zona incerta	Zona incerta	ZI

lateropolaris (L.po.). Modern homologies regard VPLc of Olsewski to be equivalent to the combined V.c.a and V.c.p. of Hassler and VPLo of Olszewski as being equivalent to V.im. of Hassler (Jones, 2007).

Mehler (1974), who seems to have misinterpreted Olsewski's (1952) VPLo nucleus as the equivalent of Hassler's V.c.a. nucleus, considered that spinothalamic fibers terminated throughout VPLc (modern VPL) and VPLo (modern VLp) and overlapped into the territory of termination of cerebellothalamic fibers. The overlap was confirmed by Berkeley (1980) and Asanuma *et al.* (1983) (Fig. 1.31) and has been confirmed in many more recent investigations. It has now been confirmed many times that spinothalamic fiber terminations extend anterior to those of the medial lemniscus which are confined to VPL, and that where the lemniscal terminals are restricted to cells that project to the somatosensory cortex, those of the spinothalamic tract, in extending into the VLp nucleus, also terminate around cells that project to the motor cortex (Friedman and Jones, 1981; Jones *et al.*, 1982; Asanuma *et al.*, 1983).

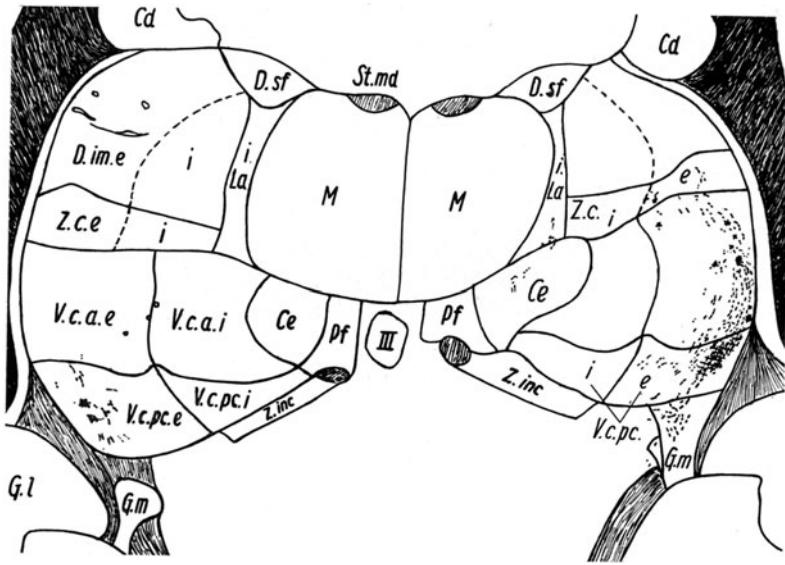


Fig. 1.29. Hassler's representation of the distribution of terminal degeneration in the thalamus ensuing from an anterolateral cordotomy at mid-cervical levels in a rhesus monkey. Relevant abbreviations as in Fig. 1.28. From Hassler (1970).

There was less semantic confusion in the descriptions of spinothalamic terminations in the intralaminar and paralaminar mediodorsal nuclei. Early reports of terminations in the centre médian nucleus (Bowsher, 1957, 1961) were soon ruled out and virtually all workers concurred in relating these terminations to the dorsal part of the parafascicular nucleus, to the central lateral nucleus and to the paralaminar regions of the mediodorsal nucleus, especially its densocellular division. This division is now regarded as part of the central lateral nucleus (Jones, 2007).

The spinoreticular projection

Mehler *et al.*'s (1960) description of the extent and terminal distribution of fibers ascending from the spinal cord to the reticular formation of the medulla, as seen with the axonal degeneration technique, remains the standard to which all subsequent studies have deferred, although there have been relatively few of them devoted specifically to monkeys or other primates (Chapter 2). Of some note is the study of Kerr and Lippman (1974) in which the authors

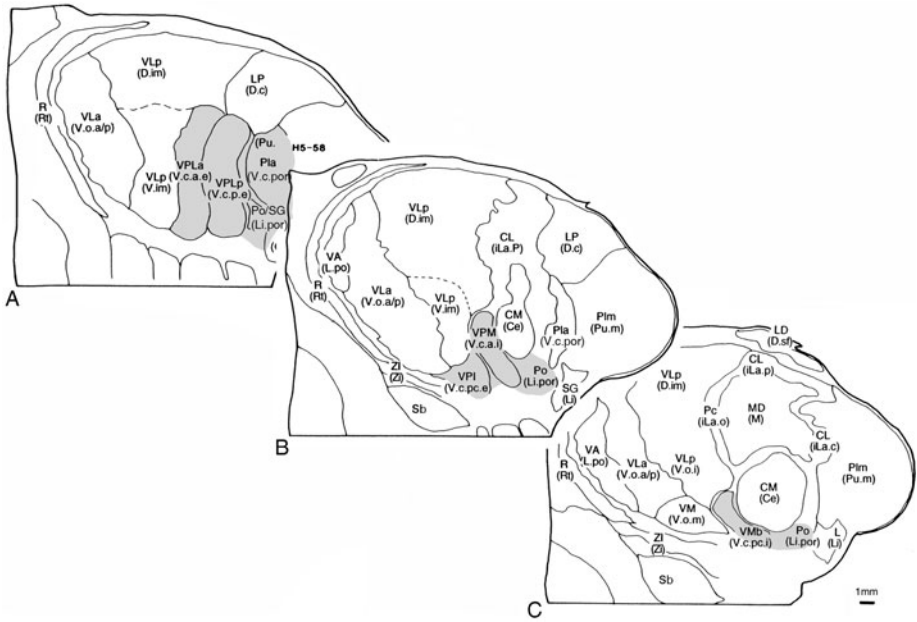


Fig. 1.30. Camera lucida tracings of sagittal sections of the human thalamus in lateral (A) to medial (C) order, comparing the nomenclatures for the divisions of the ventral nuclei of the thalamus and the regions posterior and ventral to them. Nomenclature of Hirai and Jones (1989) is in regular type and that of Hassler (1959) is in parentheses. Regions associated with the termination of spinothalamic fibers have been shaded. Modified from Jones (2007). For abbreviations see Table 1.1.

compared the extent of degenerating spinoreticular terminations in the monkey following anterolateral cordotomy or midline myelotomy. Surprisingly, after midline myelotomies the extent of terminal degeneration in the medullary reticular formation was far less extensive than after anterolateral cordotomy, being mainly confined to the central nucleus of the medulla and with very little in the gigantocellular and paragigantocellular fields. Similarly, in the periaqueductal gray matter, degeneration following midline myelotomy was less extensive than after anterolateral cordotomy and located mainly laterally in the region bordering the nucleus of Darkschewitsch. In the posterior and ventral posterior regions of the thalamus, however, the extent of degeneration was the same. These results would seem to indicate that spinoreticular projections arise from cells whose axons do not cross in the anterior commissure of the spinal cord but nearer their terminations in the reticular formation itself. Further consideration of this will be taken up in Chapter 2.

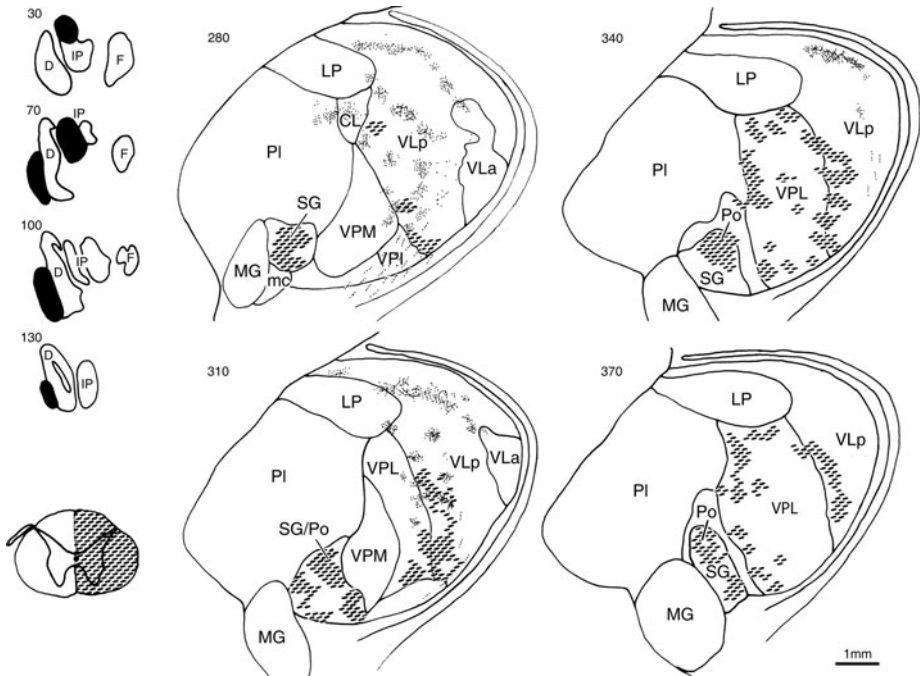


Fig. 1.31. Camera lucida drawings of sagittal sections from a rhesus monkey thalamus, showing the distribution of cerebellothalamic fibers (dots) as labeled by autoradiography following an injection of tritiated amino acids in the dentate and interposed nuclei, and of spinothalamic fibers (dashes) as labeled by axonal degeneration following a spinal hemisection in the same animal. The spinothalamic terminals extend from the ventral posterior lateral (VPL) nucleus (the terminal nucleus for medial lemniscal fibers) into the ventral lateral posterior (VLP) nucleus (the terminal nucleus for cerebellothalamic fibers). Redrawn from Asanuma *et al.* (1983).

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Organization of the central pain pathways

Inputs from nociceptors

The nature of nociceptors

Nociceptors are sensory receptors that respond to stimuli that are damaging or potentially damaging to tissues (Sherrington, 1906). The thresholds for activation of many nociceptors can be reached when stimuli of only moderate or non-damaging intensities are applied, but responses continue to increase as stimulus intensity is progressively increased to a level that produces overt damage. By contrast, other nociceptors respond only to intense stimuli and some may not respond at all, even to the strongest mechanical stimuli, unless they are first sensitized (Lynn and Carpenter, 1982; Meyer *et al.*, 1991; Kress *et al.*, 1992; Davis *et al.*, 1993; Treede *et al.*, 1998). The last mentioned have been called “silent nociceptors” (Schaible and Schmidt, 1985, 1988a, 1988b; Schmidt *et al.*, 1995, 2000). Overall, if we include receptors responding to innocuous warming and cooling of the skin, there may be as many as six receptor classes specific for cooling, warming, noxious heat or cold, destructive mechanical or mixed noxious stimuli in humans and other animals.

Types of nociceptors

Nociceptors can be subdivided according to the tissue in which they are found, the size or conduction velocity of the afferent fiber supplying them and the type of stimulus that activates them. Most experimental studies of nociceptors have been performed on common laboratory animals, especially rodents and cats. Some of the most informative, however, have been made during recordings from peripheral nerves of monkeys or human subjects (reviewed in Willis and Coggeshall, 2004).

Cutaneous nociceptors

The skin of monkeys is innervated by a variety of nociceptors. The receptor is the terminal part of the axon of a peripheral nerve fiber and is not distinguished by any morphological features other than lack of an investing Schwann cell sheath. Most are A δ or C fibers (that is, nociceptors are generally formed by thin myelinated or unmyelinated axons), but a few are formed by larger, A β , fibers (Burgess and Perl, 1967; Georgopoulos, 1976; Treede *et al.*, 1998). In humans and some other mammals, a significant population of cutaneous C fibers can be activated by light tactile stimuli (Douglas and Ritchie, 1962; Siminoff, 1964, 1965; Vallbo *et al.*, 1993, 1999; Olausson *et al.*, 2002; Wessberg *et al.*, 2003). Cutaneous nociceptors may respond specifically to noxious mechanical, thermal or chemical stimuli (specific nociceptors), or they may respond to two of these or to all three types of stimuli (polymodal nociceptors). Cutaneous nociceptors in humans are similar to those in monkeys, as shown in studies using microneurographic recordings from peripheral nerves (Torebjörk, 1974; Adriaensen *et al.*, 1980, 1983; Konietzny *et al.*, 1981; Bromm *et al.*, 1984). Intraneural microstimulation suggests that human cutaneous A δ nociceptors signal pricking pain, whereas C polymodal nociceptors evoke dull or burning pain (Konietzny *et al.*, 1981; Ochoa and Torebjörk, 1989; Torebjörk and Ochoa, 1990), or itch (Torebjörk and Ochoa, 1983; Schmelz *et al.*, 1997).

Painful thermal sensations, however, are not exclusively linked to the activation of physiologically defined high-threshold nociceptors. Psychophysical studies have shown that afferent fibers other than those with high thresholds can contribute to cutaneous pain. For example, “nociceptive sensations” (stinging, pricking, burning) and, rarely, overt pain can be elicited by selective stimulation of cutaneous spots innervated by receptors with low thermal (heat or cold) thresholds ($< 40^{\circ}\text{C}$ for heat and $> 25^{\circ}\text{C}$ for cold) (Green and Pope, 2003; Green and Akirav, 2007; Green *et al.*, 2008). Conversely, selective stimulation of skin spots with heat detection thresholds of C fiber heat nociceptors (40°C) can produce the sensation of painless warmth (Green and Cruz, 1998) (for review, see Green, 2004). For mechanically induced cutaneous pain, it appears that a critical determinant is the population response of mechanically sensitive receptors innervated by both A δ and C fibers (Greenspan *et al.*, 1997; Slugg *et al.*, 2004); these afferent fibers begin responding at innocuous stimulus intensities but the response increases as the intensity of stimulation approaches noxious levels.

Muscle nociceptors

Muscle, like skin, is innervated by nociceptors. These generally are formed by thin myelinated (Group III) or unmyelinated (Group IV) axons, although a few are mid-sized myelinated (Group II) axons (Paintal, 1960; Stacey, 1969)

(see Willis and Coggeshall, 2004, for a review of the terminology applied to axons of different diameters in nerves innervating the skin vs. deep tissues). Many of the muscle nociceptors are peptidergic (Molander *et al.*, 1987). Intraneural microstimulation of fine afferent fibers in human muscle nerves or intramuscular injection of capsaicin in humans results in a sensation of cramping pain (Simone *et al.*, 1994; Marchettini *et al.*, 1996). Muscle nociceptors can also be excited by mechanical, chemical or thermal stimuli, by injection of hypertonic saline or in response to ischemia (Lewis, 1942; Paintal, 1960; Bessou and Laporte, 1961; Hník *et al.*, 1969; Mense and Schmidt, 1974; Kumazawa and Mizumura, 1976; Kniffki *et al.*, 1978; Mense and Stahnke, 1983; Mense and Meyer, 1985, 1988).

Articular nociceptors

Many of the afferent fibers that innervate joints are nociceptors (Burgess and Clark, 1969; Clark, 1975; Schaible and Schmidt, 1983a, 1983b; reviewed by Schaible and Grubb, 1993). Some are “silent nociceptors” that are not activated by joint movements unless they are sensitized, for example, by inflammation of the joint (Schaible and Schmidt, 1983a, 1983b; Grigg *et al.*, 1986). They are responsible for much of the pain of arthritis.

Visceral nociceptors

Some visceral afferents that innervate the gastrointestinal tract or the urinary bladder respond to both weak and strong mechanical stimuli (Bahns *et al.*, 1986, 1987; Sengupta *et al.*, 1990; Jänig and Koltzenburg, 1991; Sengupta and Gebhart, 1994; reviewed by Jänig, 1996). It has been proposed that these signal pain only when the stimulus reaches a sufficient intensity (Cervero, 1994; Jänig, 1996). However, other visceral afferents have high thresholds, suggesting their specific involvement in visceral pain. Still other visceral afferents are “silent nociceptors” and respond to mechanical stimuli only after inflammation or ischemia (Haupt *et al.*, 1983; Häbler *et al.*, 1988, 1990, 1993; Sengupta and Gebhart, 1994).

Nociceptors have been observed to innervate many visceral organs besides those already mentioned, including the heart and blood vessels, meninges, respiratory system and reproductive organs (Lim *et al.*, 1962; Brown, 1967; Peterson and Brown, 1973; Uchida and Murao, 1974; Kumazawa and Mizumura, 1977, 1980a, 1980b; Baker *et al.*, 1980; Cervero, 1982; Berkley *et al.*, 1988, 1990; Cervero and Sharkey, 1988; Cervero and Sann, 1989; Sengupta and Gebhart, 1994; Giamberardino *et al.*, 1995; see review by Cervero, 1994).

Sensory transduction in nociceptors

As mentioned above, different classes of nociceptors respond to a variety of mechanical, thermal and/or chemical stimuli. The specificity of response

depends upon the presence of one or more transducer proteins in the nociceptor terminals (Patapoutian *et al.*, 2003; Wang and Woolf, 2005; Willis, 2006).

The transducer for the sensitivity of nociceptors to noxious mechanical stimuli remains incompletely known. It has been suggested (Woolf and Salter, 2000; García-Añoveros *et al.*, 2001) that the protein belongs to the DEG/ENaC family of non-specific cation channels first described in *Caenorhabditis elegans* (Waldmann and Lazdunski, 1998). However, the evidence is sketchy.

Sensitivity to noxious heat depends on the presence of vanilloid receptors for which heat is the natural ligand. The transducer proteins TRPV1 or TRPV2 form non-specific cation channels in the membranes of nociceptive terminals formed mainly by unmyelinated C fibers (Tominaga *et al.*, 1998; Caterina *et al.*, 1999; Caterina and Julius, 2001).

Decreases in pH are sensed by TRPV1 receptors (Tominaga *et al.*, 1998; Caterina *et al.*, 1999) and also by acid-sensing ion channels (ASICs; Immke and McCleskey, 2001; Sutherland *et al.*, 2001).

Noxious chemical stimuli are detected by a wide variety of receptors, including TRPV1, purinergic P2X₃ or P2X_{2/3}, bradykinin, serotonergic 5-HT₃ and glutamate receptors (see Willis and Coggeshall, 2004).

Sensitization of nociceptors

The excitability of nociceptors can be enhanced as a result of their stimulation by irritant chemicals, inflammatory agents, noxious heat and/or reduced pH (reviewed by Willis and Coggeshall, 2004). Examples of irritant chemicals are mustard oil and capsaicin (Schmelz *et al.*, 1994, 1996). Inflammatory mediators include bradykinin, prostaglandins and other arachidonic acid products, and biogenic amines such as serotonin and catecholamines (reviewed in Willis and Coggeshall, 2004). This change in the excitability of nociceptors in peripheral nerves is termed “peripheral sensitization.” Sensitized primary afferent nociceptors are thought to account for “primary” hyperalgesia, a heightened sensation of pain in a damaged skin area (Meyer and Campbell, 1981; LaMotte *et al.*, 1983).

Peripheral sensitization involves the activation of second messenger pathways following an increase in the intracellular concentration of calcium ions that is triggered by the action of the sensitizing agents on the surface membranes of the nociceptors (Guenther *et al.*, 1999; Kress and Guenther, 1999). Some of the second messenger cascades involve protein kinases C, A and G (reviewed in Willis and Coggeshall, 2004). The changed excitability of the nociceptive afferents has been attributed to actions of the protein kinases on ion channels (England *et al.*, 1996; Gold *et al.*, 1996; Fitzgerald *et al.*, 1999) or on membrane receptors, such as TRPV1 (Lopshire and Nicol, 1998). Liang *et al.* (2001) have proposed that the action of

bradykinin on heat-sensitive receptors, such as TRPV1, is to lower the threshold temperature so that even ambient temperature can excite nociceptive afferents.

The structure and chemistry of the dorsal horn and the terminations of afferent fibers

Structure of the dorsal horn

The dorsal horn of the spinal gray matter is made up of laminae I through VI of Rexed (1952, 1954) (Figs 1.21, 1.22, 2.1). Each lamina now tends to be regarded as a separate structural and functional entity with specific cell types and input-output connections but it must be remembered that the laminar borders, as described by Rexed, are based upon the staining of neuronal somata only. The dendrites of many of the cells within a lamina commonly extend over one or more adjacent laminae and the terminations of arriving afferent fibers are not necessarily restricted by the laminar boundaries. A great deal of information has come from investigations in animals other than primates but in what follows, unless particularly relevant, we shall limit our discussion and references to studies of monkey and human spinal gray matter.

Lamina I

This is the classical marginal zone, characterized by the presence of a relatively dense plexus of thin myelinated and unmyelinated axons oriented parallel to the surface of the spinal cord (Ralston, 1979) and by the giant marginal neurons originally described by Waldeyer (1888; Chapter 1) (Figs 1.16, 2.1C, D). The giant cells typically have rostro-caudally oriented dendritic fields (Light *et al.*, 1979; Woolf and Fitzgerald, 1983; Lima and Coimbra, 1986, 1988, 1989). Among them are a certain number of smaller cells as well (Molony *et al.*, 1981; Lima and Coimbra, 1986). Recent classifications of lamina I neurons tend to regard the giant and smaller cells as a single major population divided into pyramidal, multipolar and fusiform types that are found in monkeys as well as in other species (Gobel, 1978a; Zhang and Craig, 1997; Galhardo and Lima, 1999; Sedlacek *et al.*, 2007). There is evidence that the different morphological classes of cells may be nociceptor specific (Han *et al.*, 1998).

Most afferent fibers ending in lamina I enter it from the tract of Lissauer and contribute to the marginal plexus. They are collateral branches of A δ and C fibers that entered the spinal cord in the lateral division of the dorsal root (Cajal, 1899; Ranson, 1913; LaMotte, 1977; Snyder, 1977; Figs 2.2, 2.3). These include fibers that represent the major classes of nociceptors discussed in the previous section. Contrary to views expressed in the 1960s (Szentágothai, 1964a), that Lissauer's tract was made up primarily of fibers that had their origins and terminations in

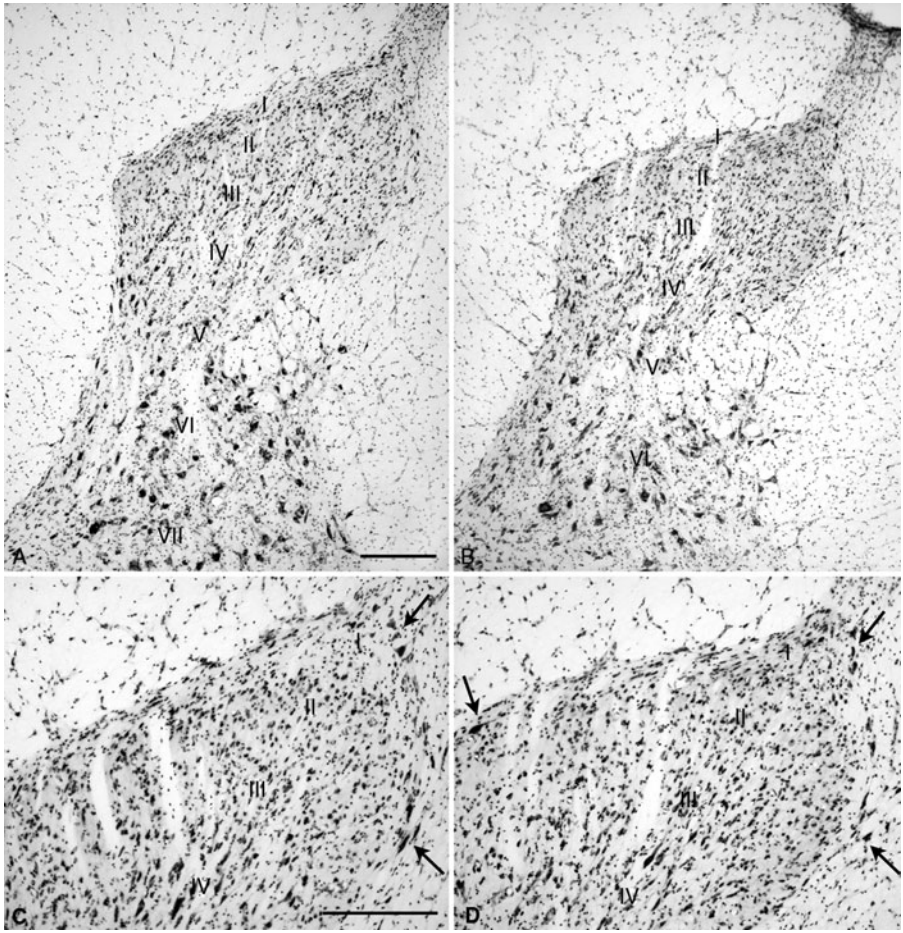


Fig. 2.1. Nissl-stained sections of the dorsal horn in the cervical enlargement of a rhesus monkey, showing the differences in cell density and size that define the laminae of the dorsal horn. Arrows in C and D indicate large marginal cells of lamina I. Bars: 250 μ m (A, B and C, D).

the substantia gelatinosa (Chapter 1), it is now recognized again that the tract contains the fine primary afferents as well as short propriospinal fibers, many of which also end in lamina I (Chung and Coggeshall, 1982). In monkeys, as many as 80% of the tract fibers are primary afferents (Coggeshall *et al.*, 1981). Both A δ and C fiber terminations are heavily represented in lamina I and the parent fibers come from smaller dorsal root ganglion cells whose peripheral branches are found in cutaneous, muscle and visceral nerves (reviewed in Willis and Coggeshall, 2004). In the dorsal horn, the primary afferent fibers typically end in large synaptic terminals that form the central elements of complex synaptic aggregations termed glomeruli (Szentágothai, 1964b; Ralston, 1968a, 1968b, 1979;

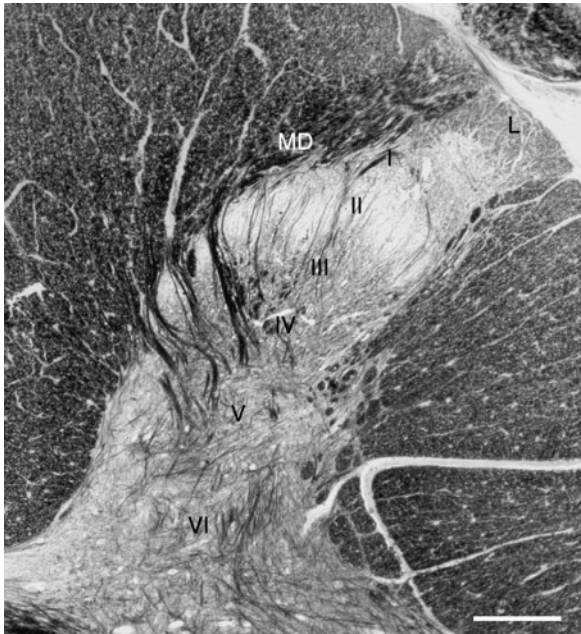


Fig. 2.2. Myelin-stained preparation from a lumbar segment of the human spinal cord showing the entering large diameter, myelinated fibers of the medial division (MD) of the dorsal root, the thinly myelinated and unmyelinated fibers of Lissauer's tract (L) and the laminae of the dorsal horn (I–VI). Bar: 500 μ m.

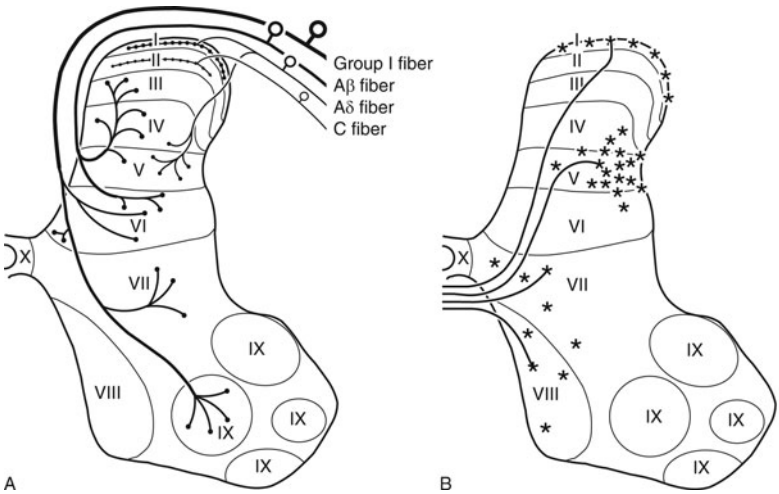


Fig. 2.3. (A) Schematic drawing of the terminations of afferent fibers of different diameters in the dorsal horn and deeper laminae of the spinal cord. (B) Schematic drawing of the locations of the principal sets of neurons whose axons contribute to the spinothalamic tract.

Réthelyi and Szentágothai, 1969; Kerr, 1970a, 1970b). These will be described below in the section on lamina II. In monkeys, these aggregations appear to be simpler than in certain other species such as the cat in which the primary afferent terminal receives many axo-axonic synapses (Gobel *et al.*, 1981).

Lamina II

Lamina II is now regarded as corresponding essentially to the substantia gelatinosa (Cervero and Iggo, 1980) (Figs 2.1, 2.2). There was some debate in the past as to whether the subjacent part of lamina III should also be included in the substantia gelatinosa (Gobel, 1978b; Gobel *et al.*, 1980); this debate is now past, although it is recognized that the terminations of primary afferents may not be strictly constrained by the border between laminae II and III (Woodbury *et al.*, 2000) and it is customary as well to divide lamina II into outer (IIo) and inner (Ili) sublaminae.

All the neurons of lamina II are small and have extensive systems of local axon collaterals (Li *et al.*, 1999a, 1999b). Many have primary axons that project out of lamina II into the white matter of Lissauer's tract and the dorsal columns (Cajal, 1899, 1909; Szentágothai, 1964a, 1964b; Sugiura, 1975; Light and Kavookjian, 1988). Although it was once thought that these axons all re-entered the substantia gelatinosa after ascending for 4–5 segments (Szentágothai, 1964a; Réthelyi and Szentágothai, 1973), recent work indicates that a few can have more distant targets (Giesler *et al.*, 1978; Willis *et al.*, 1978).

The important elements of lamina II are not only its particular cells (Fig. 2.4) but also the large dendrites of so-called antenna cells extending up from their parent somata in deeper laminae. Both are major synaptic targets of primary afferent terminals. The lamina II cells have been categorized into several types of which the major classes are the limiting or stalked cells and the central or islet cells first described by Cajal (1899, 1909) and later by Gobel (1975, 1978b).

Stalked cells are the neurons that Cajal called limiting cells and were renamed for their possession of numerous short, stalk-like dendritic spines. Their cell bodies are located along the border between laminae I and II (Fig. 2.4). Their dendrites descend in a cone-like array into laminae II, III and sometimes IV. They are innervated by primary afferent nociceptors in the glomeruli (Bennett *et al.*, 1980). They are thought to be excitatory interneurons. The unmyelinated axon ramifies extensively within lamina II and the main trunk after ascending directly or after a short course within Lissauer's tract ramifies with many terminals in lamina I (Price *et al.*, 1979).

Islet cells are located throughout lamina II and take their name from their aggregation into small clusters. Cajal (1899, 1909) called them central cells. The dendritic trees of the islet cells are characteristically flattened mediolaterally

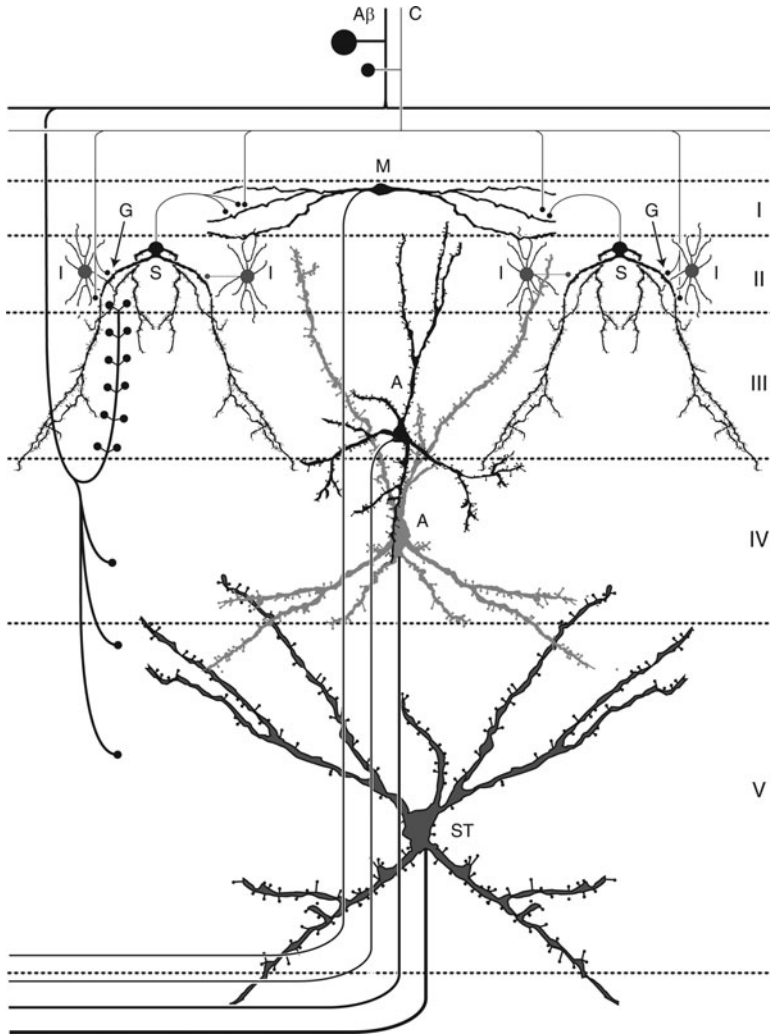


Fig. 2.4. Drawing illustrating the principal neuronal types of the dorsal horn, their relationships to the terminations of A β and C fibers, and some of the intrinsic connections of the superficial laminae. A, antennal cell; G, glomerulus; I, islet cell; M, marginal cell; S, stalked cell; ST, spinothalamic tract cell of lamina V.

and oriented in the parasagittal plane, each cell forming a disk-like structure extending through the full dorso-ventral thickness of lamina II and rostrocaudally over a considerable extent (Fig. 2.4). They are GABAergic and therefore inhibitory interneurons (see below). Like certain inhibitory interneurons in the olfactory bulb, thalamus and some other sites, their dendrites and dendritic appendages contain synaptic vesicles and make presynaptic junctions, in this case on the large terminals of primary afferent fibers (Gobel *et al.*, 1980; see below).

A number of other seemingly minor cell types have also been described in lamina II (Gobel, 1978b), and other classifications of the range of cells in lamina II have been proposed (Beal, 1983), including in the human (Schoenen, 1982). The whole system of classification on the basis of relatively fixed dendritic patterns, as seen primarily in Golgi-stained preparations, has however been questioned (Li *et al.*, 1999b).

Many fine, mainly unmyelinated fibers descend into lamina I from Lissauer's tract. These form the streaks that can be seen traversing the substantia gelatinosa in unstained and myelin-stained preparations (Fig. 2.2) and referred to in Chapter 1. It is claimed that primary afferent fibers can be distinguished from re-entering propriospinal fibers by the facts that the primary afferents end in showers of terminal boutons while propriospinal fibers end as boutons en passant (Scheibel and Scheibel, 1968; Réthelyi, 1977; Réthelyi and Capowski, 1977). Identified primary afferent fibers of the A δ and C classes were identified in guinea pigs as high-threshold mechanoreceptors, polymodal nociceptors and thermal nociceptors (Sugiura *et al.*, 1986). Other afferent fiber terminals ending in lamina II are derived from collaterals of larger diameter myelinated fibers entering the spinal cord in the medial division of the dorsal root. These collaterals curve into lamina III and there form the flame-like arbors demonstrated originally by Cajal (Figs 1.12, 2.4) and also by Szentágothai (1964b) and Scheibel and Scheibel (1968). But the terminal parts of these ascend into the deeper sublamina of lamina II. Modern studies have confirmed the extension of the arbors into deep lamina II in monkeys (Beal and Fox, 1976; Ralston *et al.*, 1984) and other species (Woodbury *et al.*, 2000). For a comprehensive review of the literature pertaining to all mammalian species examined, see Willis and Coggeshall (2004).

At the fine structural level, afferent fiber terminals are involved in complex synaptic aggregations called glomeruli that are distinctive features of lamina II in monkeys and certain other species (Fig. 2.5) (Ralston, 1968a, 1979; Réthelyi and Szentágothai, 1969, 1973; Réthelyi *et al.*, 1982; Knyihar-Csillik *et al.*, 1999). The glomeruli are made up of a large central axon terminal that has a characteristic electron-dense appearance and is glutamatergic. It is derived from a primary afferent fiber (Ralston and Ralston, 1979; Knyihar-Csillik *et al.*, 1982a, 1982b; Maxwell *et al.*, 1993) and different terminals can exhibit different morphologies or degrees of electron density, possibly indicative of their origins from different classes of afferent fiber. Around the central terminal are arranged a series of conventional dendrites, apparently derived from stalked cells and from the ascending dendrites of antennal cells; these are postsynaptic at asymmetric membrane contacts to the central axon terminal. Also around the perimeter of the glomerulus are dendrites, apparently derived from islet cells, that contain

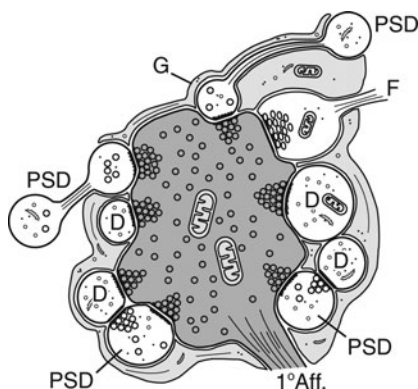


Fig. 2.5. Drawing of a glomerulus of laminae I-III of the dorsal horn, as seen in electron microscopic preparations. The central terminal is formed by a primary afferent fiber (1°Aff.); around it are clustered conventional dendrites (D) of stalked or antennal cells and presynaptic dendrites (PSD) of the GABAergic islet cells, with occasional GABAergic axon terminals (F) also formed by islet cells. Synaptic triads are formed where the primary afferent terminal, presynaptic dendrite and a conventional dendrite are interconnected (at lower left and lower right).

synaptic vesicles; these dendrites receive an asymmetrical synapse from the primary afferent terminal and are themselves presynaptic at a symmetrical synapse to the conventional dendrites. On occasion triadic synaptic complexes are formed in which the primary afferent terminal is presynaptic to a presynaptic dendrite which is in turn presynaptic to a conventional dendrite which also receives a synapse from the primary afferent terminal. Completing the glomerulus are a smaller number of small peripheral axon terminals that have been proven to be GABAergic and therefore inhibitory. Some of these can end presynaptically on the central primary afferent terminal itself but others end on the peripheral dendrites of both types.

Lamina III

Lamina III contains slightly larger and less densely packed cells than lamina II (Fig. 2.1) but it is best distinguished from lamina I in myelin-stained preparations (Figs 1.23, 1.24, 2.2) for, unlike lamina II, it contains a plexus of myelinated fibers that is quite dense. The dendrites of lamina III cells form vertical arrays that ascend as far as the outer division of lamina II (Cajal, 1899, 1909; Szentágothai, 1964b; Scheibel and Scheibel, 1968; Maxwell *et al.*, 1983). This characteristic feature has led to them being called antennal cells (Fig. 2.4). Collectively, the dendrites form parasagittally oriented plexuses that may devolve into separate components in outer lamina II, in inner lamina II and adjacent lamina III, and in the deeper part of lamina III itself (Beal and Cooper,

1978). In cats, lamina III neurons that send their axons into the dorsal columns or into the spino-cervical tract are described with differing degrees of dendritic penetration into the overlying layers (Brown and Fyffe, 1981; Bennett *et al.*, 1984). The neurons also tend to give off a rich collateral axon plexus within lamina III and many of the axon branches descend into underlying laminae as deep as lamina VI (Light and Kavookjian, 1988).

The major primary afferent input to lamina III comes from the collaterals of the larger diameter fibers that form the medial division of the dorsal roots entering the dorsal horn from its medial surface (Figs 2.2, 2.3). Within lamina III these low-threshold, mechanoreceptive afferents terminate in the classical flame-like arborizations that ascend into the inner subdivision of lamina II. They are only flame-like in transverse section. Longitudinal sections reveal that they extend, sheet-like, over considerable distances (Beal and Fox, 1976; Ralston *et al.*, 1984; Woodbury *et al.*, 2000). The terminals of these axonal arborizations form the central elements of synaptic glomeruli that are a characteristic feature of lamina III (see above) (Ralston *et al.*, 1984; Maxwell and Réthelyi, 1987). The extent to which A δ and C fibers may terminate in lamina III is uncertain and may not be particularly great.

Lamina IV

Lamina IV contains many relatively small neurons but among these are very large neurons that, despite their small numbers, dominate the visual impression of lamina IV (Fig. 2.1). Lamina IV and lamina V together make up the old nucleus proprius of the dorsal horn (Fig. 1.20). The large cells are the classical antennal cells (Cajal, 1899, 1909; Szentágothai, 1964b; Scheibel and Scheibel, 1968; Schoenen, 1982) whose dendrites are typically covered in dendritic spines and ascend through lamina III into lamina II. A paucity of descending dendrites gives them an inverted cone-like dendritic field (Fig. 2.4). Other, generally smaller, neurons in lamina IV have either transversely or longitudinally oriented dendritic fields. Many variants have been described in different species (Willis and Coggeshall, 2004).

Antennal cells and perhaps other cells of lamina IV send their primary axon across the midline in the anterior gray commissure to ascend in the contralateral anterior column (Fig. 2.4). They give off a relatively extensive set of intralaminar collaterals and other collaterals may be given off to deeper laminae on both sides of the gray matter as they pass towards and as they exit from the anterior commissure.

Considerable afferent input to lamina IV neurons comes, like that to lamina III, from the collaterals of myelinated large diameter fibers running down the medial side of the dorsal horn. Most of these, however, do not form the

flame-like endings typical of those in lamina III. Instead, they spread extensively through lamina IV and adjacent parts of laminae III and V (Brown *et al.*, 1977). Unlike lamina IV, there is also a significant A δ and C fiber input to lamina IV neurons via the synapses made by these primary afferent fibers upon the long antenna-like dendrites that ascend into laminae III, II and even I (LaMotte, 1977; Light and Perl, 1979a, 1979b; Ralston and Ralston, 1982). Glomeruli are rare in lamina IV.

Lamina V

Lamina V is the neck of the dorsal horn and in terms of cytoarchitecture is transitional between lamina IV and lamina VI. Its lateral aspect is broken up by the penetrating bundles of fibers that once resulted in this part of the dorsal horn being referred to as the reticular zone (Chapter 1; Fig. 2.1). The dendritic fields of the major population of large cells are flattened mediolaterally and are thus disk-like, with long spiny dendrites ascending into the supervening layer IV and descending into layer VI (Fig. 2.4). They are more columnar than the longitudinally extended layer IV cells. The axons of the major population of cells project across the anterior commissure into the spinothalamic tract; some also ascend to the dorsal column nuclei via the dorsal columns, and to the lateral cervical nucleus via the dorsolateral funiculus (reviewed in Willis and Coggeshall, 2004). The afferent input to these cells is made up primarily of collaterals of the large myelinated fibers that enter the dorsal horn from its medial aspect (Figs 2.2–2.4), but there appears to be a significant A δ input as well, perhaps mainly from muscle and visceral afferents (Light and Perl, 1979a, 1979b).

Lamina VI

Lamina VI is the base of the dorsal horn (Figs 2.1, 2.2). Deep to it, lamina VII forms the intermediate zone between the dorsal and ventral horns. The cells of lamina VI are relatively homogeneous but smaller, more compact cells tend to aggregate medially and larger, deeply stained cells laterally. The dendritic fields of lamina VI cells are columnar like those of lamina V cells and ascend and descend through supra- and subjacent laminae, although dorsally they do not extend into laminae I and II (Brown, 1981a; Réthelyi, 1984). The major inputs to these cells come from collaterals of Group IA fibers descending towards the ventral horn and perhaps from other large diameter afferents descending down the medial aspect of the dorsal horn (Scheibel and Scheibel, 1968; Fig. 1.12). Other inputs come from the descending fiber systems of the lateral funiculus (Tredici *et al.*, 1985). The axons of the cells project to the same sites as those of cells in lamina V.

Input-output relationships in the dorsal horn

Terminations of afferent fibers

We can see from the above that the terminations of most afferent fibers are by no means restricted to single laminae of the dorsal horn. The terminations of A δ and C fibers are perhaps the most confined, being restricted in the main to laminae I and II, although there appears to be a significant A δ input to lamina V as well (Light and Perl, 1979a, 1979b; Craig and Mense, 1983; Sugiura *et al.*, 1986, 1989; Craig *et al.*, 1988) (Fig. 2.3).

C-polymodal afferents appear to terminate primarily on cells in the outer division of lamina II, the cells in the deeper division receiving inputs primarily from low-threshold mechanoreceptors, whose flame-like terminals ascend into this part of lamina II from below. Low-threshold cutaneous afferents in the A β range terminate extensively throughout laminae III–VI; low-threshold muscle afferents in the Group I range, along with some joint afferents, terminate in the dorsal horn mainly in lamina VI (Brown, 1981a).

The chief peripheral afferent input to lamina I is from A δ fibers (Fig. 2.3). Kumazawa *et al.* (1975) and Kumazawa and Perl (1978), in recordings from the dorsal horn of monkeys, divided the population of neurons that they identified on the basis of their responses to natural cutaneous stimuli into three classes: (i) cells activated only by intense mechanical stimuli; (ii) cells activated by innocuous skin cooling; (iii) cells responding to noxious mechanical and thermal stimuli. Observations in cats and other species have generally borne out the fact that many lamina I neurons are thermoceptive and/or nociceptive and that many such cells project their axons into the spinothalamic tract (e.g. Andrew and Craig, 2001; Craig *et al.*, 2001; Craig, 2003). Craig *et al.* felt that there was little convergence of cooling-specific, nociceptive-specific or polymodal afferents onto individual lamina I cells and that these cells were morphologically distinct. These later studies also observed inputs from muscles, joints and viscera as well as from the skin (Craig and Mense, 1983; Craig *et al.*, 1988; Sugiura *et al.*, 1989; reviewed in Willis and Coggeshall, 2004).

Lamina I also receives extensive excitatory input from the stalked cells of lamina II (Fig. 2.4). Its chief output is into the spinothalamic tract. As many as 50% of the cells contributing to the spinothalamic tract in the monkey are located in lamina I (Apkarian and Hodge, 1989a). The chief peripheral afferent input to lamina II comes from C-polymodal receptor fibers (Kumazawa and Perl, 1977a, 1977b) (Fig. 2.3). The terminals of these fibers are located on the stalked cells whose cell bodies are located at the border between laminae I and II as well as on islet cells scattered throughout lamina II. Terminals in the deeper division of lamina II seem to be primarily derived from C mechanoreceptors. Cells in this

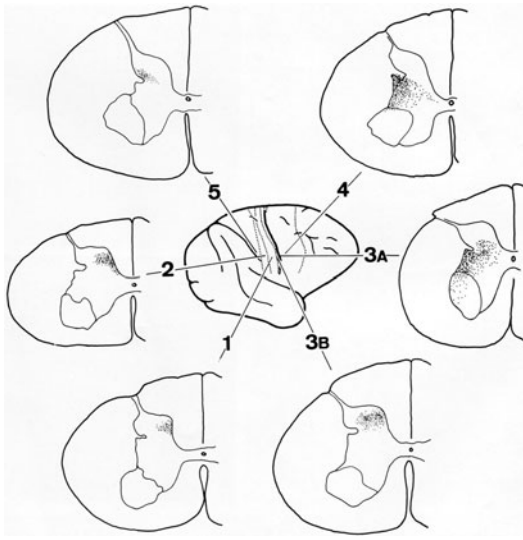


Fig. 2.6. Terminal distribution of corticospinal axons arising from the motor cortex (4), fields of the primary somatosensory cortex (3A, 3B, 1, 2) and anterior parietal cortex (5), as demonstrated in experiments in which the terminals were labeled by anterograde axonal transport of radioactive amino acids injected into each of the areas. From Coulter and Jones (1977).

location also receive inputs from low-threshold mechanoreceptors via terminations of these fibers ascending from lamina III.

Another input to lamina II and possibly to the overlying lamina I descends in the corticospinal tract from the somatosensory cortex (Coulter and Jones, 1977; Cheema *et al.*, 1984; Ralston and Ralston, 1985) (Fig. 2.6). Perhaps the most important descending input to lamina II (extending into the overlying lamina I) is made up of serotonergic and noradrenergic fibers arising from neurons in the nucleus raphe magnus and adjacent medullary reticular formation or from the locus coeruleus and parabrachial regions respectively and descending in the dorsal part of the lateral funiculus. Entering lamina II from its lateral aspect (Fig. 2.7), these fibers terminate on interneurons within the outer division of lamina II or directly on spinothalamic tract cells of lamina I (Basbaum and Fields, 1978; Bowker *et al.*, 1982a, 1982b; Dubner and Bennett, 1983; Fulwiler and Saper, 1984; Bowker and Abbott, 1990; Jones and Light, 1990; Jones, 1991; Kwiat and Basbaum, 1992). The action, described in Chapter 7, is to inhibit spinothalamic tract cells directly or indirectly via the interneurons of lamina II (Fig. 2.7).

Numerous other sources of descending input to lamina II have been described anatomically. These include the hypothalamus, parts of the midbrain central gray, the red nucleus, the lateral reticular nucleus, other parts of

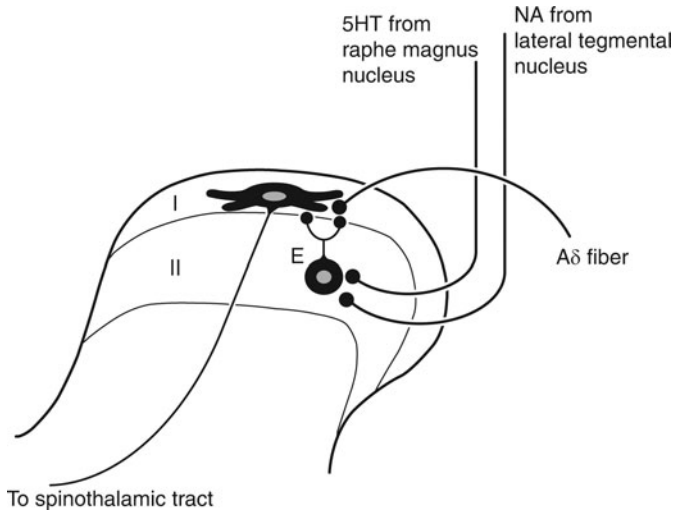


Fig. 2.7. Schematic diagram illustrating the serotonin (5HT) and noradrenergic (NA) projections descending from the brainstem. The fibers terminate on enkephalinergic neurons (E) that are innervated by A δ fibers in the superficial dorsal horn and which inhibit large marginal cells of lamina I.

the medullary reticular formation and the solitary nucleus (see Willis and Coggeshall, 2004 for details).

The two classes of neurons in lamina II, the stalked cells and the islet cells, are key elements in dorsal horn circuitry. Stalked cells, located mainly in the outer division of lamina II, receive inputs primarily from high-threshold afferents (Light and Perl, 1979b; Bennett *et al.*, 1980) and in projecting their axons to lamina I cells in the same and adjacent segments can influence the marginal cells of lamina I that project to the thalamus. Islet cells, by contrast, are inhibitory interneurons that receive A δ and C as well as low-threshold mechanoreceptive inputs. The islet cells located in the deeper division of lamina II may be influenced only by low-threshold afferents (Bennett *et al.*, 1980). By means of their presynaptic dendrites in the glomeruli, islet cells receiving both kinds of input can permit the shorter latency A β inputs to inhibit the effects of later arriving A δ and C fiber inputs and thus modulate nociception.

The extent to which afferent fibers ending in lamina II terminate on the dendrites of the antenna cells that ascend into lamina II from laminae III–V is uncertain in primates, although it has been demonstrated in rats (Todd, 1989).

Lamina II neurons are connected by extensive two-way connections with one another via the axons of stalked cells that ascend and descend in Lissauer's tract over a few segments (Light and Kavookjian, 1988). The islet cells mediate an extensive set of local inhibitory connections. Lamina II neurons also send axons

down into laminae III–V (Light and Kavookjian, 1988) so the substantia gelatinosa cannot be thought of as an entirely closed system as once postulated (Réthelyi and Szentágothai, 1973). Although a few spinothalamic tract cells are located in lamina II (Willis *et al.*, 1978, 1979), their numbers are quite modest.

The chief peripheral inputs to laminae III–VI are from low-threshold mechanoreceptors (Fig. 2.3). Terminations of thinner A δ fibers derived from down hair follicles tend to be located in the part of lamina III adjoining lamina II while those of thicker A β fibers from guard hair follicles and from other forms of cutaneous and deep mechanoreceptors tend to extend throughout laminae III–V. It is typical, although not invariable, that the various forms of receptor input can converge on the same cells. The upper ends of the flame-like ramifications of all the mechanoreceptors tend to extend into the deeper division of lamina II where they make contact with certain islet cells (Fig. 2.4). Lamina V also receives an input from A δ fibers that derive from cutaneous mechanical nociceptors (Light and Perl, 1979a, 1979b) (Fig. 2.3) as well as from similar fibers originating in muscles, joints and viscera (Craig and Mense, 1983; Craig *et al.*, 1988; Sugiura *et al.*, 1989). These different inputs can converge on the same cells (Schaible *et al.*, 1987). Lamina VI, in addition to low-threshold cutaneous afferents, also receives peripheral afferent input from Group I muscle afferents and from other low-threshold mechanoreceptors in muscles, joints and other deep tissues (Brown, 1981a).

Other inputs to laminae III–VI come from the corticospinal tract (Coulter and Jones, 1977; Ralston and Ralston, 1985) (Fig. 2.6), the fibers arising principally in the somatic sensory areas of the cerebral cortex and terminating mainly in laminae IV and V. Fibers from the motor areas end more deeply in laminae VI–IX. Fibers of other descending systems such as the rubrospinal tract also tend to terminate in deeper laminae, especially laminae V–VII (Murray and Haines, 1975). Reticulospinal and vestibulospinal fibers end in laminae VII and VIII, at least in cats (reviewed in Brodal, 1957). Propriospinal fibers, many of whose origins are uncertain, also target laminae III–VI.

The principal outputs of laminae III–VI are into the spinothalamic tract (Fig. 2.3), the spinocervical pathway and the postsynaptic dorsal column pathway (described in detail later in the chapter). Cells contributing to the postsynaptic dorsal column pathway in monkeys are mainly located in laminae IV–VI (Rustioni *et al.*, 1979) but an occasional cell may be found in more superficial and deep laminae as well (Bennett *et al.*, 1983). Cells contributing axons to the spinocervical tract of the lateral funiculus are found primarily in ipsilateral laminae III–V in the cat with a few cells also found in other laminae and in the same laminae contralaterally (Brown *et al.*, 1980a, 1980b; Brown, 1981b). Spinocervical cells in monkeys are found in similar locations (Bryan *et al.*, 1974).

Spinothalamic cells are concentrated contralaterally in lamina V but many can also be found in laminae VI–VII, as well as the major population in lamina I (Fig. 2.3). Ipsilaterally, they tend to be found mainly in lamina VIII (Trevino and Carstens, 1975; Trevino, 1976; Willis *et al.*, 1979, 2001; Hayes and Rustioni, 1980; Apkarian and Hodge, 1989a, 1989b). For further details, see below. Among other cells to be found in laminae III–VI are those that contribute to the spino-reticular (Kevetter *et al.*, 1982), spino-mesencephalic (Menétrey *et al.*, 1982), spino-parabrachial (Saper, 1995) and spino-hypothalamic (Burstein *et al.*, 1990) projections, although these projections also arise from cells in superficial and deeper laminae as well. The relative numbers of fibers in each of these pathways in primates are not known.

Chemistry of the dorsal horn

Immunocytochemical and related studies on a variety of species have identified a large and at times bewildering array of chemical agents of various forms that are localized in the dorsal horn of the spinal cord and caudal medulla. An exhaustive review and summary can be found in Willis and Coggeshall (2004), although not all the studies referenced were carried out on the monkey or human spinal cord. A brief review of findings specifically in the human spinal cord can be found in Schoenen and Faull (2004). The present account provides numerous illustrations of preparations from the monkey spinal or trigeminal dorsal horn (Figs 2.8–2.12) that largely confirm patterns of organization and chemical anatomy that have previously been known only from studies of rodents. We will attempt to highlight the chemical anatomy of the dorsal horn in the context of its synaptic connectivity, focusing only on those substances that are the most heavily represented in the spinal cord and on the synaptic connections with which they are associated. In this discussion, we will primarily reference works on the monkey and human but will be obliged to draw data from non-primate species when they are lacking in primates. The major compounds identified include amino acid and monoamine transmitters, neuropeptides, their receptors and a number of other compounds associated with the process of neurotransmission and its modulation.

Primary afferent fibers and their terminations

Glutamate Glutamate is localized in all primary afferent fibers and glutamate immunoreactive fibers form a dense plexus in laminae I and II. At an ultrastructural level, glutamate can be demonstrated in virtually all the central terminals of synaptic glomeruli in the dorsal horn (Weinberg *et al.*, 1987; Battaglia and Rustioni, 1988; De Biasi and Rustioni, 1988, 1990; Sluka *et al.*, 1992). Aspartate is

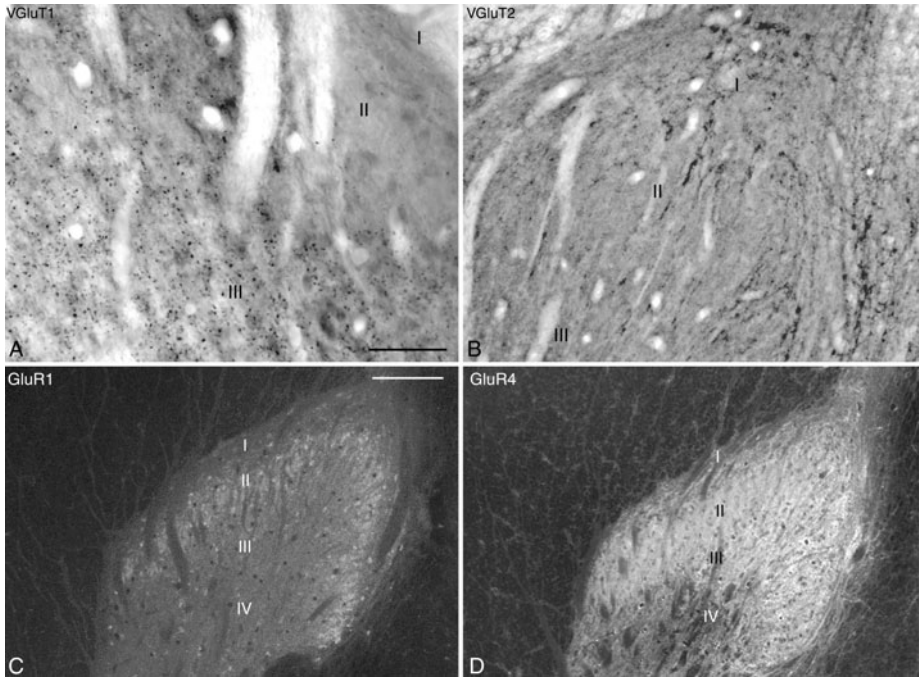


Fig. 2.8. Bright field (A, B) and fluorescence (C, D) images of immunocytochemical preparations of the monkey dorsal horn showing the terminal distribution of primary afferent fibers immunoreactive for the vesicular glutamate transporters VGluT1 (A) and VGluT2 (B) in laminae III and I respectively and the laminar distribution of immunoreactivity for two subunits of ionotropic glutamate receptors, GluR1 (C) and GluR4 (D). Bars: 100 μ m (A, B), 250 μ m (C, D).

commonly co-localized with glutamate in the primary afferents (Tracey *et al.*, 1991). Ionotropic glutamate receptors of both the AMPA/kainate and NMDA types can be identified by immunocytochemistry or in situ hybridization histochemistry in cells throughout the dorsal horn with concentrations in the superficial laminae (Fig. 2.8). The NR1 subunit is the dominant NMDA subunit expressed. For the AMPA receptor subunits, GluR1 and GluR2 are expressed at highest levels in laminae I–III with GluR1 predominating in lamina II; GluR3 and GluR4 are at highest levels in the ventral horn but GluR4 is also heavily expressed in laminae II and III (Fig. 2.8). Kainate receptors are expressed at low levels throughout (reviewed in Willis and Coggeshall, 2004).

Of the metabotropic glutamate receptors, as identified by immunocytochemistry or in situ hybridization histochemistry, mGluR1, mGluR5 and mGluR7 are found in neurons of laminae I and II (Fig. 2.9), mainly associated with cells that receive the terminals of primary afferent fibers (reviewed in Willis and

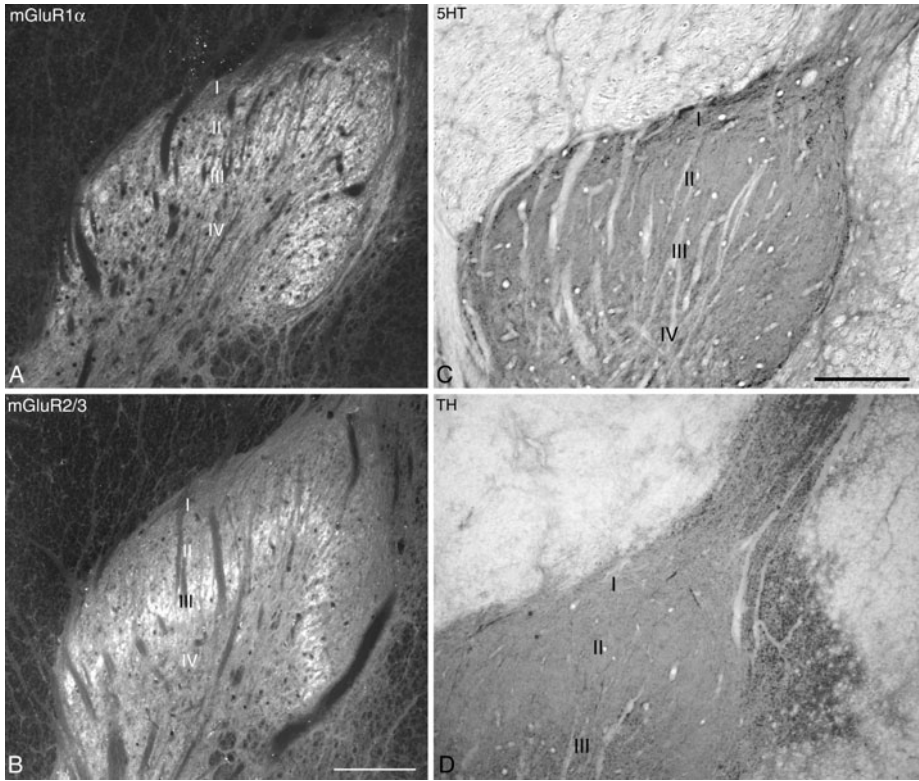


Fig. 2.9. Fluorescence (A, B) and bright field (C, D) images of immunocytochemical preparations of the monkey dorsal horn showing the distribution of immunoreactivity for three metabotropic glutamate receptor subunits, mGluR1 α (A) and mGluR2 and 3 (B), and the terminal distributions of fibers immunoreactive for serotonin (5HT) or noradrenalin (TH). Bars: 250 μ m (B and C).

Coggeshall, 2004). Many synapses made by primary afferents on dorsal horn cells are associated with immunoreactivity for mGluR5 (Tao *et al.*, 2000). mGluR2 and mGluR3 immunoreactivity (Fig. 2.9) is mainly associated with presynaptic receptors on the terminals of the primary afferent fibers (Carlton *et al.*, 2001).

Parallel studies localizing the vesicular glutamate transporters, molecules that are involved in the movement of the transmitter into synaptic vesicles (Naito and Ueda, 1985; Winter and Ueda, 1993), reveal two sets of glutamate-containing mechanosensory primary afferents (Alvarez *et al.*, 2004; Landry *et al.*, 2004; Persson *et al.*, 2006; Graziano *et al.*, 2008). One associated with the transporter, VGLUT1, is located within axons ending in deeper laminae while the other, associated with VGLUT2, is located within axons ending in superficial laminae (Fig. 2.8). There is a similar pattern of localization in the medullary dorsal horn (Li *et al.*, 2003).

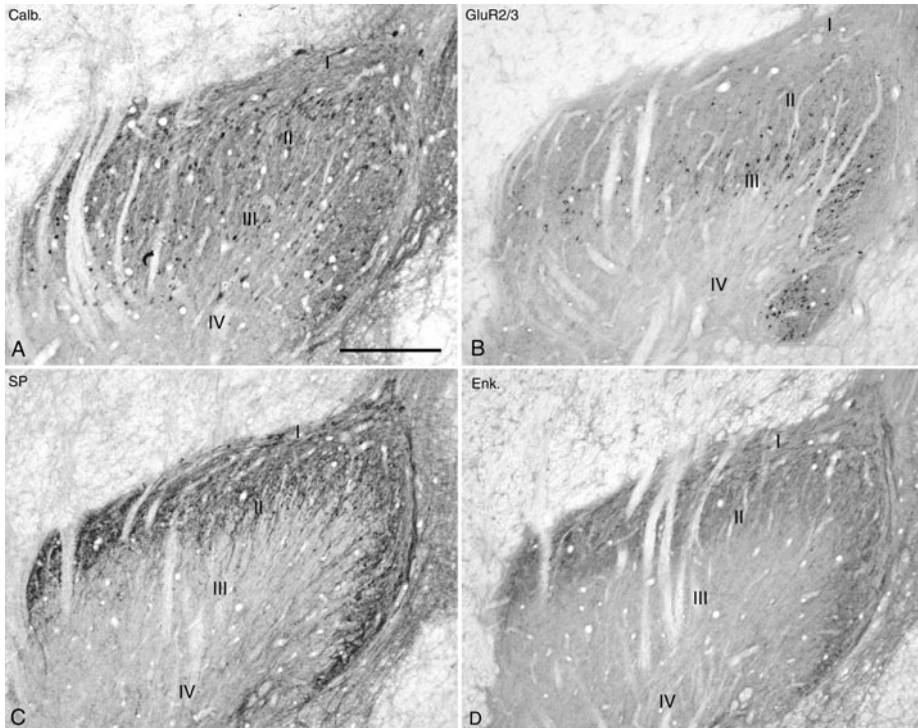


Fig. 2.10. Bright field images of immunocytochemical preparations of the monkey dorsal horn showing the laminar distributions of neuronal and neuropil immunoreactivity for the calcium binding protein, calbindin (Calb.), for the GluR2 and 3 subunits of the glutamate receptor (GluR2/3), and for the neuropeptides, substance P (SP) and leu-enkephalin (Enk.). Bar: 250 μ m.

Substance P The neurokinin, substance P, is found in unmyelinated and thinly myelinated axons that terminate in lamina I and superficial lamina II (Fig. 2.10), and in their parent dorsal root ganglion cells (Hökfelt *et al.*, 1975; Cuello and Kanazawa, 1978; DeLanerolle and LaMotte, 1982, 1983; Schoenen *et al.*, 1985; Bennett *et al.*, 1986; Otsuka and Yanagisawa, 1990; Ribeiro-da-Silva and Hökfelt, 2000). Dorsal rhizotomy, however, does not deplete all substance P immunoreactivity from fibers of the dorsal horn (e.g. Barber *et al.*, 1979; Del Fiaccio and Cuello, 1980), indicating that some substance P fibers are of intrinsic cord or brainstem origin. Within the superficial dorsal horn, substance P-containing terminals of primary afferent origin form the central axon terminal of many glomeruli (DeLanerolle and LaMotte, 1983; Ribeiro-da-Silva *et al.*, 1989), the terminals usually being identifiable by the presence of large dense core vesicles. Generally speaking, all substance P-containing terminals also contain glutamate but the converse is not the case, emphasizing the special association of the peptide with

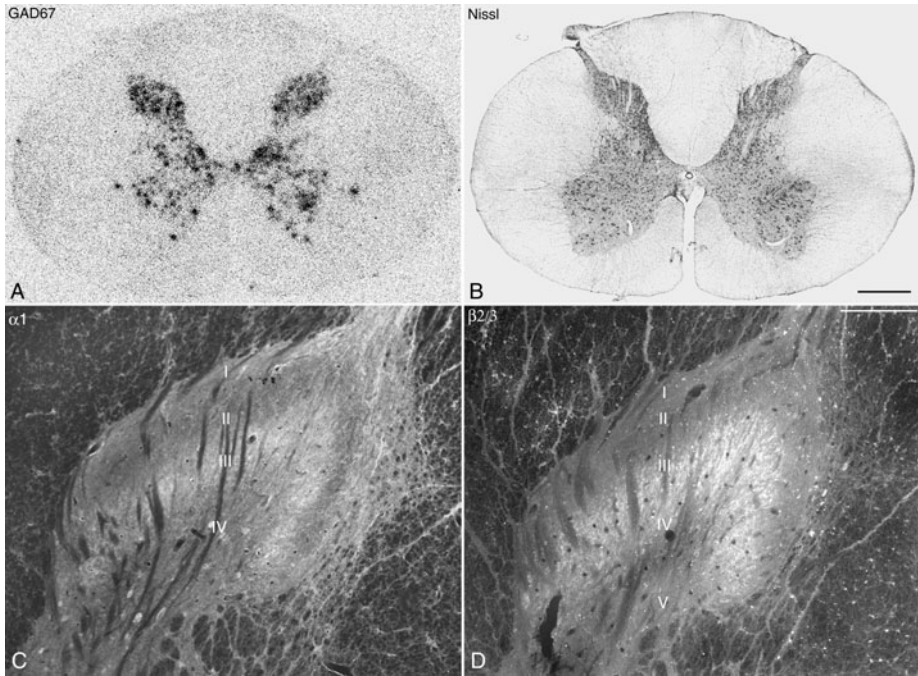


Fig. 2.11. (A, B) Film autoradiogram (A) and the Nissl-stained section (B) of the monkey spinal cord from which it was taken after in situ hybridization of a radioactive cRNA probe that recognizes the mRNA for the 67 kDa form of the GABA synthesizing enzyme, glutamic acid decarboxylase (GAD67). GABA cells are found throughout the gray matter and are concentrated in the dorsal horn. (C, D) Fluorescence images of the monkey dorsal horn showing the distribution of immunoreactivity for the $\alpha 1$, $\beta 2$ and $\beta 3$ ($\beta 2/3$) subunits of the GABA-A receptor. Bar: 1 mm (A, B), 250 μ m (C, D).

smaller diameter primary afferent fibers. Substance P levels in the spinal or medullary dorsal horns are sensitive to peripheral nerve lesions or cauda equina compression which lead to reduction in transcription of the gene coding for preprotachykinin mRNA in dorsal root ganglion cells (e.g. Jessell *et al.*, 1979; Hökfelt *et al.*, 1994), an effect that is dependent upon loss of the trophic agent, nerve growth factor, which is normally transported from the periphery to the neurons (Fitzgerald *et al.*, 1985; Siri *et al.*, 2001).

Substance P-containing terminals (Fig. 2.10C) end on marginal cells in lamina I and on islet, stalked and spinothalamic cell dendrites in lamina II (LaMotte and DeLanerolle, 1981; DeLanerolle and LaMotte, 1982) as well as upon dynorphin-containing cells (Katoh *et al.*, 1988a, 1988b). Neurokinin receptors associated with substance P-containing terminals (NK-1 receptors) are found on neurons in both lamina I and outer lamina II (McLeod *et al.*, 1998; Ribeiro-da-Silva *et al.*, 2000) and

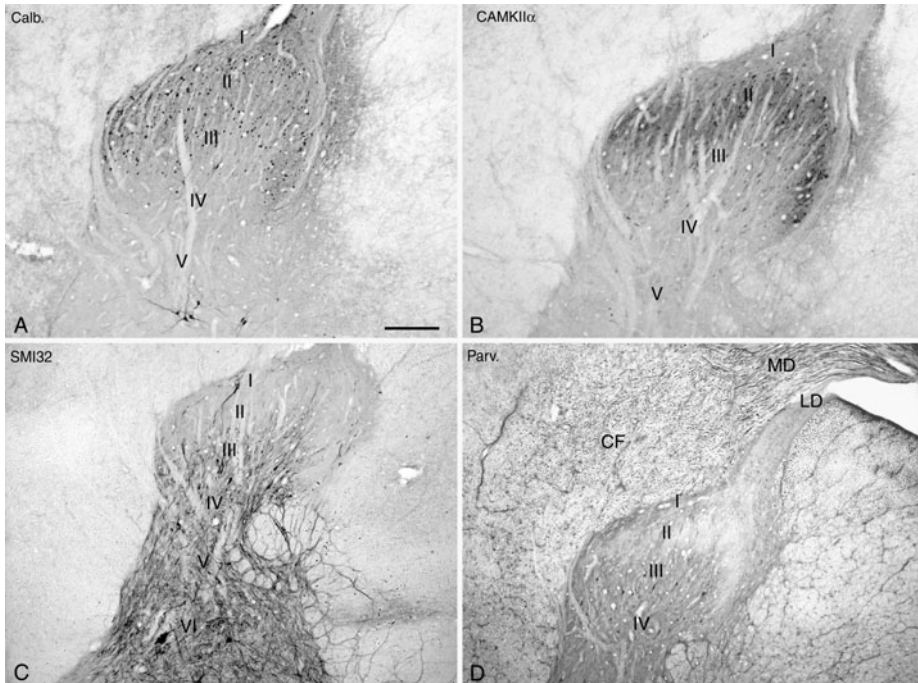


Fig. 2.12. Bright field images of the dorsal horn of the monkey spinal cord showing the distribution of immunoreactivity for the calcium binding proteins, calbindin (Calb.) and parvalbumin (Parv.), and for α Type II calcium/calmodulin dependent protein kinase (CAMKII α) and immunostaining with the monoclonal antibody SMI32 which recognizes a neurofilament epitope. In D note the specific immunostaining of the entering medial division fibers (MD) of the dorsal root for parvalbumin and the lack of immunoreactivity in the fine fibers of the lateral division (LD). CF, cuneate fasciculus. Bar: 250 μ m.

on the dendrites of antenna cells with somata located in laminae III and IV (Honore *et al.*, 1999; Li *et al.*, 2000). Cells expressing this receptor include those projecting to brainstem and thalamic sites (Ding *et al.*, 1995a, 1995b; Marshall *et al.*, 1996; Todd *et al.*, 2000). Cells postsynaptic to substance P-containing terminals are reported to be primarily nociceptive-specific or wide dynamic range cells rather than non-nociceptive cells (Ma *et al.*, 1997), confirming the association of substance P with the pain system.

Other peptides Calcitonin gene-related peptide (Carlton *et al.*, 1988) is expressed by many dorsal root ganglion cells and in primary afferent fibers terminating in laminae I and II of the dorsal horn (Wiesenfeld-Hallin *et al.*, 1984; Ju *et al.*, 1987; Chung *et al.*, 1988). Some but by no means all of the CGRP-expressing ganglion cells, their axons and terminals are also immunoreactive for substance P. CGRP

is also found in somatostatin immunoreactive primary afferent fibers ending mainly in lamina II (e.g. Alvarez and Priestley, 1990; Merighi *et al.*, 1992), in association with somatostatin receptors. Other peptides identified in primary afferent fibers or in their laminae of termination in the dorsal horn include: atrial natriuretic peptide, angiotensin, bombesin, cholecystokinin, endothelin, galanin, hypocretin, neuropeptide FF and neurotensin (reviewed in Willis and Coggeshall, 2004). Some of these peptides are located within fibers descending from the brainstem.

Fluoride resistant acid phosphatase (FRAP) This enzyme is found in a sub-population of small dorsal root ganglion cells and in their terminals which form a prominent band in lamina I and inner or middle lamina II of the dorsal horn (Hunt and Rossi, 1985; Carr *et al.*, 1990; Silverman and Kruger, 1990). It is generally agreed that, at least in rodents, FRAP is found mainly if not exclusively in small-diameter primary afferent fibers that are non-peptidergic. FRAP fibers, unlike peptidergic fibers, depend for survival in adults upon glial-derived nerve growth factor rather than upon nerve growth factor (Bennett *et al.*, 1998).

Intrinsic systems

Opioid peptides Met- and leu-enkephalin immunoreactive nerve cells and their processes are found in large numbers in laminae I and II of the dorsal horn (Fig. 2.10D) (Hökfelt *et al.*, 1977; Hunt *et al.*, 1981; Miller and Seybold, 1987, 1989; Li *et al.*, 1999c). The dendrites of enkephalin-containing neurons in lamina II receive significant numbers of synapses from substance P-containing primary afferent fibers (Cuello, 1983; Ribeiro-da-Silva *et al.*, 1991) and from noradrenergic and serotonergic fibers descending from the brainstem (Figs 2.6, 2.9C, D). Many of the enkephalin-containing neurons also co-localize substance P, at least in non-primates (Senba *et al.*, 1988; Ribeiro-da-Silva *et al.*, 1991). All enkephalin immunoreactive fibers in the dorsal horn probably have their origins in the dorsal horn itself. It is doubtful that significant numbers represent primary afferent fibers or fibers descending from higher levels. The axons of the enkephalinergic intrinsic cells of the dorsal horn make synapses on both spinothalamic tract neurons and on neurons that contribute to the postsynaptic dorsal column pathway (Nishikawa *et al.*, 1983; Ruda *et al.*, 1984).

Immunoreactivity for the μ -opioid receptor is highly concentrated in deep lamina II where it is localized in the somata and dendrites of dorsal horn neurons, particularly islet cells, as well as in axon terminals, some of which may be of dorsal root fiber origin (Honda and Arvidsson, 1995; Cheng *et al.*, 1996; Kemp *et al.*, 1996; Zhang *et al.*, 1998). The specificity of the localization suggests

that the receptors are primarily associated with the endings of unmyelinated afferent fibers. Delta-opioid receptors are less densely concentrated but more widely distributed across laminae I and II and may be associated therefore with the endings of A δ afferent fibers (Honda and Arvidsson, 1995). Kappa-opioid receptors are the least concentrated. Immunoreactivity for all three opioid receptor subtypes is greatly reduced after dorsal rhizotomy and the evidence suggests that this is due to degeneration of the primary afferent fibers and loss of presynaptic receptors rather than to a trans-synaptic down-regulation of postsynaptic receptors (Besse *et al.*, 1992; Lombard *et al.*, 1995; deGroot *et al.*, 1997). Many, if not all, opioid receptors in primary afferent fibers are found in those containing the neuropeptides, especially substance P. The significant amount of receptor immunoreactivity that remains in rhizotomy cases undoubtedly represents postsynaptic opioid receptors located on the dendrites of dorsal horn neurons. Electron microscopic evidence indicates that these receptors are not associated with classical morphologically definable synaptic contacts (Cheng *et al.*, 1997; Zhang *et al.*, 1998).

GABA and glycine Neurons expressing genes for glutamic acid decarboxylase (GAD), the synthetic enzyme for the inhibitory transmitter, gamma aminobutyric acid (GABA), are found throughout the spinal gray matter (Fig. 2.11). GABA cells in the dorsal horn are concentrated in laminae I–III where they make up 30–40% of the neuronal population (Todd and Sullivan, 1990). In lamina II, it is the islet cells, not the stalked cells, that are GABAergic (Barber *et al.*, 1982; Todd and McKenzie, 1989). Fusiform cells of layer I and some antennal cells of deeper layers are also GABAergic (Coimbra and Lima, 1982; Waldvogel *et al.*, 1990). In the glomeruli of the superficial dorsal horn (Fig. 2.5), the terminals of the GABAergic islet cells end on the terminals of primary afferent fibers in the glomeruli, on dendrites of other dorsal horn neurons and on the presynaptic dendrites of islet cells themselves (Barber *et al.*, 1978; Basbaum *et al.*, 1986; Carlton and Hayes, 1990; Alvarez *et al.*, 1992; Spike and Todd, 1992; Iliakis *et al.*, 1996; Bae *et al.*, 2000). The majority of terminals derived from A δ fibers, from rapidly and slowly adapting cutaneous mechanoreceptive afferents, from hair follicle receptor afferents and from Group IA fibers receive GABAergic presynaptic terminals (Maxwell and Noble, 1987; Maxwell *et al.*, 1990a, 1990b; Alvarez *et al.*, 1992; Sutherland *et al.*, 2002; Watson *et al.*, 2002). Substance P-containing afferent fiber terminals, however, do not receive a presynaptic GABAergic innervation, indicating that this class of nociceptive afferents is not subjected to presynaptic inhibition in the dorsal horn (Todd and Spike, 1993; Bernardi *et al.*, 1995).

Among cell classes in the dorsal horn, neurons characterized by the presence of μ -opiate receptors (Gong *et al.*, 1997) and neurons projecting into the

spinothalamic, spinocervical and trigeminothalamic tracts and the dorsal columns (Maxwell *et al.*, 1991, 1995; Carlton *et al.*, 1992; Lekan and Carlton, 1995) have all been identified as receiving GABAergic inputs.

Glycine, the other major inhibitory amino acid transmitter, is generally expressed only in GABAergic cells of the dorsal horn, although not all GABA cells located there are glycinergic (Todd and Sullivan, 1990; Wang *et al.*, 2000). In general, glycine tends to be found only in GABA cells that do not contain enkephalin or other peptides (Fleming and Todd, 1994).

GABA-A receptors In the dorsal horn of the rat spinal cord, several α subunits, $\beta 2$ and/or $\beta 3$ subunits and $\gamma 2$ subunits of the GABA-A receptor are the most highly expressed of the many GABA-A receptor subunits (Bohlhalter *et al.*, 1996). In monkeys (Fig. 2.11C, D), similar patterns of distribution appear. The $\alpha 1$, $\alpha 2$, $\alpha 3$, $\alpha 5$, $\beta 2/\beta 3$ and $\gamma 2$ subunits are all heavily concentrated in cells of lamina III but display varying patterns in other layers. The $\alpha 1$ and $\alpha 5$ subunits are not found at all in laminae I and II while the $\alpha 2$ and $\alpha 3$ subunits and to a lesser extent the $\beta 2/\beta 3$ and $\gamma 2$ subunits are heavily concentrated there. The deeper layers of the dorsal horn show immunostaining for all the subunits but staining for the $\alpha 1$ and $\alpha 5$ subunits is substantially weaker than for the other subunits. The overall pattern suggests the presence of GABA-A receptors formed from $\alpha 2/\alpha 3$, $\beta 2/\beta 3$ and $\gamma 2$ subunits in laminae I and II, from $\alpha 1/\alpha 5$, $\beta 2/\beta 3$ and $\gamma 2$ subunits in lamina III, and from $\alpha 2/\alpha 3$, $\beta 2/\beta 3$ and $\gamma 2$ subunits in deeper laminae of the dorsal horn.

GABA-B receptors Cells expressing GABA-B receptors are found throughout the central gray of the spinal cord with increased concentrations in laminae I and II, especially for the GABA-B1a and GABA-B1b subtypes (Towers *et al.*, 2000).

Noradrenaline and serotonin Although there are occasional noradrenergic cells in the deep dorsal horn, by far the majority of noradrenergic fibers in the spinal cord descend from origins in cells of the brainstem (as described earlier in this chapter). The noradrenergic fibers descend beside the dorsal horn (Fig. 2.9D) and terminate primarily in lamina I and the outer division of lamina II (Westlund *et al.*, 1983; Fritschy and Grzanna, 1990). Their terminals are known to contact enkephalinergic interneurons and the majority of spinothalamic and postsynaptic dorsal column neurons (Fig. 2.6; Westlund *et al.*, 1991; Doyle and Maxwell, 1993).

Serotonin-containing fibers arising in the nucleus raphe magnus of the brainstem descend along the lateral aspect of the dorsal horn (Fig. 2.9C) and terminate in virtually all layers of the spinal gray matter but with the highest density of terminals in laminae I and outer II (reviewed in Basbaum *et al.*, 1988; Ruda, 1988; Westlund *et al.*, 1992). There, the terminals of the serotonin fibers end on

enkephalin- and neurotensin-containing interneurons (Fig. 2.6; Glazer and Basbaum, 1984; Miller and Salvatierra, 1998) as well as directly on spinothalamic and spinomesencephalic neurons (Hylden *et al.*, 1986; Wu and Wessendorf, 1992).

Acetylcholine Choline acetyltransferase, the enzyme involved in the synthesis of acetylcholine, is found in a considerable number of mostly GABAergic cells of laminae III–IV (Houser *et al.*, 1983). The axon terminals of these cells can be found ending on primary afferent terminals in the glomeruli of the superficial dorsal horn (Ribeiro-da-Silva and Cuello, 1990). No primary afferent fibers are cholinergic.

Nitric oxide (NO) There is a concentration of cells and fibers that exhibit the enzyme, NADPH diaphorase, in laminae I–III (e.g. Mizukawa *et al.*, 1989; Ruda *et al.*, 1994). It is thought that the expressing cells are mainly inhibitory interneurons (Willis and Coggeshall, 2004).

Hormones Corticotrophin-releasing factor (CRF) and thyroid-releasing hormone (TRH) are found in fibers concentrated in laminae I and II (e.g. Mantyh *et al.*, 1989; Fleming and Todd, 1994). These fibers may derive from primary afferents and/or from hypothalamic or brainstem sites (Willis and Coggeshall, 2004).

Calcium binding proteins and other substances

Calbindin Primary afferent fibers entering the spinal cord in the lateral divisions of the dorsal roots are all immunoreactive for 28 kDa calbindin in monkeys (Figs 2.10A, 2.12A). Calbindin immunoreactive fibers are concentrated in laminae I and II of the spinal and medullary dorsal horns (e.g. Li *et al.*, 1999d; Craig *et al.*, 2002; Graziano and Jones, 2004). Large marginal cells of lamina I and many small cells of lamina II are also immunoreactive for calbindin, along with a very small number of larger antennal cells in deeper layers (Fig. 2.12A). Certain lamina II cells also express 29 kDa calretinin (Rogers and Resibois, 1992). Many calbindin cells project their axons to higher centers which include other levels of the spinal cord, the parabrachial region, the nucleus of the solitary tract, the hypothalamus and the thalamus (Aronin *et al.*, 1991; Bennett-Clarke *et al.*, 1992; Men  trety *et al.*, 1992; Li *et al.*, 1999d; Gamboa-Estev  s *et al.*, 2001; Craig *et al.*, 2002; Graziano and Jones, 2004). Most of the axons appear to ascend in the dorsolateral funiculus (Fig. 2.13). Although it has been claimed that lamina I calbindin cells in monkeys project specifically to posterior regions of the thalamus (Craig *et al.*, 2002), this has not been confirmed in double-labeling studies (Rausell *et al.*, 1992a; Graziano and Jones, 2004).

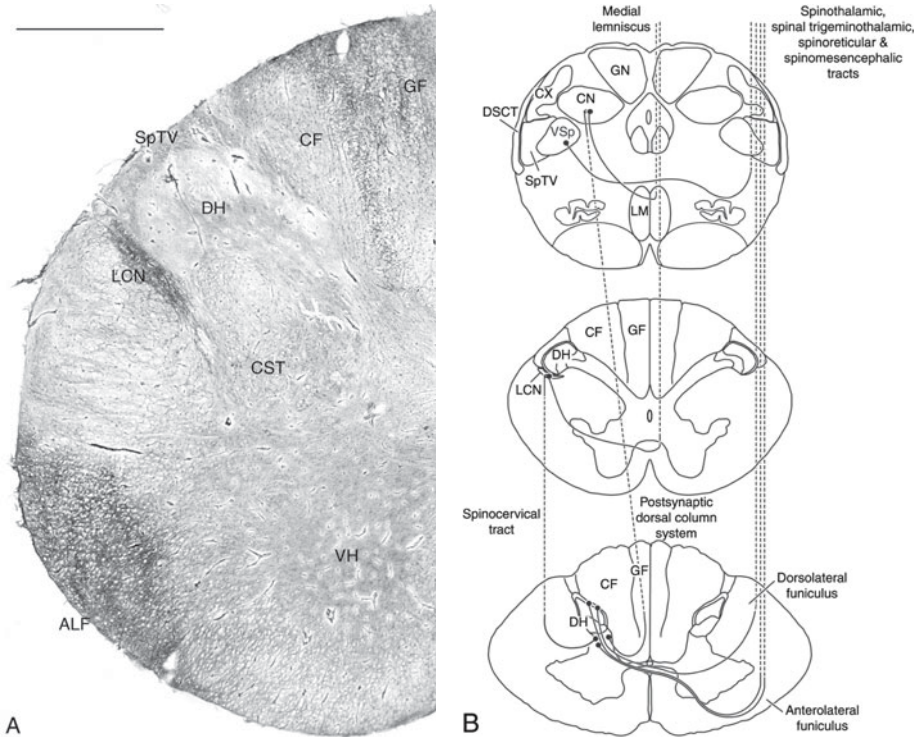


Fig. 2.13. (A) Nauta staining of a section at the C1 level of the spinal cord of a monkey in which the cord was hemisected at the C2–3 segments 14 days previously. Anterograde degeneration of ascending fibers can be seen in the gracile (GF) and cuneate fasciculi (CF), in the anterolateral funiculus (ALF) and in the dorsolateral funiculus innervating the lateral cervical nucleus (LCN). CST, corticospinal tract, DH, dorsal horn; SpTV, spinal tract of the trigeminal nerve; VH, ventral horn. Bar: 1 mm. From a preparation of E. G. Jones and W. D. Willis Jr. (see Fig. 2.16). (B) Schematic view of the laminar origins and white matter locations of the three spinal pain pathways. Spinothalamic fibers originate in lamina I and deeper laminae and, after crossing in the anterior white commissure, ascend in the contralateral dorsolateral funiculus or deeper in the anterolateral funiculus; they are joined in the lower brainstem by similar fibers arising in the caudal spinal trigeminal nucleus (VSp). Fibers of the spinocervical system originate from deeper laminae of the dorsal horn and ascend ipsilaterally in the dorsolateral funiculus to terminate in the lateral cervical nucleus (LCN); second-order fibers decussate and join the medial lemniscus (LM) in which they ascend to the thalamus. Fibers of the postsynaptic dorsal column system arise from deeper seated cells of the dorsal horn and ascend deep in the ipsilateral dorsal columns to terminate in the cuneate (CN) or gracile (GN) nucleus; second-order fibers decussate and ascend with the medial lemniscus to terminate in the thalamus. CX, external cuneate nucleus; CF, cuneate fasciculus; DH, dorsal horn; DSCT, dorsal spinocerebellar tract; GF, gracile fasciculus; SpTV, spinal tract of trigeminal nerve.

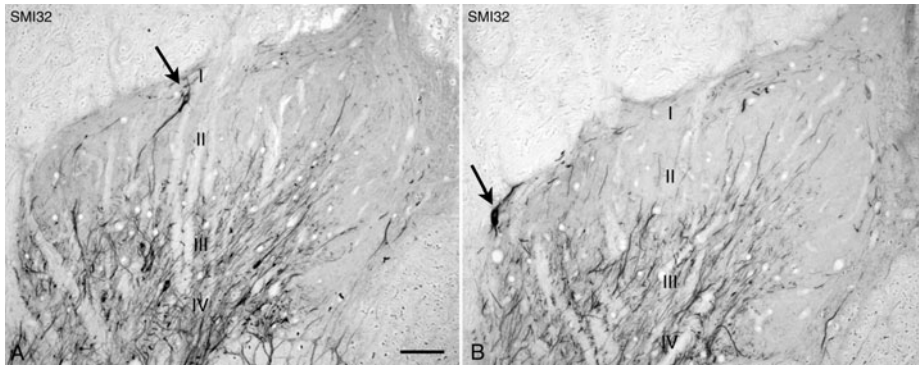


Fig. 2.14. Sections of the dorsal horn of the monkey spinal cord, stained immunocytochemically with the monoclonal antibody SMI32. Arrows indicate specifically stained marginal neurons. Bar: 100 μ m.

Parvalbumin Parvalbumin immunoreactivity distinguishes the large-diameter primary afferent fibers that enter the spinal cord in the medial divisions of the dorsal roots and ascend in the dorsal columns (Fig. 2.12D) (Jones and Pons, 1998; Woods *et al.*, 2000). In the spinal gray matter, parvalbumin-expressing cells and fibers are concentrated in laminae II–III (Fig. 2.12D; Celio and Heizmann, 1981; Ren and Ruda, 1994). Many of these cells are GABAergic interneurons, at least in the rat (Polgar and Antal, 1995) but others project axons to other spinal and brainstem targets (Aronin *et al.*, 1991; Bennett-Clarke *et al.*, 1992; Men  trety *et al.*, 1992; Li *et al.*, 1999d; Gamboa-Esteves *et al.*, 2001).

SMI32 SMI32 is a monoclonal antibody that recognizes an epitope on non-phosphorylated neurofilament protein. In the dorsal horn, immunostaining with this antibody identifies large marginal cells of lamina I and numerous smaller cells and their processes in laminae III and IV (Figs 2.12C, 2.14).

Alpha type II calcium calmodulin dependent protein kinase (CAMKII  ) Immunostaining for CAMKII   reveals numerous small cells in laminae I–III and a dense fiber plexus concentrated in lamina II (Fig. 2.12B), a distribution that mimics that of calbindin.

Spinal pathways, brainstem and forebrain terminations

The spinothalamic system

Cells of origin Antidromic activation of projecting cells from thalamic terminal sites, and retrograde labeling after injection of dye tracers in thalamic terminal sites reveal that spinothalamic axons arise in large numbers from nociceptive,

thermoceptive and polymodal neurons in lamina I and from a second population of neurons with mixed sensory inputs located mainly in lamina V (Fig. 2.3B). Small numbers of spinothalamic tract cells can also be found in laminae III–IV and even in lamina II; small numbers can also be found in the deeper laminae VI–VIII (Figs 2.3B, 2.15) (Trevino *et al.*, 1972, 1973; Trevino and Carstens, 1975; Carstens and Trevino, 1978; Willis *et al.*, 2001; Craig and Zhang, 2006). Spinothalamic tract cells in lamina I and many in lamina V are innervated monosynaptically by primary afferent fiber terminals but many others in lamina V and those in other laminae are innervated indirectly, di- or tri synaptically, through dorsal horn interneurons. Others in laminae III–V can receive a combination of direct and indirect primary afferent innervation.

In monkeys, it has been calculated that more than 18,000 spinal cells project to the contralateral thalamus, the majority located in laminae I and V (Apkarian and Hodge, 1989a). More than 90% of these cells project to the contralateral ventral posterior lateral (VPL) nucleus, except in the most caudal segments of the spinal cord where the number projecting ipsilaterally is higher (Willis *et al.*, 1978, 1979; Hayes and Rustioni, 1980; Apkarian and Hodge, 1989a, 1989c). Cells projecting to intralaminar and other medial nuclei of the monkey thalamus are mostly located in laminae VI–VIII. Some of these have branched axons to VPL as well (Giesler *et al.*, 1981).

The extent to which individual spinothalamic tract cells innervate only VPL or the posterior or medial nuclei and the extent to which their axons branch to innervate more than one thalamic nucleus remain unclear and to some extent controversial. Unfortunately, most of the relevant data come from non-primate species. Between 15–20% of the projecting neurons in the rat are reported to have branches ending in medially and laterally located thalamic nuclei (Kevetter and Willis, 1984). In cats, only 12–13% of those located in any spinal lamina were reported to project to both medial and lateral thalamus (Craig *et al.*, 1989; Stevens *et al.*, 1989). But there is a discrepancy in the numbers of medially or laterally projecting cells. Craig *et al.* (1989) described 62% projecting to medial thalamus and 25% to lateral thalamus but Stevens *et al.* (1989) reported 40–50% projecting to medial thalamus and 36–57% projecting laterally. There was also a discrepancy in these reports of the number of lamina I cells projecting laterally or medially, Craig *et al.* (1989) reporting laterally located cells projecting to medial thalamic nuclei and medially located cells projecting laterally. Stevens *et al.* (1989), however, reported more lamina I cells projecting to lateral than to medial thalamic nuclei. In general, these findings were in line with those reported from antidromic activation studies in monkeys in which more than one thalamic site was stimulated while recording from neurons in the dorsal horn (Price *et al.*, 1976; Applebaum *et al.*, 1979; Giesler *et al.*, 1981; Zhang *et al.*, 2000a, 2000b). Recent retrograde

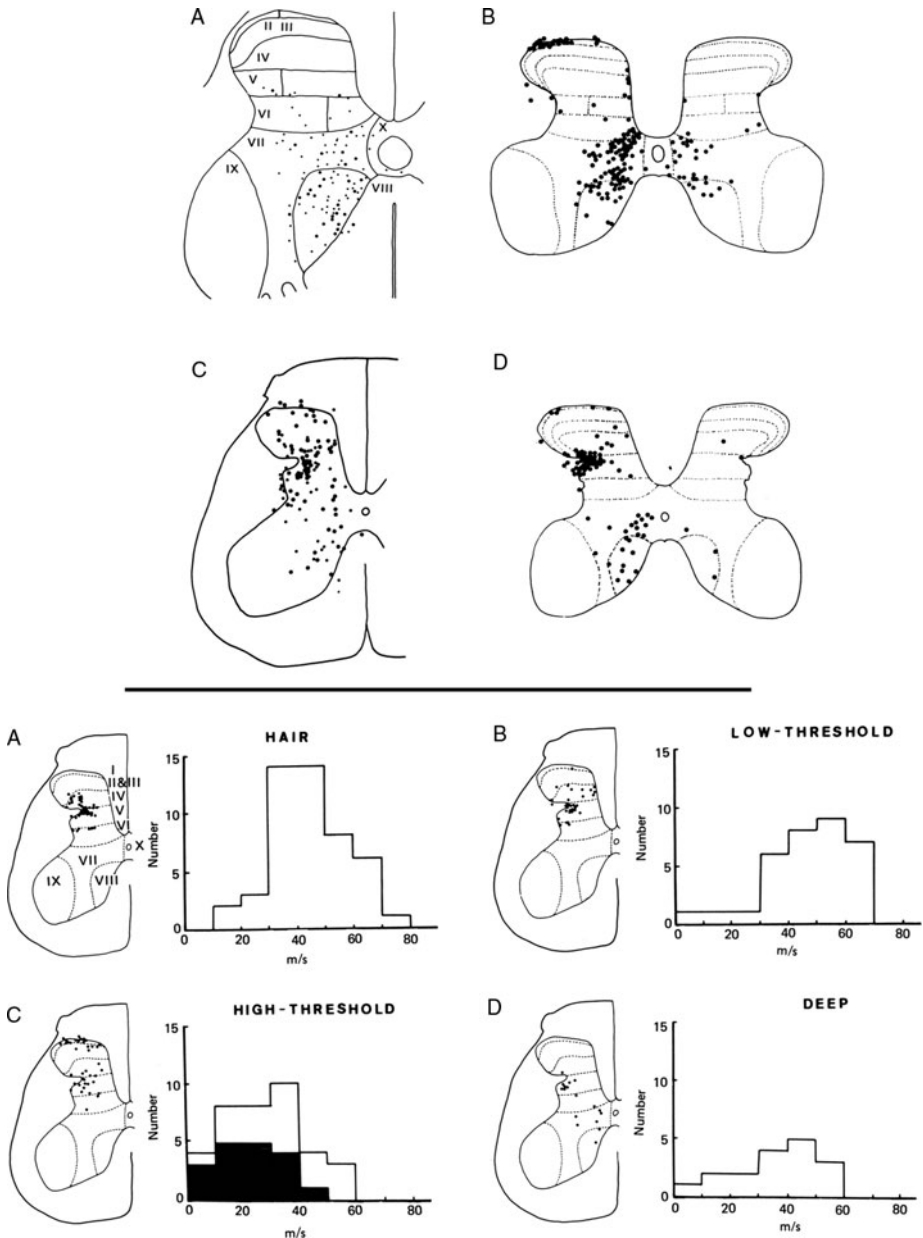


Fig. 2.15. Upper panel. Laminar distribution of antidromically activated (A, C) and retrogradely labeled (B, D) spinothalamic cells in the lumbar and sacral enlargement of the spinal cord of the cat (A, B) and monkey (C, D). From Willis and Coggeshall (1991) after Trevino *et al.* (1972, 1973) and Trevino and Carstens (1975). Lower panel. Laminar distribution of identified spinothalamic tract cells with different types of receptive fields and different latencies to antidromic stimulation in the spinal cord of the monkey. Many of the hair movement and low-threshold cells had wide dynamic ranges of responsiveness. From Willis and Coggeshall (2004).

labeling work in monkeys by Craig (2006) and Craig and Zhang (2006) claimed that inputs to a region that includes the posterior nucleus but probably also medial parts of the ventral posterior medial (VPM) nucleus, along with the ventral posterior inferior (VPI) and basal ventral medial (VMb) nuclei, receives its spinothalamic input almost exclusively from lamina I cells throughout the spinal cord (discussed later in this chapter); inputs to VPL proper were said to arise exclusively from cells located in lamina V. The intralaminar and other medial nuclei were not mentioned. The comments on VPL conflict with the results of a study, carried out with similar techniques by Willis *et al.* (2001) in which injections of the same tracer in VPL, clearly avoiding the posterior, VPI and VMb nuclei, led to retrograde labeling of both lamina I and lamina V cells. The results from Craig's laboratory, nevertheless, point to a very substantial lamina I input to the nuclei around the caudal pole of VPL and this is of significance, given the longstanding relationship that these nuclei have had with a thalamic pain center (Chapter 1; see also later in this chapter). Unfortunately, reports from Craig's laboratory have created a great deal of confusion about the terminations of spinothalamic fibers in the primate thalamus, largely on account of a somewhat idiosyncratic view of the nuclei of the caudal part of the thalamus. An attempt at clarifying the present position is made in a following section.

Fiber trajectories

The concept of a lateral spinothalamic tract concerned with pain and a ventral spinothalamic tract concerned with crude touch, as developed from the studies of Foerster (Chapter 1) is no longer accepted, mainly because no evidence could be found for segregation of fibers arising from spinal cells responding to nociceptive or mechanoreceptive inputs (e.g. Applebaum *et al.*, 1975). There is, however, a definite dissociation of fibers arising from different laminae of the dorsal horn as they ascend in the contralateral lateral funiculus. In monkeys, spinothalamic fibers arising from neurons located in more superficial laminae of the spinal central gray, including those arising from nociceptive or thermoceptive lamina I cells, tend to follow a more dorsal trajectory and are located in the middle part of the lateral funiculus¹ at a level close to the denticulate ligament (Fig. 2.13A). Those arising from neurons in deeper laminae of the central gray, along with those of a few lamina I cells, are positioned more ventrally in the position of the classical spinothalamic tract and are apparently more diffusely distributed within this part of the lateral funiculus (Fig. 2.13B) (Kerr, 1970a, 1970b; Apkarian and Hodge, 1989b, 1989d; Stevens *et al.*, 1991; Ralston and Ralston, 1992; Zhang and Craig, 1997; Zhang *et al.*, 2000a, 2000b). The fibers are myelinated and in monkeys have a

diameter of less than 10 microns (Lippman and Kerr, 1972). This correlates with a measured conduction velocity of approximately 40 m/s in humans (Mayer *et al.*, 1975; Tasker, 1982).

The spinocervicothalamic system

The spinocervical pathway is located in the dorsal part of the lateral funiculus (Fig. 2.13A, B). It is a rapidly conducting system whose fibers arise from neurons in the dorsal horn and terminate in the lateral cervical nucleus of the same side. Postsynaptic fibers leave the lateral cervical nucleus, cross to the opposite side and ascend with the medial lemniscus to terminations in and around the ventral posterior nucleus of the thalamus (Willis and Coggeshall, 2004).

In non-primates such as the rat and the cat, neurons that project axons to the lateral cervical nucleus can be found throughout most laminae of the ipsilateral dorsal horn but with a decided concentration in laminae III and IV (Craig, 1978; Brown *et al.*, 1980a, 1980b; Baker and Giesler, 1984). These cells extend their dendrites rostro-caudally along the border between laminae II and III (Brown *et al.*, 1977). Brown *et al.* (1980a) estimated that there were about 550–800 spinocervical cells on each side of the lumbosacral enlargement of the cat.

Many of the cells of origin of the spinocervical tract can be activated by hair movement indicating input from A β fibers. Some respond to pressure or pinch applied to the skin, suggesting that they receive input from peripheral nociceptors (Brown and Franz, 1969, 1970; Bryan *et al.*, 1973, 1974; Cervero *et al.*, 1977; Brown *et al.*, 1980b, 1986a, 1987; Brown and Noble, 1982; Downie *et al.*, 1988). Noxious heat and cold and inputs from high-threshold muscle afferents will also activate some of the cells (Brown and Franz, 1970; Kniffki *et al.*, 1977). At least some spinocervical tract neurons in monkeys respond specifically to noxious mechanical or thermal stimuli or both to innocuous and noxious mechanical stimuli, although some are activated by clearly innocuous mechanical stimuli (Bryan *et al.*, 1974; Downie *et al.*, 1988). Despite this, clinical evidence is lacking for a significant involvement of the spinocervical pathway in pain. Some clinical studies suggest that its integrity is more important for vibratory sensation and kinesthesia (Ross *et al.*, 1979).

The axons of spinocervical cells give off local collaterals and then enter the white matter to ascend in a superficial position in the dorsolateral aspect of the lateral funiculus (Brown *et al.*, 1977) (Fig. 2.13B). They are myelinated and their conduction velocities range from 7 to 103 m/s in cats (Bryan *et al.*, 1973; Cervero *et al.*, 1977) and from 7 to 71 m/s in monkeys (Bryan *et al.*, 1974; Downie *et al.*, 1988).

The lateral cervical nucleus (Fig. 2.13A) has been identified in several species of monkey (Gardner and Morin, 1955; Ha and Morin, 1964; Mizuno *et al.*, 1967; Kircher and Ha, 1968; Shriver *et al.*, 1968; Ha, 1971) and inconsistently in the human (Kircher and Ha, 1968; Truex *et al.*, 1970). It is an interrupted column of moderately large neurons located within the white matter of the lateral funiculus, just beneath the superficial aspect of the dorsal horn at the first, second and upper third cervical segment levels. In monkeys, Smith and Apkarian (1991) estimated that the nucleus contained 1617 neurons. Axons of the spinocervical tract enter it from its dorsolateral and lateral aspects (Cajal, 1899, 1909; Ha and Liu, 1966; Westman, 1968) and terminate in a seemingly rather crude somatotopic order (Svensson *et al.*, 1985; Craig *et al.*, 1987, 1992; Broman *et al.*, 1990; Kechagias and Broman, 1994). The nucleus may also receive collaterals of other tracts ascending in the dorsolateral funiculus (Lu and Willis, 1999).

Lateral cervical cells projecting to the contralateral thalamus in monkeys have receptive fields and stimulus-response relationships that permitted Downie *et al.* (1988) to classify them as low-threshold cutaneous neurons (45%), wide dynamic range neurons (47.5%) or high-threshold neurons (7.5%), resembling those of the spinothalamic system. The low-threshold neurons had receptive fields larger than those of cells in the dorsal column-lemniscal system. Noxious heating was a powerful stimulus for many of the high-threshold neurons.

The axons of lateral cervical nucleus cells give off intranuclear collaterals and then cross to the opposite side in the anterior white commissure and join the medial lemniscus in which they ascend to the contralateral thalamus (in monkeys: Ha, 1971; Boivie, 1980; Downie *et al.*, 1988; for other species see Willis and Coggeshall, 2004). Smith and Apkarian (1991) determined that only 506 out of 1617 neurons located in the lateral cervical nucleus of the monkey projected to the thalamus. The remaining neurons were thought to project only to the midbrain, to regions described as the superior colliculus, the periaqueductal gray matter, nucleus of the brachium of the inferior colliculus, nucleus of Darkschewitsch and posterior pretectal nucleus (Wiberg *et al.*, 1987). The conduction velocities of cervicothalamic fibers in monkeys are ~ 17 m/s (Downie *et al.*, 1988). In the thalamus, they appear to terminate with the other lemniscal fibers mainly in the deep shell region that lies anterodorsal to the cutaneous core of VPL in monkeys (Boivie, 1980; Jones, 2007) and in an apparently equivalent region in cats (Landgren *et al.*, 1965; Zhang and Broman, 1998, 2001). Transmission to the cerebral cortex via the spino-cervico-thalamic pathway is faster than that in the dorsal column-lemniscal pathway in cats (Landgren *et al.*, 1965) but slower in monkeys (Downie *et al.*, 1988). In the cat, electrical stimulation of appropriate fiber pathways demonstrates the convergence of

cervicothalamic and dorsal column-lemniscal afferents upon single, antidromically identified thalamo-cortical relay cells (Andersen *et al.*, 1966).

The terminal ramifications of cervicothalamic fibers in the ventral posterior nucleus closely resemble those of dorsal column-lemniscal fibers and possess the large clustered boutons typical of those of dorsal column-lemniscal fibers although a few thinner axons with less dense clusters of boutons are found around the periphery of VPL in cats (Zhang and Broman, 2001). Cervicothalamic terminals, when examined electron microscopically, cannot be distinguished morphologically from those of dorsal column-lemniscal or trigeminal lemniscal fibers (Blomqvist *et al.*, 1985; Broman and Ottersen, 1992).

The postsynaptic dorsal column system

Axons arising from neurons in deeper laminae of the dorsal horn and ascending in the medial aspect of the dorsal columns of the spinal cord (Fig. 2.13B) have come to be recognized as having a role in the central conduction of pain following the observation of Gildenberg and Hirschberg (1984) that a limited midline myelotomy could have a significant effect in alleviating pelvic cancer pain (reviewed in Willis *et al.*, 1999 and Willis and Coggeshall, 2004). Subsequent studies in monkeys have confirmed that the postsynaptic dorsal column pathway and its cells of origin appear to have a special role in the signaling of visceral pain and in viscerosomatic interactions (Hirschberg *et al.*, 1996; Al-Chaer *et al.*, 1999). A lesion of the dorsal columns, for example, will block much of the input from receptors responding to colorectal distension to the VPL nucleus of the thalamus (Al-Chaer *et al.*, 1998).

In monkeys, many of the cells of origin of the postsynaptic dorsal column pathway are located in laminae III–VI (Rustioni *et al.*, 1979; Bennett *et al.*, 1983). There are estimated to be ~1000 such neurons in the lumbar enlargement of cats and monkeys (Bennett *et al.*, 1983). Cells contributing to the pathway that receive inputs from pelvic visceral structures are mainly located in the vicinity of the central canal (Al-Chaer *et al.*, 1996a, 1996b). In cats the cells are characterized morphologically by dorsally directed dendrites that ascend into laminae II and even I (Brown and Fyffe, 1981). Some of the cells have sagittally oriented dendritic fields and others transversely oriented dendritic fields.

In cats, most of the parent cells of the postsynaptic dorsal column pathway have relatively large receptive fields and respond to innocuous stimuli applied to hairy or glabrous skin (Uddenberg, 1968a, 1968b; Brown and Fyffe, 1981; Brown *et al.*, 1983, 1986b). Input from glabrous skin distinguishes these cells from cells of the spinocervical system which rarely, if ever, receive glabrous input. As many as half of the cells, however, respond to noxious cutaneous and deep stimuli as well and thus should be classified as wide dynamic range cells (Bennett *et al.*,

1984), the input apparently coming from A δ nociceptive fibers (Kamogawa and Bennett, 1986). A few of the cells are high-threshold cells and respond to noxious thermal and mechanical stimuli (Noble and Riddell, 1988). In monkeys the cells can also be classified as primarily wide dynamic range cells, many of which receive input from visceral nociceptors (Al-Chaer *et al.*, 1999).

The axons of the postsynaptic dorsal column-projecting cells give off local collaterals and enter the ipsilateral dorsal column directly. In cats the axons have conduction velocities of 38–55 m/s. Fibers from the lumbar region terminate in the gracile nucleus (Rustioni *et al.*, 1979) and those from the cervical region terminate in the cuneate and external cuneate nuclei (Cliffer and Willis, 1994). The principal sites of termination in the gracile and cuneate nuclei are the pars rotunda and pars triangularis. It is probable that wide dynamic range cells recorded in the dorsal column nuclei of cats and monkeys are innervated by these fibers (Angaut-Petit, 1975a, 1975b; Ferrington *et al.*, 1988; Cliffer *et al.*, 1992). The postsynaptic dorsal column pathway and its relay in the gracile nucleus appear to be critically concerned in the relay of pelvic visceral sensations to the thalamus (Al-Chaer *et al.*, 1996a, 1996b, 1997a, 1997b, 1998).

Certain other fibers ascending in the dorsal part of the lateral funiculus also terminate in the dorsal column nuclei (Rustioni *et al.*, 1979). It is thought that these are fibers that arise from cells of the postsynaptic dorsal column system and these cells may even have branches ascending both in the dorsal columns and in the dorsolateral funiculus (Willis and Coggeshall, 2004).

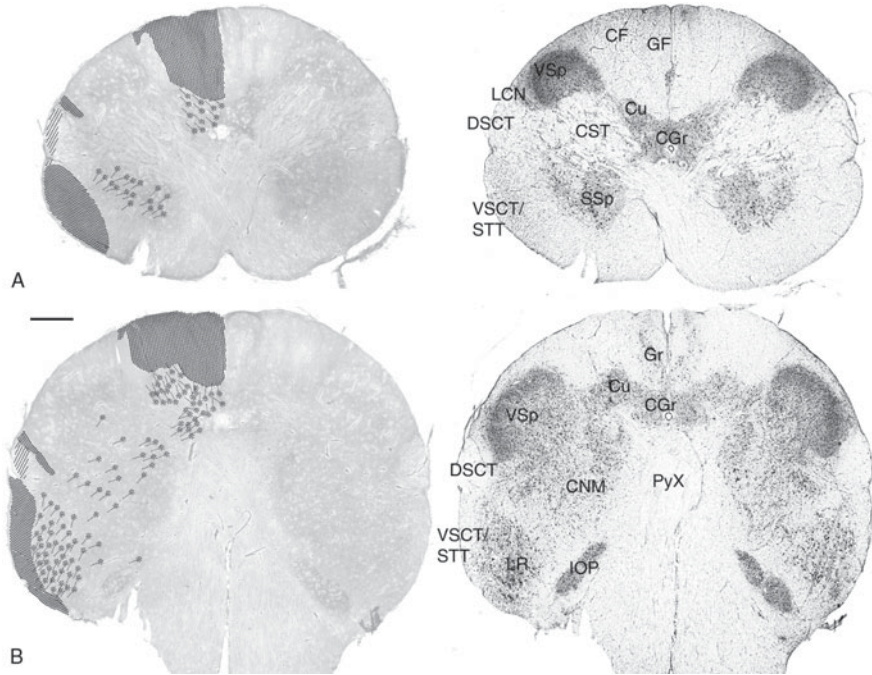
Terminations within the brainstem

Reticular formation

Fibers forming what has been loosely called the “spinoreticular tract” largely ascend with the spinothalamic fibers in the anterolateral funiculus (Mehler *et al.*, 1960; Fig. 2.16) and, judged by what is left by the time the anterolateral fiber system reaches the thalamus, far outnumber the spinothalamic fibers. Although it has been widely believed from the earliest times (Chapter 1) that the spinoreticular pathway was the first step in a pathway that ultimately reached the thalamus after a relay in the reticular formation, this belief can now be discounted, at least for the cat (Blomqvist and Berkley, 1992). Although it is true that certain groups of brainstem neurons among which spinoreticular fibers terminate, project axons up to the thalamus, the terminations of spinoreticular fibers are far more widespread than these groups of cells and engage many other cell groups that have no ascending projections to the thalamus.

Certain brainstem nuclei that receive spinoreticular fibers, for example the inferior olivary complex and the lateral reticular nucleus, are precerebellar relay

Part 1



Part 2

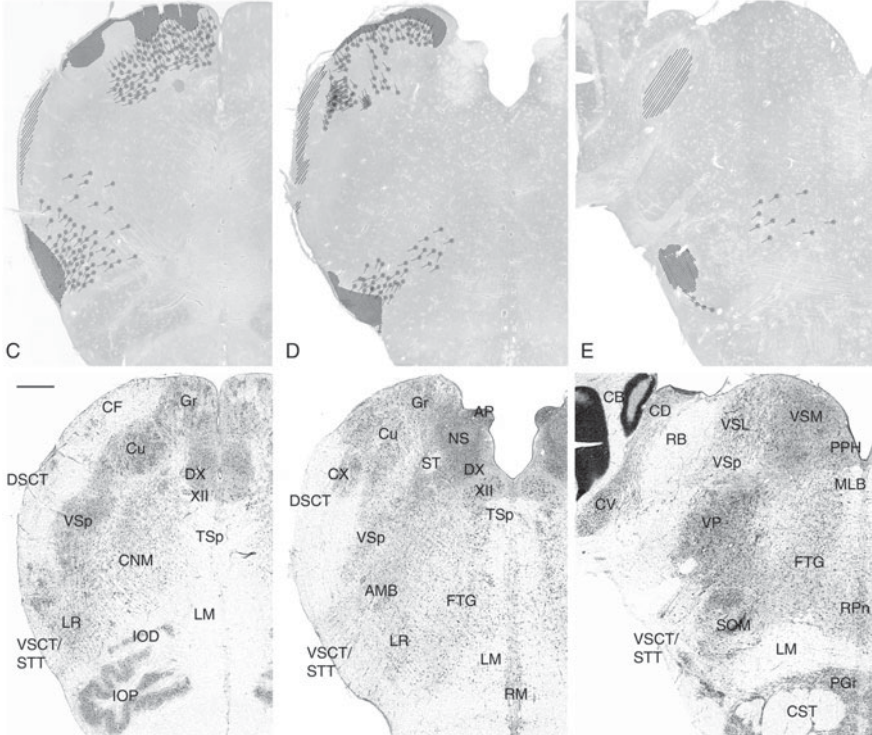
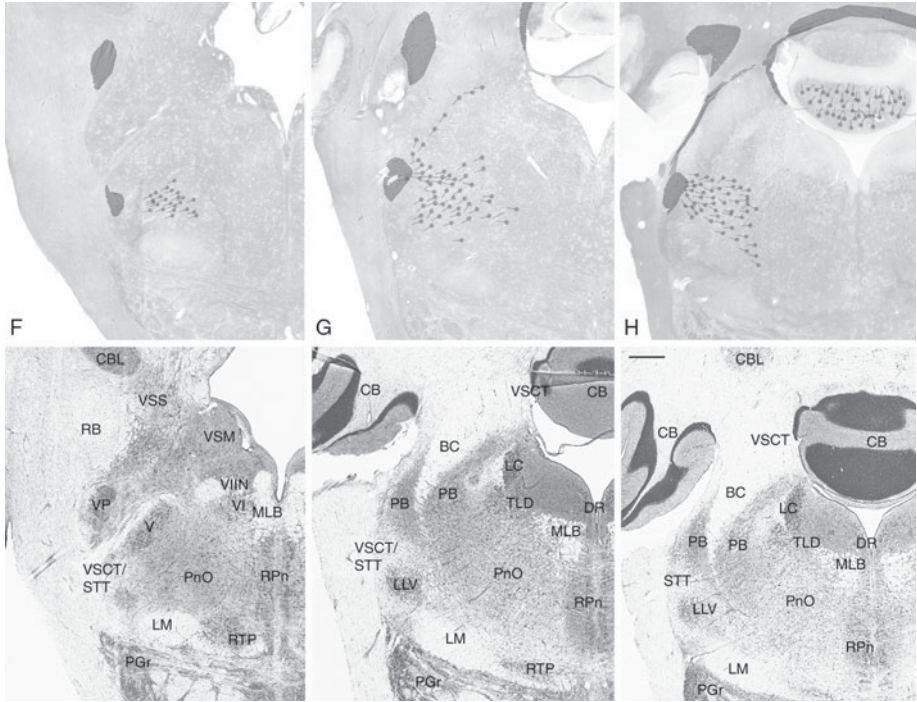


Fig. 2.16. (cont.)

Part 3



Part 4

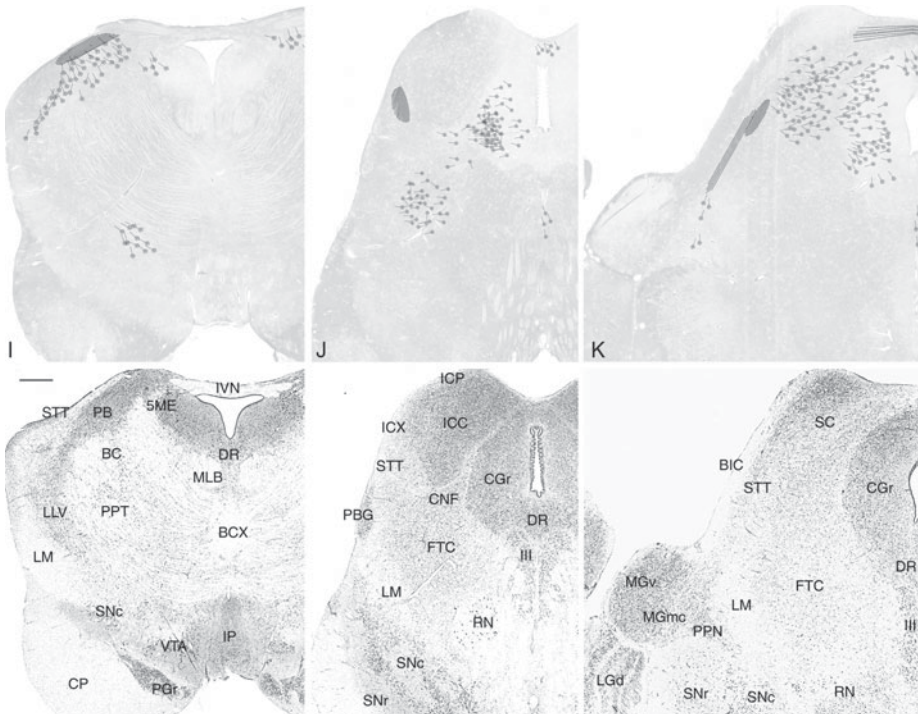


Fig. 2.16. (cont.)

Part 5

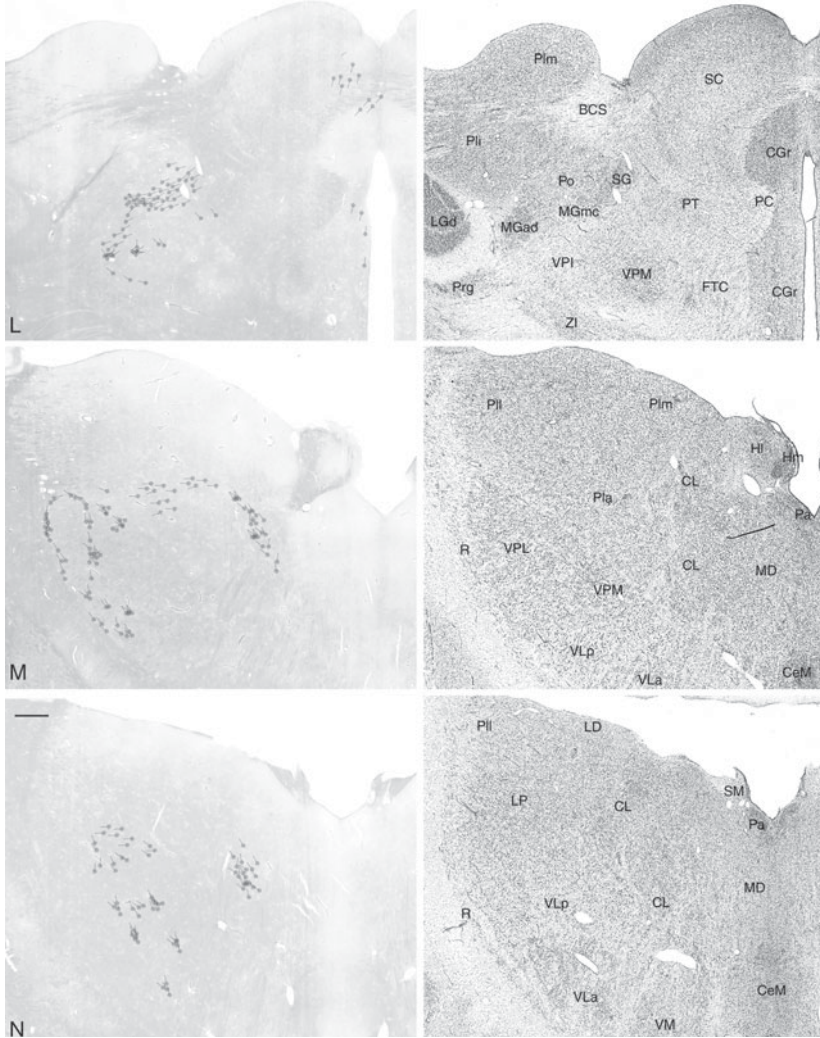


Fig. 2.16. Parts 1–5. Pairs of adjacent sections cut in a plane at right angles to the axis of the brainstem of a monkey in which the spinal cord was hemisected at the C2–3 segments 14 days previously. On the left or upper parts of each figure, the locations of stained degenerating fibers and terminal ramifications in the brainstem and diencephalon have been plotted on reduced contrast images of Nauta-stained sections. (Degenerating fibers: hatching; degenerating terminations: rosettes). The adjacent, Nissl-stained sections show the locations of principal fiber tracts and cellular aggregations. Bars: 1 mm. From an unpublished experiment of E. G. Jones and W. D. Willis Jr. For a complete set of images from this brain, see www.brainmaps.org. AMB, nucleus ambiguus; AP, area postrema; BC, brachium conjunctivum; BCS, brachium of superior colliculus; BCX, decussation of brachium conjunctivum; BIC, brachium of inferior colliculus; CB, cerebellum; CBL, lateral cerebellar nucleus; CD, dorsal cochlear nucleus; CeM, central medial nucleus of thalamus; CF, cuneate

nuclei and will not be considered further. Others, located primarily in the medial ponto-medullary reticular formation and receiving an input from the spinal cord that is both dense and widespread, are the sources of fiber systems that both descend to the spinal cord or ascend to higher brainstem and forebrain sites. It is these with which we shall be mostly concerned. In general, the named

Caption for Fig. 2.16. (*cont.*)

fasciculus; CGr, central gray matter; CL, central lateral nucleus of thalamus; CNF, cuneiform nucleus; CNM, central nucleus of medulla oblongata; CP, cerebral peduncle; CST, corticospinal tract; Cu, cuneate nucleus; CV, ventral cochlear nucleus; CX, external cuneate nucleus; DR, dorsal raphe; DSCT, dorsal spinocerebellar tract; DX, dorsal nucleus of vagus nerve; FTC, central tegmental field; FTG, gigantocellular reticular field; GF, gracile fasciculus; Gr, gracile nucleus; HL, lateral habenular nucleus; Hm, medial habenular nucleus; ICC, central nucleus of inferior colliculus; ICP, pericentral nucleus of inferior colliculus; ICX, external nucleus of inferior colliculus; III, oculomotor nucleus; IOD, dorsal inferior olivary nucleus; IOP, principal inferior olivary nucleus; IP, interpeduncular nuclei; IVN, trochlear nerve; LC, locus coeruleus; LCN, lateral cervical nucleus; LD, lateral dorsal nucleus; LGd, dorsal lateral geniculate nucleus; LLV, ventral nucleus of lateral lemniscus; LM, medial lemniscus; LP, lateral posterior nucleus of thalamus; LR, lateral reticular nucleus; MD, mediodorsal nucleus of thalamus; MGad, anterodorsal medial geniculate nucleus; MGmc, magnocellular medial geniculate nucleus; MGv, ventral medial geniculate nucleus; MLB, medial longitudinal bundle; NS, nucleus of solitary tract; Pa, paraventricular nucleus of thalamus; PB, parabrachial nuclei; PBG, parabigeminal nucleus; PC, posterior commissure; PGr, pontine gray matter; Pla, anterior pulvinar nucleus; Pli, inferior pulvinar nucleus; PlI, lateral pulvinar nucleus; Plm, medial pulvinar nucleus; PnO, oral pontine reticular formation; Po, posterior nucleus of thalamus; PPH, nucleus prepositus hypoglossi; PPN, peripeduncular nucleus; PPT, pedunculo-pontine tegmental nucleus; Prg, pregeniculate nucleus; PT, pretectal nuclei; PyX, pyramidal decussation; R, reticular nucleus of thalamus; RB, restiform body; RM, raphe magnus; RN, red nucleus; RPn, pontine raphe; RTP, reticulotegmental pontine nucleus; SC, superior colliculus; SG, suprageniculate nucleus; SM, stria medullaris; SNc, pars compacta or substantia nigra; SNr, pars reticulata of substantia nigra; SOM, medial superior olivary nucleus; SSp, supraspinal nucleus; ST, solitary tract; STT, spinothalamic tract; TLD, laterodorsal tegmental nucleus; TSp, tectospinal tract; V, motor trigeminal nucleus; VI, abducens nucleus; VIIN, facial nerve; VLp, ventral lateral posterior nucleus of thalamus; VLs, ventral lateral anterior nucleus of thalamus; VM, ventral medial nucleus of thalamus; VP, principal trigeminal sensory nucleus; VPI, ventral posterior inferior nucleus of thalamus; VPL, ventral posterior lateral nucleus of thalamus; VPM, ventral posterior medial nucleus of thalamus; VSCT, ventral spinocerebellar tract; VSL, lateral vestibular nucleus; VSM, medial vestibular nucleus; VSp, spinal trigeminal nucleus; VSS, superior vestibular nucleus; VTA, ventral tegmental area; XII, hypoglossal nucleus; ZI, zona incerta; 5ME, mesencephalic trigeminal nucleus.

nuclei of the medial reticular formation that receive spinoreticular terminations were accurately identified by Mehler *et al.* in 1960 (Chapter 1). Among them, the most significant as confirmed in subsequent studies are (Fig. 2.16): the central nucleus of the medulla oblongata, the gigantocellular reticular nucleus, the dorsal and lateral paragigantocellular nuclei, the caudal and oral pontine reticular nuclei, the subcoeruleus nucleus and the parabrachial nucleus. Some of these reticular formation neurons may help signal pain, but others are more likely to modulate pain signals, often by projections that descend into the spinal cord.

In monkeys, most neurons projecting to the medial pontomedullary reticular formation are located in lamina VII of the spinal gray matter, although a few can be found in more superficial layers as well (Kevetter *et al.*, 1982). Projecting cells are located on both sides but the majority project contralaterally. They are large cells with extensive dendritic fields. Their numbers are significantly fewer than those of spinothalamic cells. The axons are myelinated and conduct at a rate of 9–54 m/s (Haber *et al.*, 1982). Because some of the cells can be antidromically activated by stimulation of both the thalamus and the reticular formation, it is apparent that they project by branched axons to both sites (Giesler *et al.*, 1981; Haber *et al.*, 1982).

Many spinoreticular neurons cannot be activated by natural stimuli applied to the skin or other tissues. Others are wide dynamic range neurons with cutaneous and occasionally visceral receptive fields. The remainder consists of cells with low-threshold cutaneous receptive fields, with receptive fields in muscle and other deep tissues, or with complex convergent receptive fields (Haber *et al.*, 1982; Hobbs *et al.*, 1990).

Midbrain

The principal midbrain sites of termination of fibers ascending from the spinal cord and spinal trigeminal nucleus in monkeys are the tectum and its environs, the periaqueductal gray matter and the parabrachial nuclear complex as it extends into the midbrain (Fig. 2.16). Specific nuclei in and around the tectum include the deep layers of the superior colliculus, the nucleus cuneiformis and the intercollicular region. Other nuclei of termination are the nucleus of Darkschewitsch, interstitial nucleus of Cajal, anterior and posterior pretectal nuclei and the nucleus of Edinger and Westphal (Mehler *et al.*, 1960; Mehler, 1969; Kerr, 1975a, 1975b; Wiberg *et al.*, 1987). The terminations are bilateral but heaviest ipsilateral to the side of the spinal cord and medulla through which the fibers ascend.

Wiberg *et al.* (1987) have calculated that there may be as many as 10,000 neurons in the monkey spinal cord that project to the midbrain. Retrograde labeling studies reveal many of the projecting cells to be located in lamina I with others in laminae IV–VII, mostly contralateral to the site of an injection of tracer

in the midbrain (Trevino *et al.*, 1973; Willis *et al.*, 1979; Wiberg *et al.*, 1987). Of cells projecting to the periaqueductal gray matter, both those located in lamina I and in deeper layers of the dorsal horn project to lateral parts, while only those located in deeper laminae project to medial parts (Mantyh, 1982). Some project by branched axons to the midbrain and thalamus (Price *et al.*, 1978; Yeziarski *et al.*, 1987). The mean conduction velocity of these axons is 47.8 m/s. The parent cells have receptive fields and stimulus-response characteristics that enable them to be classified as low-threshold, nociceptive-specific and wide dynamic range neurons (Yeziarski *et al.*, 1987).

Studies in rats indicate that the axons of lamina I cells projecting to the midbrain ascend in the dorsolateral funiculus while those of deeper layer cells ascend via the anterolateral funiculus (McMahon and Wall, 1983; Baker and Giesler, 1984) (see Fig. 2.13B). Those terminating in the parabrachial nucleus contain dynorphin or enkephalin (Standaert *et al.*, 1986).

The inputs to the parabrachial nucleus can be considered to form part of the visceral afferent system that relays in this extensive nuclear complex located in the rostral pons (Saper, 1995, 2002). Other inputs to the parabrachial complex include those derived from gustatory and visceral systems of the brainstem. Large parts of the parabrachial complex in rats project to the intralaminar and medioventral nuclei of the dorsal thalamus and to the paraventricular nuclei of the epithalamus; the specific regions receiving spinal and brainstem inputs and apparently concerned with gustatory, visceral and possibly nociceptive functions (Ogawa *et al.*, 1987; Slugg and Light, 1994; Bernard *et al.*, 1995; Bester *et al.*, 1995; Menendez *et al.*, 1996) project to the basal ventral medial nucleus (VMb) of the dorsal thalamus (Fig. 2.17D–G) (Saper and Loewy, 1980; Bester *et al.*, 1999; Krout and Loewy, 2000; Krout *et al.*, 2002). The fibers ending in the basal ventral medial nucleus of the rat are associated with calcitonin gene-related peptide immunoreactivity (Kruger *et al.*, 1988a, 1988b; Yasui *et al.*, 1989; Williamson and Ralston, 1993; de Lacalle and Saper, 2000; Saper, 2002). The VMb nucleus (parvocellular division of the VPM nucleus in older terminologies; Chapter 1) of the rat is divided into a medial division which is the primary terminus of second-order taste afferents and a lateral division that is innervated by visceral afferents carrying information from cardiac, arterial and gastric baroreceptors, chemoreceptors and mechanoreceptors (Cechetto and Saper, 1987). Many of these afferents may form part of the spinothalamic and spinal trigeminothalamic pathways whose diffuse patches of terminations in all mammals extend from VPI and adjacent nuclei into VMb (Craig and Burton, 1985; Iwata *et al.*, 1992; Rausell *et al.*, 1992a; Apkarian and Shi, 1994; Craig, 2003; Graziano and Jones, 2004; Jones, 2007) but the predominant inputs may come from the parabrachial complex. In monkeys, the VMb nucleus is divided into an anterior non-gustatory

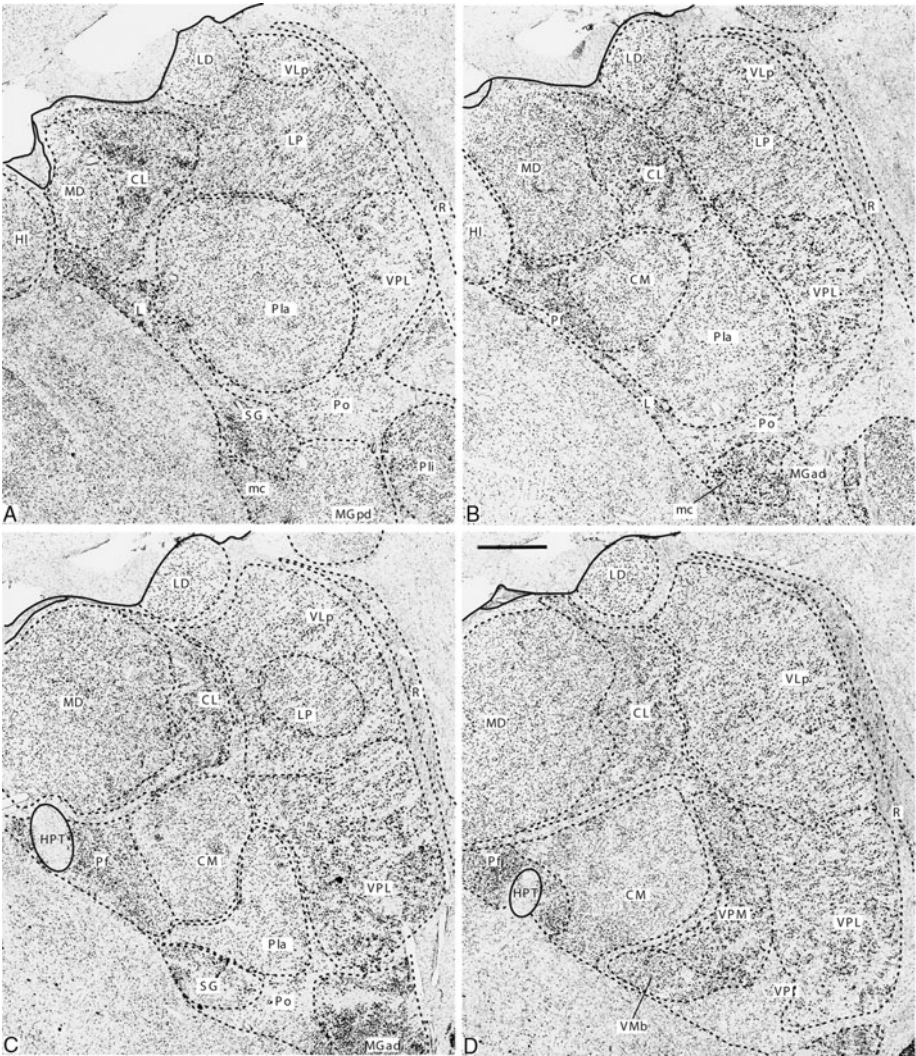


Fig. 2.17. (cont.)

division and a posterior gustatory division (Pritchard *et al.*, 2000). Neurons in the VMb region show convergent cutaneous, muscular and noxious visceral inputs (Monconduit *et al.*, 2003).

Hypothalamus

Nearly all studies of spinohypothalamic projections have been carried out in rats. Most projecting neurons are found in deeper laminae of the dorsal horn but a few have been described in lamina I as well, mostly contralaterally

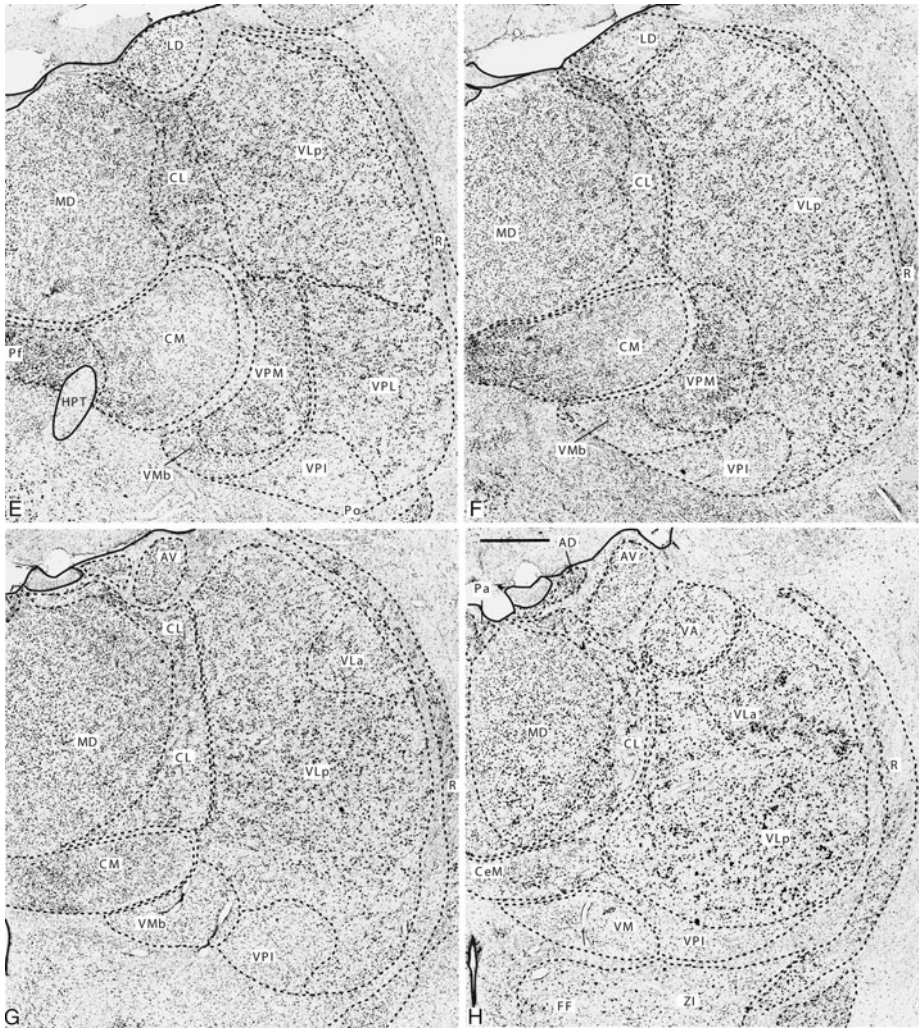


Fig. 2.17. Photomicrographs of Nissl-stained frontal sections in posterior (A) to anterior (H) order through the ventral nuclei of a macaque monkey, upon which have been superimposed the outlines of the nuclei. Bar: 0.5 mm. Modified from Jones (2007).

(Burstein *et al.*, 1990; Katter *et al.*, 1991). The sites of termination have not been accurately defined; some clearly target the zona incerta of the ventral thalamus rather than the hypothalamus proper (Boivie, 1979; Berkley, 1980; Ma *et al.*, 1992). Some of these may have branched axons to the thalamus and hypothalamus (Zhang *et al.*, 1995). The cells of origin, in monkeys and rats, include low-threshold, wide dynamic range and a few nociceptive-specific types; some have visceral inputs (Zhang *et al.*, 1999, 2002).

Terminations within the thalamus

Architectonics of primate thalamic nuclei

Major divisions of the ventral nuclear mass

Nissl and histochemically stained preparations of the primate thalamus give a delineation of the three major, large divisions of the ventral nuclei that is clear in Old World monkeys but even clearer in humans (Figs 1.30, 2.17–2.23). From posterior to anterior (Fig. 2.17A–H), these principal nuclear masses are the ventral posterior (VP), ventral lateral (VL) and ventral anterior (VA) nuclei, each of which has further subdivisions. A ventral medial division (VM) is less well-defined. Experimental studies in monkeys show that these nuclei contain the principal thalamic relays for the medial lemniscus, deep cerebellar nuclei, globus pallidus and substantia nigra (Percheron, 1977; Tracey *et al.*, 1980; De Vito and Anderson, 1982; Asanuma *et al.*, 1983a, 1983b; Goldman-Rakic *et al.*, 1985; Alexander *et al.*, 1986; Ilinsky and Kultas-Ilinsky, 1987; Jones, 1987, 2007; Percheron *et al.*, 1993; Rouiller *et al.*, 1994; Sakai *et al.*, 1996). Terminations of spinothalamic fibers can be found in the ventral posterior and ventral lateral nuclei.

The ventral posterior nucleus is a nuclear complex made up of two principal divisions, the ventral posterior medial (VPM) and ventral posterior lateral (VPL) nuclei which are the targets of the trigeminal and medial lemnisci respectively (Fig. 2.22). Within it are two subsidiary divisions, the ventral medial basal (VMb) and ventral posterior inferior (VPI) nuclei. The ventral lateral nucleus is divided into posterior (VLp) large-celled and anterior (VLa) small-celled divisions that are the principal terminal regions for the cerebellothalamic and pallidothalamic projections respectively (reviewed in Jones, 2007). The ventral anterior nucleus is divided into a very clear cut magnocellular (VAmc) division closely associated with the intralaminar complex, and a less well-defined smaller-celled principal division (VA) which with the also ill-defined principal ventral medial nucleus (VMp) is associated with the terminations of nigrothalamic fibers (Jones, 2007).

The ventral posterior complex

The ventral posterior nucleus is one of the most clearly defined nuclei of the thalamus because of the large size and dense staining of its constituent cells, and because of the lobulated appearance imposed on it by penetrating bundles of myelinated fibers (Figs 2.17–2.29). It is divided by a distinct medullary lamina, the *arcuate lamella*, into cytoarchitectonically distinct ventral posterior medial (VPM) and ventral posterior lateral (VPL) subnuclei, representing the termini of the trigeminal and medial lemnisci respectively. The ventral posteromedial

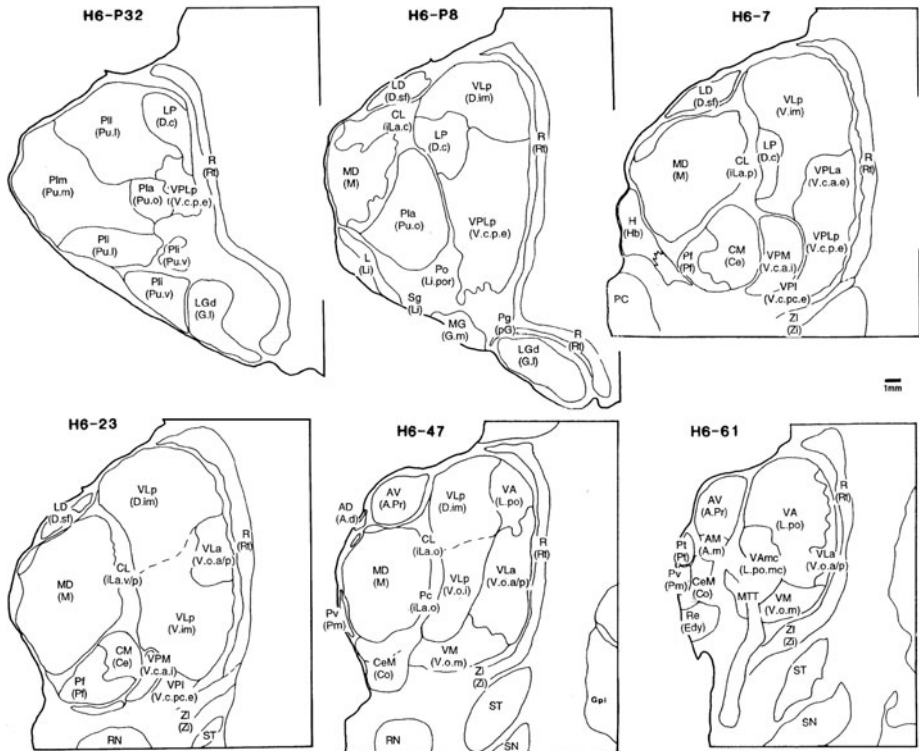


Fig. 2.18. A series of camera lucida drawings of frontal sections through the human thalamus in posterior (top left) to anterior (lower right) order, with nuclei indicated by the current terminology and with Hassler's (1959) terminology in parentheses. Based on Hirai and Jones (1989a). Bar: 1 mm.

nucleus (VPM) tends to be composed of somewhat smaller, relatively closely packed cells, and the ventral posterolateral (VPL) nucleus of larger cells, arranged in clusters.

The ventral posterior complex as a whole stretches latero-medially from the external medullary lamina to the internal medullary lamina, and has a tapering posterior pole in close proximity to the medial geniculate complex (Fig. 2.17A). In primates, VPL is larger than VPM on account of the larger representations of the hands and feet, and extends more posteriorly than VPM. Posteriorly, islands of its cells tend to be split off from the main nucleus and invade the posterior nucleus (Po). Here, they can be recognized by their larger size and deeper staining.

The ventral posterior complex is more extensive than the combined VPM and VPL nuclei, as they are outlined by the terminations of the trigeminal and medial lemnisci and by their particular cytoarchitectures. In Nissl-stained preparations, and especially in histochemically or immunocytochemically stained

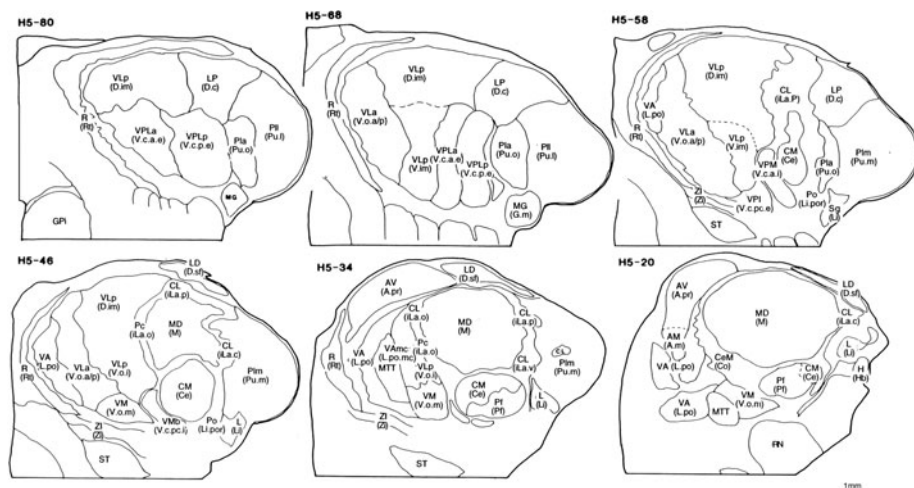


Fig. 2.19. A series of camera lucida drawings of sagittal sections through the human thalamus in medial (top left) to lateral (lower right) order, with nuclei indicated by the current terminology and with Hassler's (1959) terminology in parentheses. Based on Hirai and Jones (1989a). Bar: 1 mm.

preparations (Figs 2.20, 2.21, 2.29), the ventral posterior nuclear complex as a whole is outlined by a thin unstained fiber rim. Within the complex, in addition to VPL and VPM, there are two zones of smaller cells distinguished by weak cytochrome oxidase staining and by intense immunostaining for 28 kDa calbindin (Figs 2.21, 2.29). One, extending medially from the medial tip of the VPM nucleus and undershooting the centre médian nucleus, is characterized by closely packed small to medium sized neurons. It represents the thalamic terminus for taste and other visceral afferents and is relatively large, approximately half the extent of VPM in the monkey and slightly less in the human. In the past this small-celled nucleus was called the parvocellular division of the VPM nucleus (Olszewski, 1952), but it has come to be called the basal ventral medial nucleus (VMb) (Jones, 1985, 2007). It is approximately the same as Hassler's nucleus ventrocaudalis parvocellularis internus (V.c.pc.i) (Figs 2.18, 2.19). A further small-celled subnucleus contained within the larger ventral posterior complex is dominated by neuroglial cells but contains many small neurons as well, all of which, like VMb, stain intensely for calbindin (Figs 2.21, 2.29). It is called the ventral posterior inferior nucleus (VPI) and is the zone traversed by the medial lemniscus and the brachium conjunctivum as they enter the thalamus. It lies on the external medullary lamina in the angle between the ventral aspects of the VPL and VPM nuclei and is continuous with the basal ventral medial nucleus along the surface of the lamina. It is deeply invaded by large cells of the VPL nucleus. The VPI nucleus is

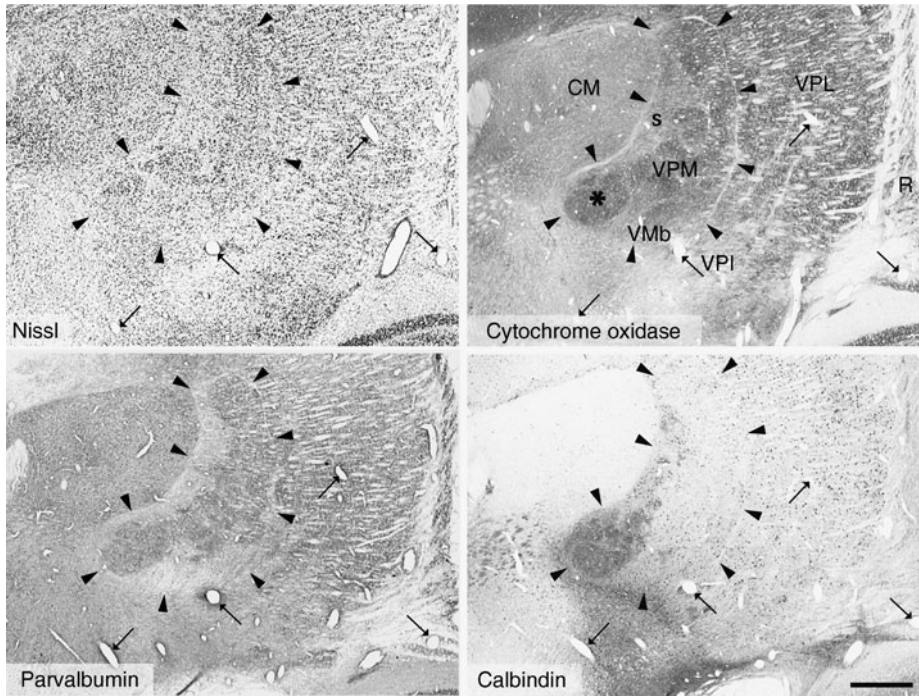


Fig. 2.20. Adjacent frontal sections through the ventral posterior complex of a macaque monkey, stained with thionin (Nissl), for cytochrome oxidase or immunocytochemically for parvalbumin or 28 kDa calbindin. Arrows indicate profiles of the same blood vessels. Arrowheads indicate the thin fiber lamina that outlines the VPM nucleus. Heavy cytochrome oxidase staining and parvalbumin immunostaining generally coincide and tend to be complementary to weak calbindin immunostaining. Asterisk indicates medial rods of VPM in which, uncharacteristically, heavy cytochrome oxidase, parvalbumin and calbindin immunostaining coincide. Bar: 1 mm. From Graziano and Jones (2004).

approximately the same as Hassler's nucleus ventralis caudalis parvocellularis externus (V.c.pc.e) (Fig. 2.30).

Anterior and posterior divisions of VPL

Physiologically, in monkeys, the VPL nucleus can be divided into a thin, anterodorsally located shell region in which neurons respond to movements of joints, stretching of tendons and manipulation of muscle bellies (Fig. 2.22), and a more extensive, central "core" region in which neurons respond at low threshold to various forms of cutaneous stimulation (Jones *et al.*, 1982; Kaas *et al.*, 1984). The segregation of neurons with deep or cutaneous receptive fields within the anterodorsal shell and cutaneous core, respectively, implies that terminations of lemniscal fibers arising from different divisions of the dorsal column nuclei have segregated terminations within the shell and core.

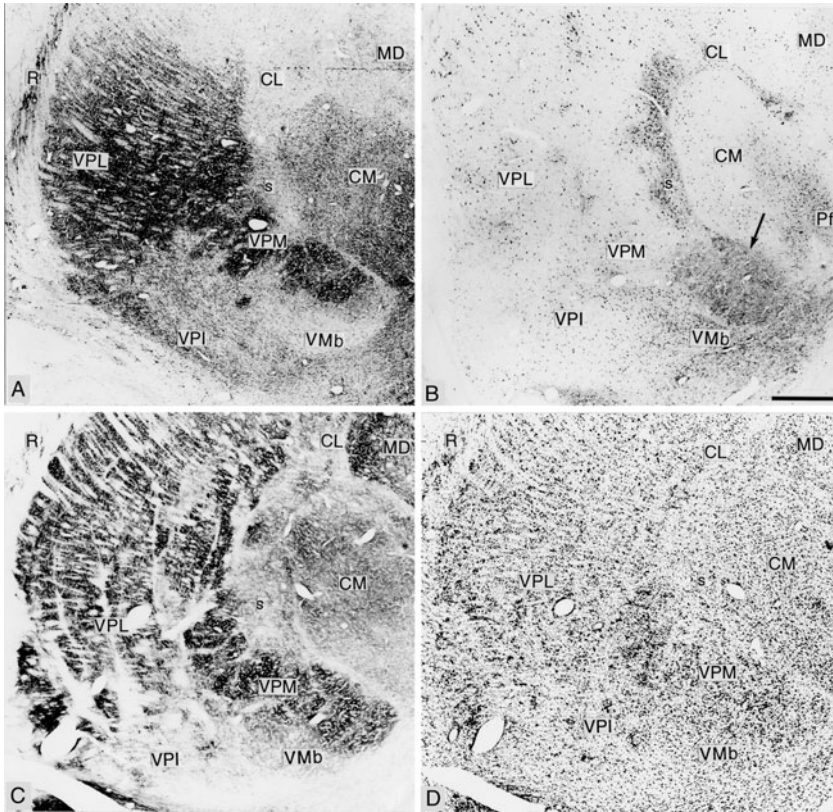


Fig. 2.21. Adjacent frontal sections through the ventral posterior complex of a rhesus monkey, stained immunocytochemically for parvalbumin (A), calbindin (B), for cytochrome oxidase activity (C) or with the Nissl stain (D). Arrow in B indicates the medialmost rods of VPM cells in which parvalbumin and calbindin immunoreactivity coincide. Elsewhere, parvalbumin and calbindin immunoreactivity tends to be complementary. Note especially the VPI and VMb nuclei. Bar: 500 mm. Based on Rausell and Jones (1991a).

In monkeys there is no consistent anatomical distinction between the anterodorsal “deep” shell of VPL and its central “cutaneous” core (Figs 2.22, 2.23). The shell, however, tends to have rather more large neurons than the core in which the population tends to consist of a mixture of both large and smaller neurons. Kaas *et al.* (1984) and Krubitzer and Kaas (1992) have referred to the shell in New World monkeys as a ventral posterior superior nucleus but the cytoarchitecture is not sufficiently clear-cut in monkeys to warrant such a distinction. However, in the human thalamus there is a much more clear-cut cytoarchitectonic differentiation of the shell and core into separate subnuclei (Figs 2.19, 2.23). The anterodorsal shell is made up of neurons that do not greatly differ in size from the larger neurons of the core but the shell lacks the second smaller population

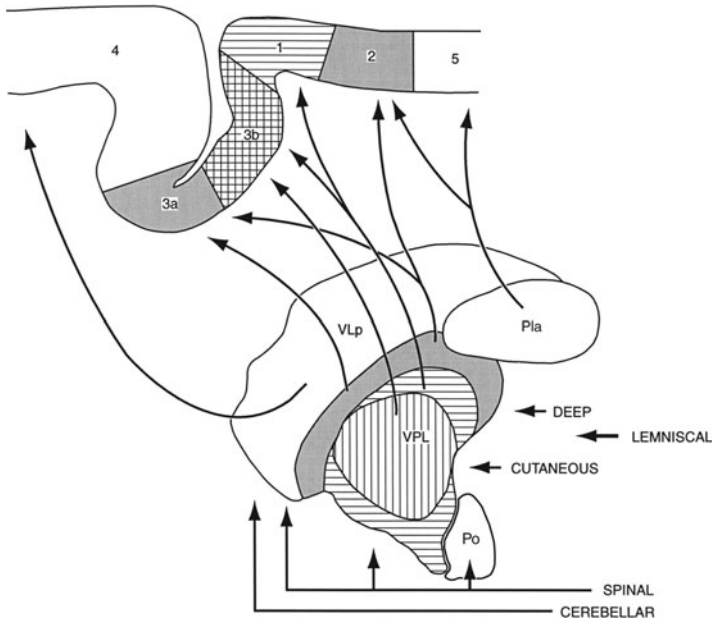


Fig. 2.22. Schematic sagittal section showing the input-output relationships of the deep shell and cutaneous core of the ventral posterior nucleus and of the adjacent VLp and Pla nuclei in primates. Based on Jones and Friedman (1982).

that also inhabits the core. On these grounds the shell was termed *nucleus ventrocaudalis anterior externus* (V.c.a.e) by Hassler (1959) or the *anterior division of the ventral posterior lateral nucleus* (VPLa) by Hirai and Jones (1989a), and the larger core was termed *nucleus ventrocaudalis posterior externus* (V.c.p.e) by Hassler (1959) or the *posterior division of the ventral posterior lateral nucleus* (VPLp) by Hirai and Jones (1989a) (Figs 1.30, 2.18, 2.19, 2.23). In humans, as in monkeys, cells responding to movements of joints and/or deep pressure are mainly found in the shell (in VPLa), anterodorsal to those responding to light cutaneous stimuli (in VPLp) (Friedman and Jones, 1981; Jones *et al.*, 1982; Lenz *et al.*, 1988, 1994a).

There are insufficient data to determine if the division of the VPL nucleus into an anterodorsal deep shell and a cutaneous core is also present in VPM. In the human, Hassler (1959) described anterior and posterior divisions of VPM (his V.c.i), which he called *nucleus ventrocaudalis internus anterior* (V.c.a.i) and *nucleus ventrocaudalis posterior internus* (V.c.p.i) but mainly by analogy with his divisions of VPL (his V.c.e).

Nuclei anterior to the ventral posterior complex

The border between the VPLa nucleus and the VLp nucleus is marked by a transition from mixed large and smaller cells and dense acetyl cholinesterase staining to one characterized by large cells and less dense histochemical staining. VLp is a large nucleus typically consisting of large, deeply staining cells

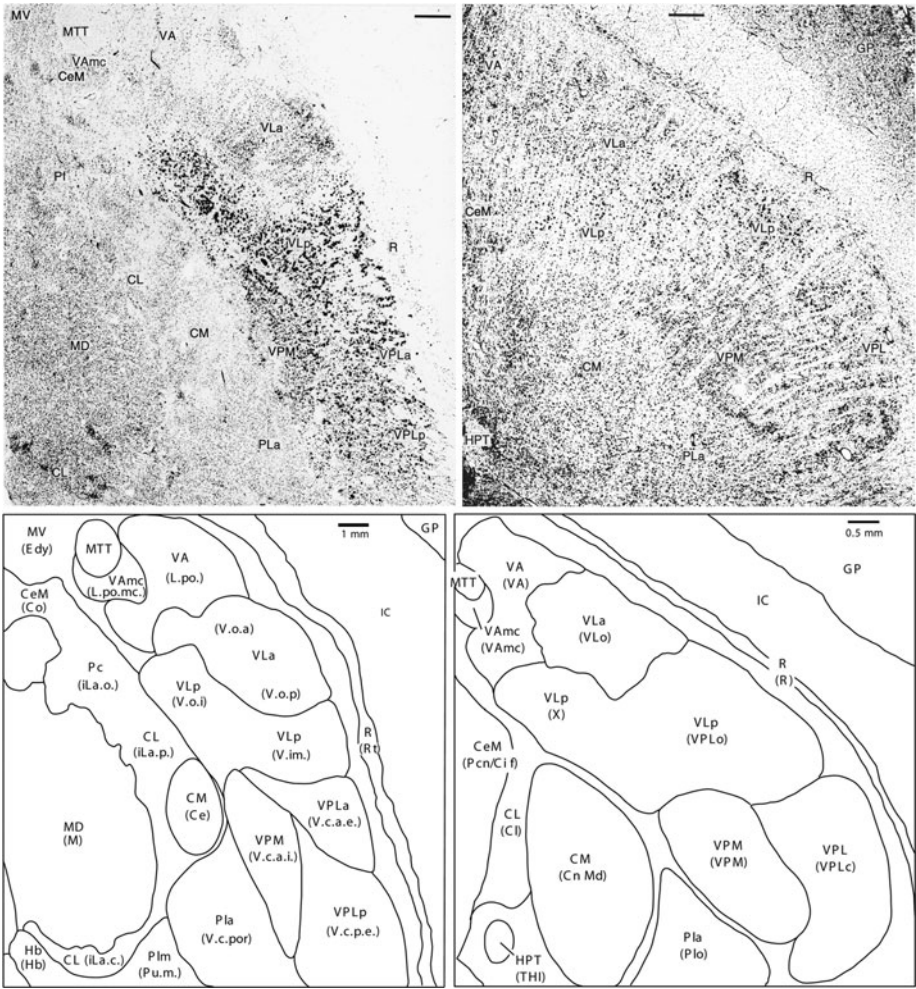


Fig. 2.23. (Upper left) Horizontal section through a human thalamus, stained with thionin, showing the major nuclei of the ventral nuclear group. Note how differences in cell size and packing density permit delineation of the borders of each nucleus. (Upper right) Horizontal section through the thalamus of a macaque monkey (*Macaca fascicularis*) at a comparable level thionin stain. Bars: 1 mm (left), 0.5 mm (right). (Lower left and right) Camera lucida drawings of the sections from which the above images were taken, showing the borders of the nuclei and with the addition of Hassler's (1959) (left) and Olszewski's (1952) (right) nomenclature (in parentheses). Based on Macchi and Jones (1997).

(Asanuma *et al.*, 1983a; Hirai and Jones, 1989a) (Figs 2.17E–H, 2.23) and weak acetyl cholinesterase activity. The ventral half of VLp, lying closely adjacent to VPLa, consists of very large, deeply stained cells, which are among the largest cells in the thalamus. This larger celled, ventral and posterior part of VLp was

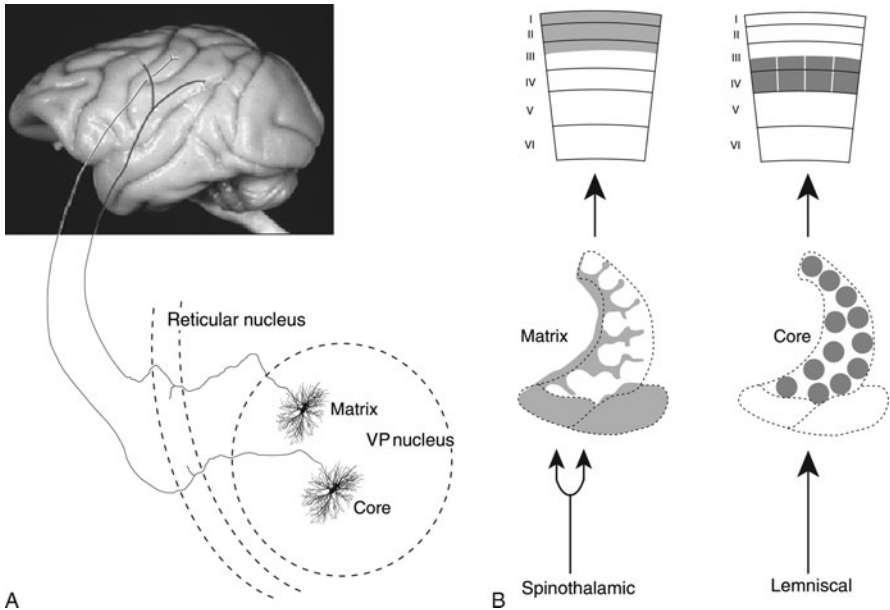


Fig. 2.24. The core and matrix of thalamic organization. (A) The two classes of relay cells with focused (core) and diffuse (matrix) projections upon the cerebral cortex. These cells, characterized by expression of parvalbumin and calbindin respectively in the primate thalamus, are found in the principal relay nuclei while matrix cells alone characterize many other nuclei. (B) The differential inputs and outputs of the core and matrix divisions of the thalamus. Inputs from the specific systems such as the lemniscal and optic tract pathways, carrying the content of a sensory or internally generated message, terminate in the core domain of the principal relay nuclei. This domain projects with a high degree of topographic order upon middle layers (IV and deep III) of a single cortical area. The afferent pathways less directly connected to the peripheral sense organs and perhaps carrying the context of a message, terminate in the matrix domain which projects more diffusely to superficial layers (I, II and superficial III) of more than one cortical area. From Jones (2007).

called VPLo by Olszewski (1952) in the monkey and nucleus ventrointermedius (V.im) by Hassler in the human (Fig. 2.19); this, Hassler divided further into medial (V.im.i) and lateral (V.im.e) subnuclei, with the addition of a transitional nucleus zentrolateralis intermedius (Z.im) along its dorsal border. In the middle of the thalamus, VLp comes to occupy the whole dorso-ventral extent of the lateral nuclear mass, extending back over the VP complex, and was called VLC by Olszewski, and he extended it posteriorly as nucleus VLps. The part of the human VLp, corresponding to Olszewski's VLC was called nucleus dorso-intermedius (D.im) by Hassler. VLps of Olszewski can be equated with Hassler's subnucleus dorso-intermedius externus magnocellularis (D.im.e.mc). Anteromedially, VLp

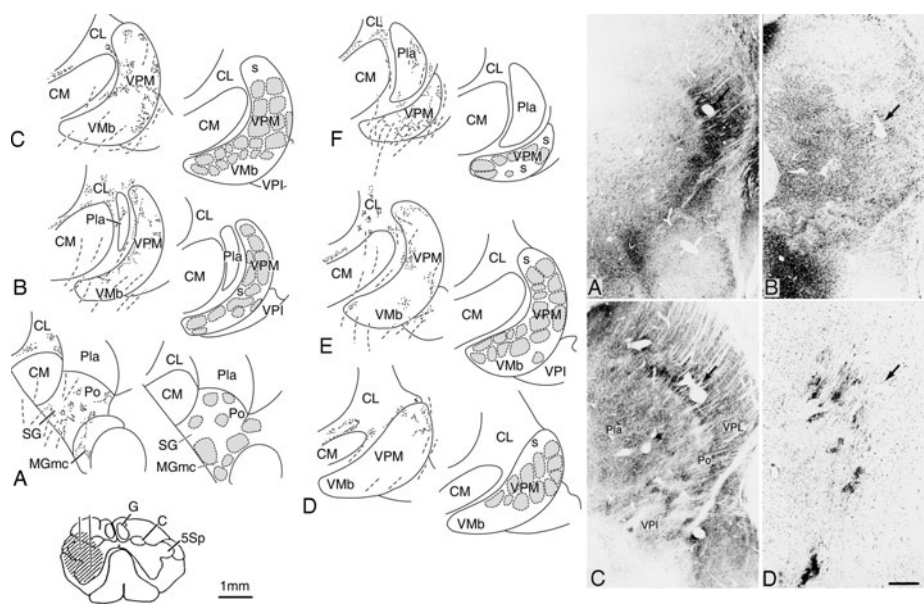


Fig. 2.25. (Left) Camera lucida drawings of pairs of frontal sections in posterior (A) to anterior (D) order, showing locations of anterogradely labeled terminal ramifications of spinal trigeminothalamic fibers (left member of each pair) in relation to the cytochrome oxidase stained rods (right member of each pair) in the VPM nucleus of a macaque monkey following injection of wheat germ agglutinin conjugated horseradish peroxidase at the spinomedullary junction (inset). Redrawn from Rausell and Jones (1991b). (Right) Photomicrographs of four adjacent frontal sections through the posterior part of the ventral posterior complex of a macaque monkey, stained immunocytochemically for parvalbumin (A) or calbindin (B), histochemically for cytochrome oxidase (C) or for the terminations of spinothalamic tract fibers anterogradely labeled with wheat germ agglutinin conjugated horseradish peroxidase (D). Arrow indicates profiles of the same blood vessel. Patches of spinothalamic tract terminals are concentrated in the calbindin-rich, parvalbumin- and cytochrome oxidase-weak matrix zone at the junction of the posterior nucleus (Po) and the ventral posterior complex. From Rausell *et al.* (1992a). Bar: 100 μ m.

forms a tongue-like extension anteromedial to VLa and lying along the internal medullary lamina; here it corresponds to Olszewski's area X in the monkey and to the nucleus ventro-oralis internus (V.o.i) of Hassler (Fig. 2.23).

VLa is characterized by small, densely stained and closely packed neurons grouped in islands separated by cell-sparse regions (Fig. 2.23), and shows heavy acetylcholinesterase staining (Jones, 1998a, 2007). It corresponds mainly to the anterior (V.o.a) subnucleus of Hassler's nucleus ventro-oralis (V.o). The posterior division (V.o.p) of Hassler corresponds to the region in which finger-like islands of VLa cells interdigitate with those of the more posterior VLp nucleus.

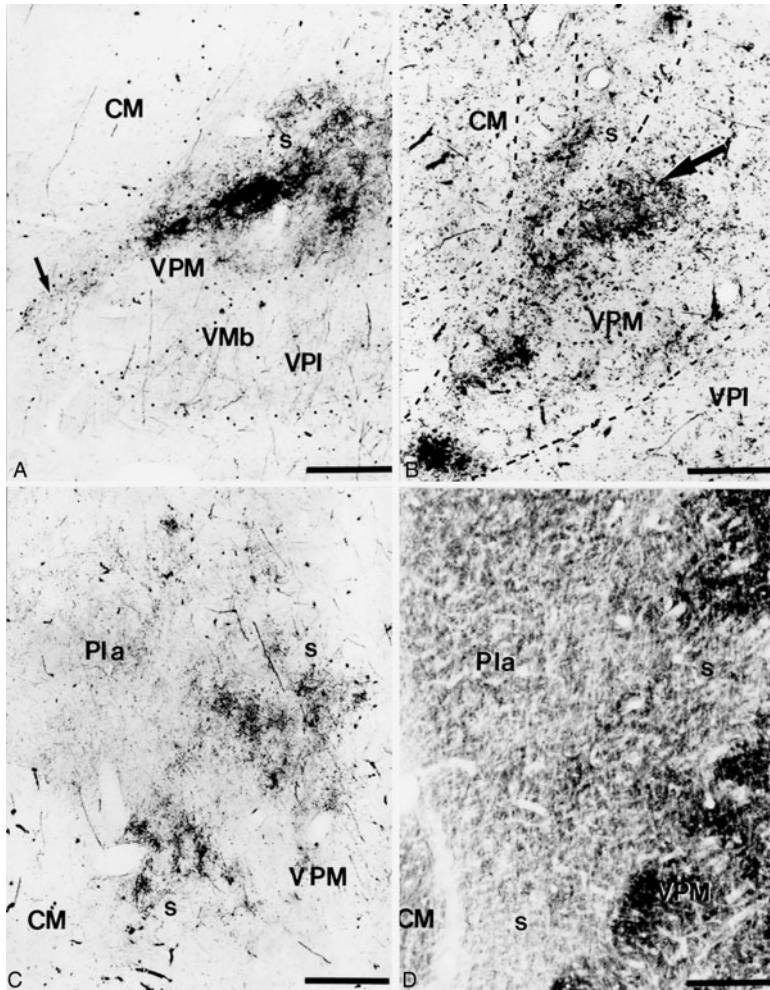


Fig. 2.26. A–C. Anterogradely labeled terminal ramifications of fibers emanating from the contralateral caudal nucleus of the spinal trigeminal complex and ending in relation to the matrix regions of VPM in a macaque monkey. A and C are uncounterstained; B is counterstained with thionin. Borders of nuclei are indicated in A and B by broken lines. D is a cytochrome oxidase stained section adjacent to C. Arrow in B indicates association of a cluster of terminations with the most dorsomedial rod of VPM. From Rausell and Jones (1991b). Bars: 150 μ m (A, C, D); 100 μ m (B).

VM lies ventromedial to VL_a (Fig. 2.17H). It has been given different names by different authors. Its relative position and its cyto- and chemoarchitecture are essentially the same as the nucleus ventro-oralis medialis (V.o.m) of Hassler in humans (Fig. 2.18).

The principal VA nucleus lies dorsolateral to VL_a and occupies the anterior pole of the ventral nuclear mass (Fig. 2.18). It is filled with dispersed, lightly

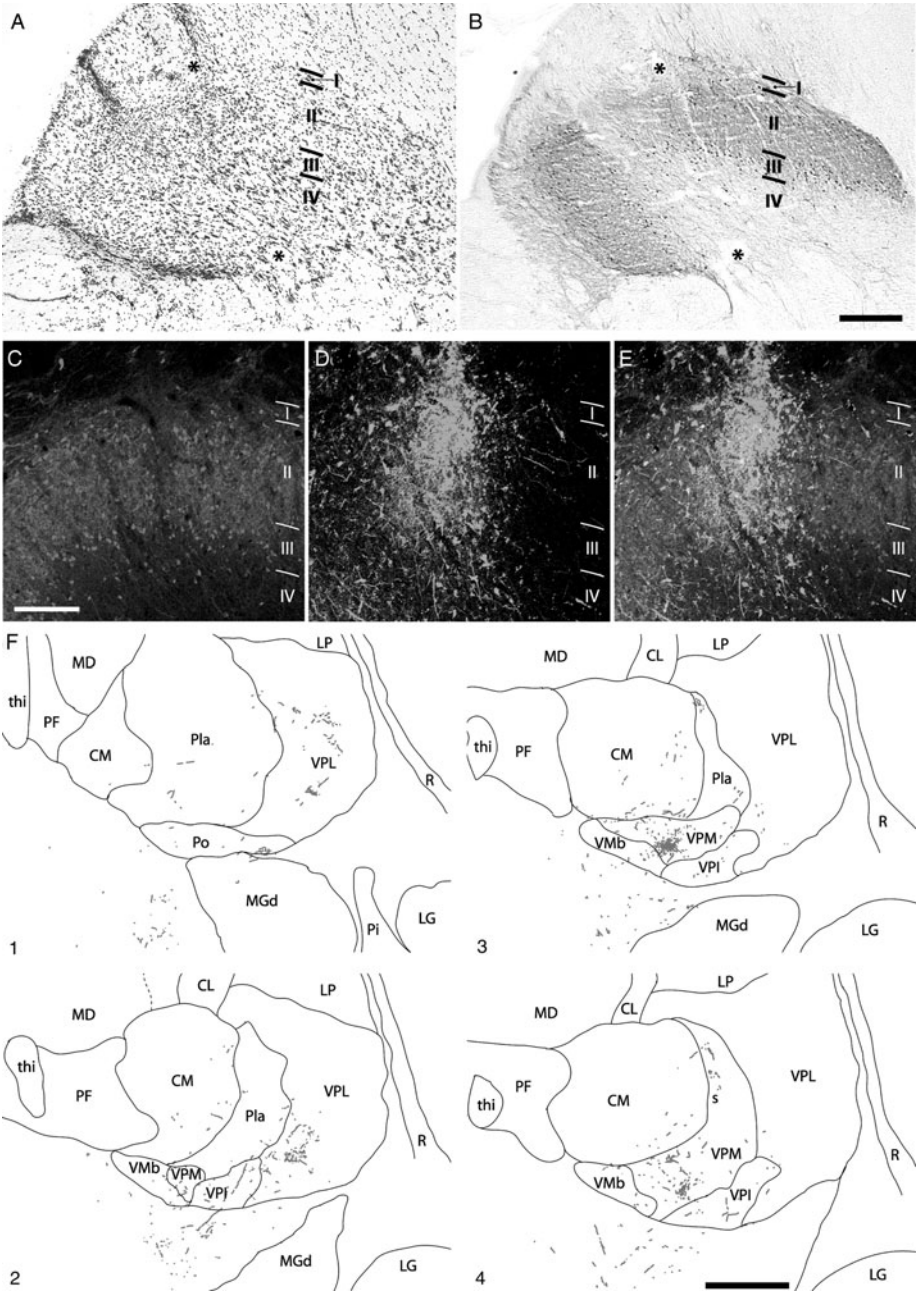


Fig. 2.27. A, B. Adjacent sections of the medullary dorsal horn in a macaque monkey, stained with thionin (A) or immunocytochemically for calbindin (B), showing laminae of the dorsal horn and two electrode tracks along one of which (asterisk) an injection of anterograde tracer was made. C-E. Fluorescence laser confocal scanning images of a section adjacent to B showing calbindin immunostaining of

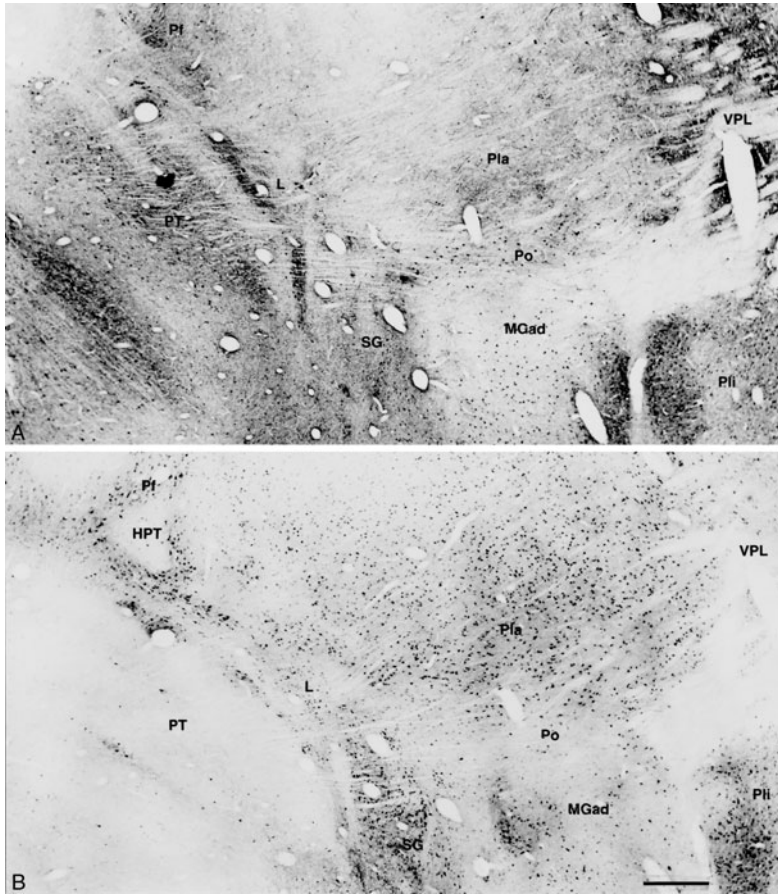


Fig. 2.28. Adjacent frontal sections showing complementary patterns of parvalbumin (A) and calbindin (B) immunostaining of the posterior (Po) and limitans-suprageniculate nucleus (L, SG) in a cynomolgus monkey. Bar: 0.5 mm.

stained, medium-sized cells and shows light-to-moderate acetylcholinesterase staining. It corresponds to Hassler's nuclei dorso-oralis and lateropolaris (D.o and L.po). The VAmc nucleus is a medial, magnocellular division that lies around the mamillothalamic tract as it penetrates the thalamus. It is distinguished by large, densely staining cells and dense acetylcholinesterase activity and is continuous with the central medial nucleus of the intralaminar complex. In the

Caption for Fig. 2.27. (cont.)

laminae I and II (C), an injection of fluorescein labeled dextran (D) and the merged images (E). F. Computer assisted plottings of the distribution of anterogradely labeled fibers and terminals in the VPM and adjacent nuclei resulting from the injection shown in D, E. Sections are in posterior (1) to anterior (4) order. From Graziano and Jones (2004). Bars: 300 μ m (A, B); 200 μ m (C-E); 1 mm (F).

Part 1

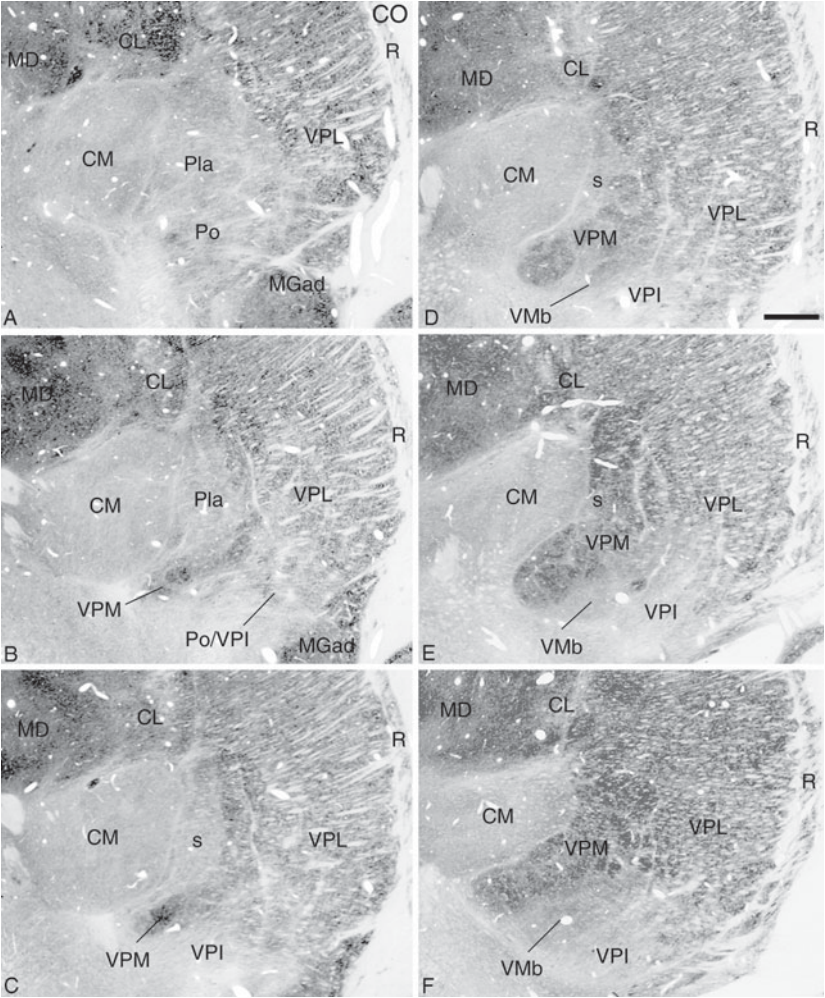


Fig. 2.29. Parts 1–3. Part 1 A–F. Digital images of frontal sections at approximately 180 μm intervals stained for cytochrome oxidase (CO) activity, arranged in posterior (A) to anterior (F) order and showing the nuclei of the ventral posterior complex and its surroundings. Bar: 1 mm. Part 2 A–F. Sections adjacent to those of Parts 1 and 3 and stained immunocytochemically for parvalbumin. Note correspondence between staining for cytochrome oxidase (Part 1) and parvalbumin. Bar: 1 mm. Part 3 A–F. Sections adjacent to those of Parts 1 and 2 stained immunocytochemically for 28 kDa calbindin. Note the overall complementarity of staining in comparison with that for cytochrome oxidase (Part 1) and parvalbumin (Part 2), except in the medial tip region of VPM where staining for all three is coincident. Bar: 1 mm. For a more extensive series of sections from this brain, see Jones *et al.* (2001), Jones (2007) or www.brainmaps.org.

Part 2

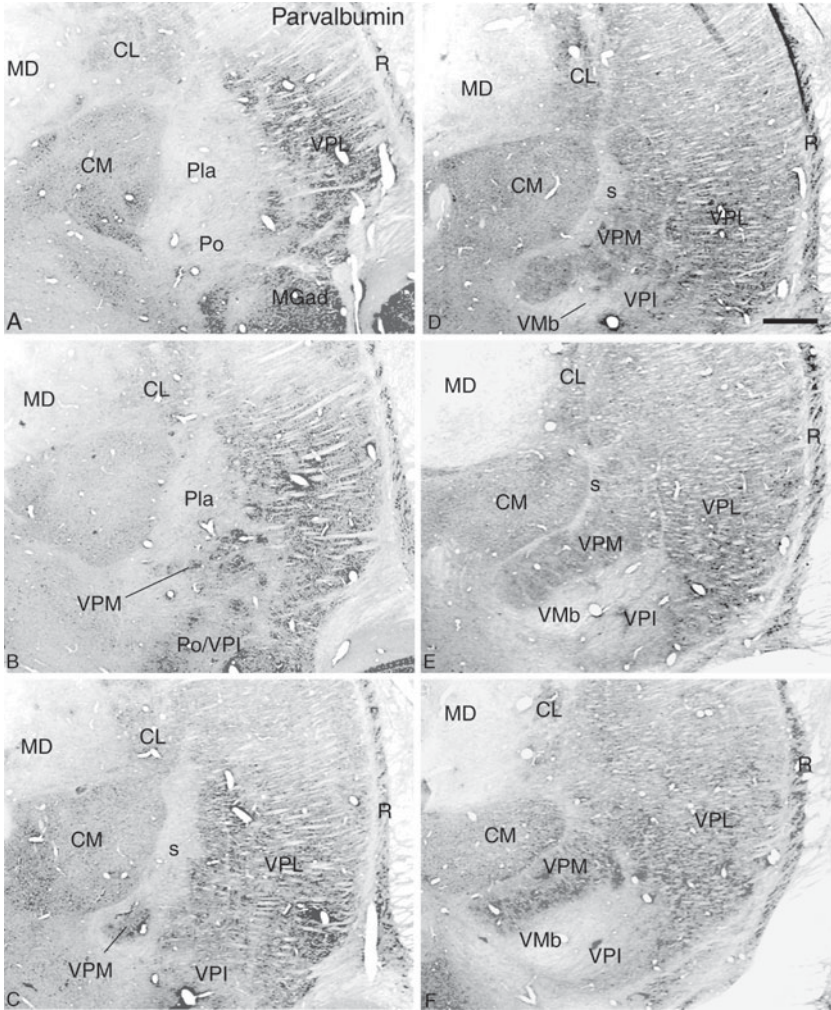


Fig. 2.29. (cont.)

human, the nucleus with corresponding features was called nucleus latero-polaris magnocellularis (L.po.mc) by Hassler (Fig. 2.18).

Histochemistry and immunocytochemistry of the ventral thalamic nuclei

The ventral posterior complex as a whole is divided into compartments that are histochemically and immunocytochemically distinct. As we shall see below, the lemniscal and spinothalamic pathways, although grossly converging on the complex, seem to engage neurons located in separate compartments, compartments whose cells relay these inputs to different layers and areas of the cerebral cortex. In monkeys (Jones *et al.*, 1986a, 1986b; Rausell and Jones 1991a,

Part 3

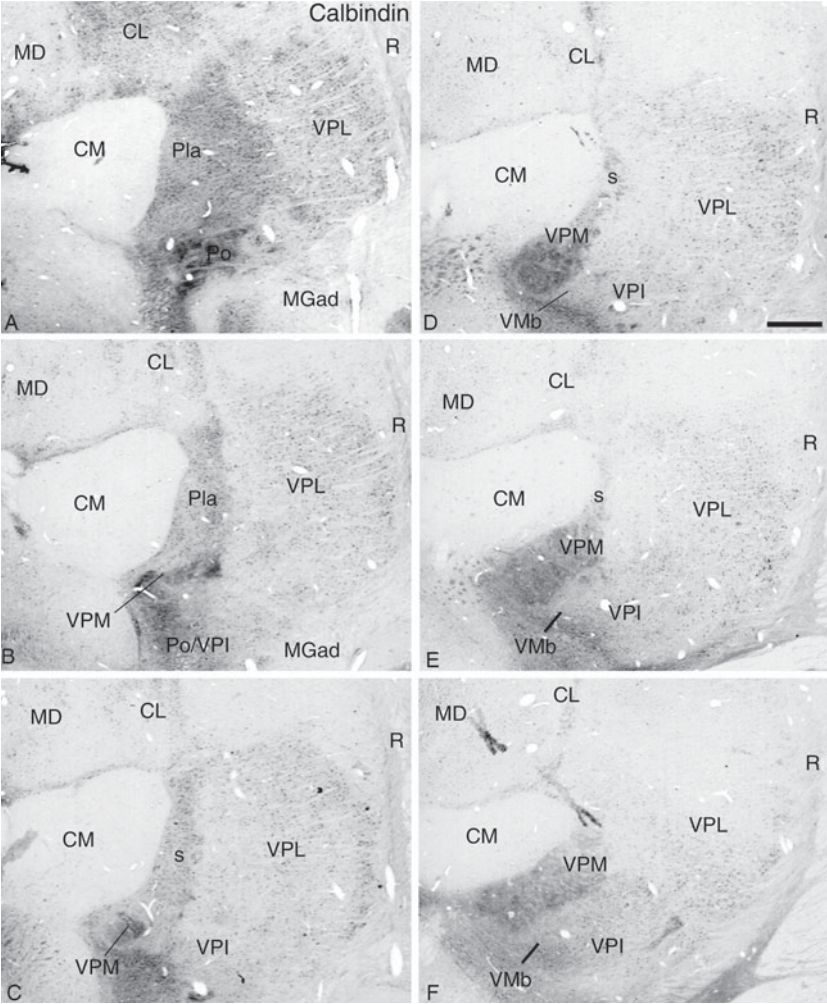


Fig. 2.29. (cont.)

1991b; Rausell *et al.*, 1992a, 1992b) and prosimians (Diamond *et al.*, 1993) the ventral posterior complex possesses a matrix of smaller (ca. 200 μm^2) relay cells that form a background to both VPL and VPM and which form the predominant cell populations of the VPI and VMb nuclei (Fig. 2.24). The cells of this matrix are immunopositive for 28 kDa calbindin, but immunonegative for parvalbumin (Figs 2.20–2.24), and the matrix as a whole shows weak histochemical staining for cytochrome oxidase (CO). The matrix forms a prominent strip (the s region) along the medial border of VPM (Figs 2.20, 2.21), intervenes between the clusters of relay cells in VPM and VPL, and extends uninterruptedly from these nuclei

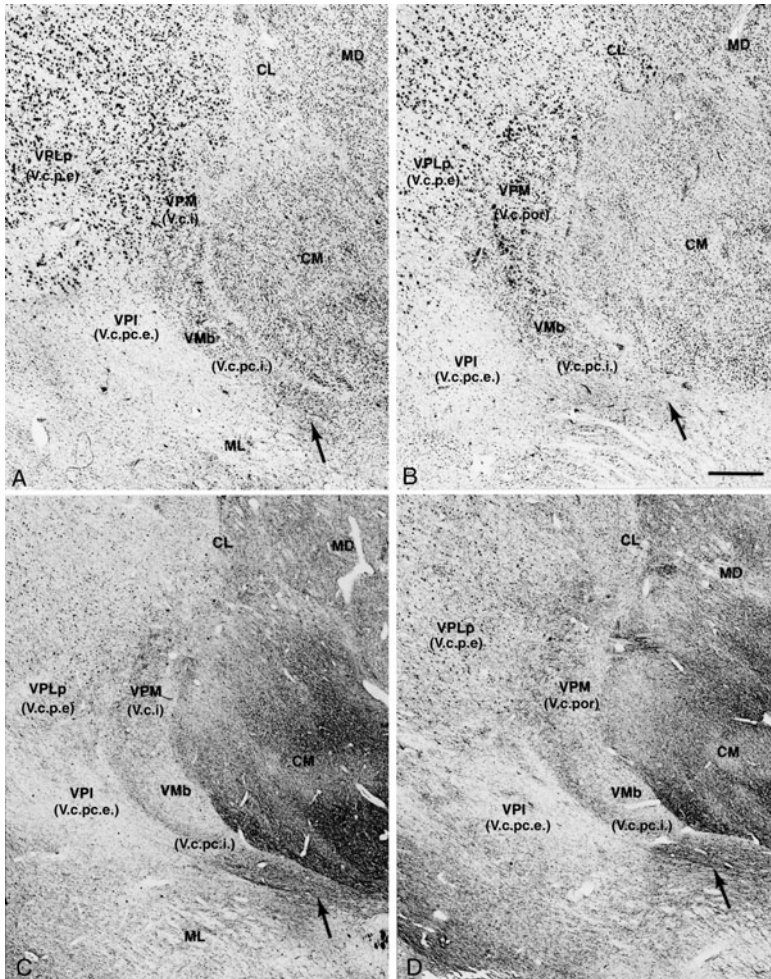


Fig. 2.30. Photomicrographs of pairs of frontal sections from a series through a human thalamus, showing the nuclei in and around the caudal pole of the ventral posterior complex. A and B (Nissl stain); C and D (acetylcholinesterase stain). Arrowed region in A and C (anterior to B and D) is the equivalent of the greater part of Hassler's (1959) V.c.pc.i nucleus and is the region containing the densest concentration of substance P immunoreactive fibers, shown in Fig. 2.32. In B and D, there are few nerve cells in this region. Hassler's abbreviations for nuclei labeled are given in parentheses. Modified from Jones (2007). Bar: 1 mm.

into the VMb and VPI nuclei (Fig. 2.29). It also continues uninterruptedly beyond them into adjacent nuclei which include the anterior pulvinar, posterior and ventral lateral. Superimposed on the matrix in VPL and VPM there is a second compartment formed by mixed large- and medium-sized cells ($\geq 250 \mu\text{m}^2$) that

are immunopositive for parvalbumin, but immunonegative for calbindin. This compartment stains densely for CO. Both the calbindin-rich, CO-weak and the parvalbumin-rich, CO-rich compartments contain GABAergic interneurons as well as relay neurons. The CO-rich compartment of large, parvalbumin positive cells forms the anteroposteriorly elongated, rod-like aggregations of neurons with overlapping peripheral receptive fields that characterize VPM in monkeys (Jones *et al.*, 1982; Rausell and Jones, 1991a). In VPM the parvalbumin-positive, CO-rich rods are separated from one another by the small-celled, calbindin positive matrix compartment; this expands medially, ventrally and posteriorly into the s region, VMb, VPI and adjacent nuclei (Fig. 2.29). Although VPL is dominated by the CO-rich compartment and by clusters of large, parvalbumin positive cells, this more or less homogeneous mass is punctuated at intervals by isolated patches of CO-weak matrix filled with calbindin-immunoreactive cells (Fig. 2.21).

Anterograde labeling studies show that the parvalbumin positive, CO-rich compartment is dominated by terminations of medial lemniscal or principal trigeminal afferent fibers which end exclusively in VPL or VPM while the CO-weak compartment is dominated by terminations of spinothalamic or spinal trigeminothalamic fibers, extending their terminals into this matrix where it forms the VPI, VMb and parts of the posterior, anterior pulvinar and ventral lateral nuclei (Figs 2.21, 2.27) (Rausell and Jones, 1991b; Rausell *et al.*, 1992a; Graziano and Jones, 2004). The spinothalamic tract terminals end in relation to cortically projecting neurons (Gingold *et al.*, 1991; Stevens *et al.*, 1993). Parvalbumin positive cells in the CO-rich compartment project to middle layers of the primary somatosensory cortex while the calbindin positive cells in the CO-weak matrix project to superficial layers of cortex, unconstrained by cytoarchitectonic borders (Rausell *et al.*, 1992a; Jones, 1998b, 1998c, 2001, 2007) (Fig. 2.24). The two compartments and their lamina-specific thalamocortical projections, therefore, form two parallel relay channels through the thalamus to the somatosensory cortex. A diffuse matrix of small, calbindin cells transfers spinothalamic and spinal trigeminothalamic influences to superficial layers of the sensory-motor and adjacent areas of the cerebral cortex; a second channel, formed by a core of larger, topographically organized parvalbumin cells, transfers lemniscal influences specifically to middle layers of the somatosensory cortex (Fig. 2.24).

Posterior and limitans-suprageniculate nuclei

These two nuclei make up a substantial part of the portal domain through which spinothalamic and medial lemniscal fibers enter the thalamus and in which there is a dense focus of spinothalamic fiber terminations. They have the same general features in New World and Old World monkeys (Figs 1.30, 2.17A–C, 2.28, 2.29) and comparable appearances are found in prosimians, apes and humans (Figs 1.28, 2.30) (Hassler, 1959; Kanagasuntheram *et al.*, 1968a, 1968b;

Hirai and Jones, 1989a). They are probably homologous to similar nuclei in the cat and other species (Jones, 2007). The limitans-suprageniculate nucleus consists of large, deeply staining, close-packed cells located along the thalamus-pretectum border, and the posterior nucleus consists of smaller, pale-staining, dispersed cells around the posterior pole of the ventral posterior nucleus, extending forwards to become continuous with the VPI nucleus and backwards along the medial edge of the medial geniculate complex. The limitans part of the limitans-suprageniculate nucleus commences at the posterior end of the habenular complex, crosses the posterior pole of the mediodorsal nucleus where it fuses with the very similar cells of the central lateral and parafascicular nuclei, and runs as a thin line of deeply staining cells down the external medullary lamina in the posteroventral aspect of the medial pulvinar nucleus (Fig. 2.17A, B). This part of the external medullary lamina separates it from the anterior pretectal nucleus. At some distance dorsomedial to the medial geniculate complex, the limitans part expands considerably as the suprageniculate part of the common nucleus. This suprageniculate part continues the oblique line of the limitans part down into the magnocellular medial geniculate nucleus with which it fuses; the magnocellular medial geniculate cells are sufficiently larger, however, that the two nuclei are readily distinguishable (Fig. 2.17B). The dorsal part of the suprageniculate element lies in the ventral aspects of the medial and anterior pulvinar nuclei. The limitans and suprageniculate parts of the common nucleus typically stain intensely for cytochrome oxidase and acetyl cholinesterase, are strongly immunoreactive for calbindin cells and fibers, and contain only a few dispersed patches of parvalbumin immunoreactive cells or fibers (Fig. 2.28).

The posterior nucleus, as named in monkeys by Emmers and Akert (1963) and Burton and Jones (1976), is made up of dispersed cells much smaller and less densely staining than those in the limitans-suprageniculate nucleus. It commences in the dorsolateral aspect of the suprageniculate nucleus in the region where the latter meets the magnocellular medial geniculate nucleus (Fig. 2.17B, C), and forms a zone of dispersed cells intercalated between the anterodorsal medial geniculate nucleus and the ventral posterior nucleus, expanding anteriorly around the posterior pole of the ventral posterior nucleus, to become continuous with the ventral posterior inferior (VPI) nucleus and with the small-celled (s) region of the ventral posterior medial (VPM) nucleus (Figs 2.21–2.29). For much of its extent it is traversed by fibers of the medial lemniscus and spinothalamic tract as they enter the thalamus (Fig. 2.21A). Typically, the posterior nucleus and the VPI and s regions with which it is continuous anteriorly stain weakly for cytochrome oxidase and acetyl cholinesterase but at intervals there are patches of dense staining that represent posterior islands of cells of the ventral posterior lateral (VPL) and VPM nuclei that invade it (Figs 2.17, 2.28). The posterior nucleus as a whole contains large numbers of calbindin immunoreactive cells and fibers but no parvalbumin immunoreactive

cells, except where invaded by islands of cells of the suprageniculate nucleus (Fig. 2.18). Laterally, the posterior nucleus merges with the anterodorsal medial geniculate nucleus, whose cells are more densely packed than those of the posterior nucleus. Differential immunostaining for calcium binding proteins in monkeys and humans shows that the limitans-suprageniculate nucleus contains just a few islands of cells that are densely immunoreactive for parvalbumin but many calbindin immunoreactive cells arranged in a densely calbindin immunoreactive neuropil (Fig. 2.28). The posterior nucleus contains few or no parvalbumin immunoreactive cells and fibers but is densely immunoreactive for calbindin, an appearance that extends continuously forwards into the matrix regions of the ventral posterior nucleus and the anterior pulvinar nucleus (Figs 2.28, 2.29).

The ill-defined posterior nucleus and its continuation into the VPI nucleus and matrix regions of the ventral posterior complex has its equivalent in humans among the group of nuclei that Hassler (1959) included in his nucleus limitans (Li) and parvocellular divisions of his ventro-caudal nucleus (V.c.). Most of these nuclei can be identified, from the cytological descriptions of Hassler, with nuclei traditionally given other names in monkeys (Figs 1.28–1.30, 2.18, 2.19, 2.30, Table 1.1). Hassler's nucleus ventrocaudalis parvocellularis (V.c.pc) is divided into medial (V.c.pc.i) and lateral (V.c.pc.e) subnuclei which are more or less the equivalents of the basal ventral medial (VMb or parvocellular division of VPM) and ventral posterior inferior (VPI) nuclei respectively, although his divisions, based mainly on myeloarchitecture, do not completely match those identified cytoarchitectonically (Figs 1.28, 2.18, 2.19). For example, much of the small-celled VMb is actually included in Hassler's V.c.i. (VPM) nucleus. Posterior to and merging with these two nuclei is an ill-defined region which Hassler called nucleus limitans portae (Li.por) (Fig. 1.28), through which lemniscal and spinothalamic fibers enter the thalamus. The region is in a position comparable to the posterior nucleus of the present account, although Hassler's description of the cytoarchitecture makes it impossible to exclude adjacent parts of the anterior pulvinar nucleus, most of which he called the nucleus ventrocaudalis portae (V.c.por), from it. Hassler's V.c.por seems also to include the posterior pole and s regions of the VPM nucleus (Fig. 2.30).

The posterior-to-anterior extent of the calbindin matrix in and around the ventral posterior complex

The calbindin-rich matrix in and around the ventral posterior complex is a key region in appreciating the relationships of spinothalamic and spinal trigeminothalamic fiber terminations to the nuclear divisions of the thalamus. The matrix can best be appreciated by following a series of frontal sections stained for calbindin and the complementary markers, cytochrome oxidase (CO) or parvalbumin in posterior to anterior order (Fig. 2.29A–F) (Jones *et al.*, 2001; Jones, 2007). Beginning

posteriorly in CO-stained sections (Fig. 2.29A, Part 1), the posterior nucleus and its immediate environs are distinguished as a region of predominantly weak CO staining that is traversed by unstained fiber bundles of the corticotectal tract and associated fiber systems. Here and there within it are patches of denser CO staining that represent the islands of neurons belonging to the suprageniculate nucleus. VPM is not present at this level but the posterior pole of VPL can be seen exhibiting dense CO activity while the adjacent anterior pulvinar and dorsal medial geniculate nuclei exhibit weak CO activity. The differential CO staining is almost exactly matched by that of parvalbumin immunostaining (Fig. 2.29, Part 2), so that where CO staining is weak, only a few scattered parvalbumin immunoreactive cells are found and where it is strong, as in the islands of suprageniculate or VPL cells, the cells are densely stained for parvalbumin. Cells and fibers in VPL are intensely immunostained for parvalbumin and, ventrally, the fibers of the medial lemniscus as they approach VPL are intensely immunostained as well.

Calbindin immunostaining of the adjacent sections (Fig. 2.29, Part 3) reveals that the weakly CO-stained posterior and anterior pulvinar nuclei are filled with cells densely immunostained for calbindin and embedded in a moderately densely immunostained neuropil. The densest calbindin immunostaining at this level consists of immunoreactive fibers in the central tegmental tract and in Forel's field H (Fig. 2.29A), located ventromedial to the posterior nucleus and dorsomedial to the (unstained) medial lemniscus. In it are contained the fibers of the spinothalamic tract and some of the stained fibers can be seen entering the posterior nucleus of the thalamus. Laterally, the caudal pole of VPL is filled with dispersed calbindin immunoreactive cells but its neuropil is far less densely stained than that of the anterior pulvinar and posterior nuclei.

On proceeding anteriorly (Fig. 2.29B, C, Part 1), a series of densely CO-stained patches that represent the posteromedial, toe-like tip of VPM appear within the weak, diffuse CO staining of the posterior nucleus. The patches of increased CO staining are exactly co-extensive with patches of enhanced fiber and cellular immunoreactivity for parvalbumin and calbindin (Fig. 2.29, Parts 2, 3). The toe-like tip of VPM stands out in the sections stained for CO and immunostained for calbindin on account of the weaker staining of the adjacent anterior pulvinar and VPI nuclei. VPI is a direct continuation of the posterior nucleus (Fig. 2.29B). In calbindin immunostained sections, the toe-like character of the medial tip of VPM is also enhanced because of the intensely immunoreactive fiber staining that surrounds it.

On proceeding further anteriorly (Fig. 2.29D, E), the four components of the ventral posterior complex are clearly distinguishable from one another in CO-stained and in calbindin and parvalbumin-immunostained sections. VPM and VPL show dense CO staining and dense cell and fiber immunoreactivity for parvalbumin. VPM is characterized by the staining of the rods of cells and

associated neuropil that extend anteroposteriorly through the nucleus. VMb is located within the arcuate lamella that confines VPM, is only weakly stained for CO and contains no parvalbumin immunoreactive cells. VPI, which lies lateral to the arcuate lamella, is also weakly stained for CO and contains only a few parvalbumin immunoreactive cells intruding into it from VPL. Both VMb and VPI are traversed by numerous parvalbumin immunoreactive fibers of the medial and trigeminal lemnisci. The medial border of VPM is characterized by the thin strip of weak CO staining and absent parvalbumin immunoreactivity that represents the s or small-celled zone, an enlarged part of the VPM matrix (Fig. 2.29C, D). This zone merges posteriorly with the similarly weakly stained anterior pulvinar nucleus and anteriorly for a short distance separates VPM proper from the centre médian nucleus, which is densely stained for CO, densely immunoreactive for parvalbumin and immunonegative for calbindin.

In the ventral posterior complex, calbindin immunoreactivity is mainly complementary to that for parvalbumin but in one part it is co-extensive (Figs 2.21, 2.29). VPL and the vertical part of the (reversed) L-shaped VPM contain many cells immunoreactive for calbindin dispersed evenly through a weakly immunoreactive neuropil. These cells are dispersed among the clustered cells that are densely immunoreactive for parvalbumin and heavily stained for CO. In VPM, the calbindin cells occupy the spaces between the rods of dense CO staining and dense parvalbumin immunoreactivity that represent the core component of this nucleus (Fig. 2.24). The medial s region of VPM is also filled with calbindin immunoreactive cells (Fig. 2.29C, D). VMb and VPI contain many calbindin immunoreactive cells and a moderately densely immunoreactive fibrous neuropil but no parvalbumin immunoreactivity and only weak CO staining. The most dense calbindin fiber immunoreactivity is in bundles located within the medial part of the H₁ field (thalamic fasciculus) (Fig. 2.29D). These fibers turn up around the medial toe-like tip of VPM outlining it clearly. All of the calbindin-rich cell and fiber regions show weak CO staining and weak or absent parvalbumin immunostaining, so the calbindin staining pattern is for the greater part complementary to that of parvalbumin. However, the ventral part of VPM (horizontal limb of the reversed L) is unique because, here, heavy immunostaining for the two calcium binding proteins is co-extensive. The half-dozen or so medial rods of VPM are densely stained for CO, parvalbumin and calbindin (Rausell and Jones, 1991a) (Fig. 2.29C–E). The calbindin immunoreactivity in these rods consists of a dense network of fiber staining that outlines the rod-like aggregations, with numerous calbindin immunoreactive cells located among the fibers. These are slightly smaller than parvalbumin immunoreactive cells in the same location and do not co-stain for parvalbumin (Rausell and Jones, 1991b; Rausell *et al.*, 1992a).

On reaching the anterior pole of VPM, the pattern of the partial complementarity and partial overlap continues (Fig. 2.29F). VPL, and all the rods of VPM, display

intense CO staining and intense cell and fiber immunoreactivity for parvalbumin but immunoreactivity for calbindin is dispersed and mainly cellular. VMb and VPl still display weak CO staining and no cellular immunoreactivity for parvalbumin but intense cellular and modest fiber immunoreactivity for calbindin. The most medial rods of VPM continue to display dense CO activity and dense parvalbumin cell and fiber immunoreactivity as well as intense fiber and cellular immunoreactivity for calbindin. The cellular immunostaining for calbindin here tends to be obscured by the intense fiber immunostaining. The CO-weak, parvalbumin-weak, calbindin-dense s region of VPM gradually disappears anteriorly so that near its anterior pole VPM is separated from the centre médian nucleus (which contains very few calbindin cells) by only a thin unstained fiber lamina (Fig. 2.29F).

Intralaminar and submedial nuclei

The intralaminar nuclei of the thalamus take their name from their association with the internal medullary lamina, a thin Y-shaped sheet of fibers whose arms enclose the anterior nuclei and whose stem embraces the mediodorsal nucleus (Figs 2.17, 2.23, 2.31). The lamina can be clearly visualized in fiber-stained preparations and in those reacted histochemically for cytochrome oxidase or acetyl cholinesterase activity (Jones, 1998a, 2007). Certain cell groups located outside the lamina are now included in the intralaminar group by virtue of their similar patterns of connectivity and certain other factors. The obvious cell masses within the internal medullary lamina are the central medial, paracentral and central lateral nuclei. The central medial nucleus is a single nucleus in the part of the lamina that crosses the midline to join its neighbor of the opposite side. At the midline there are additional cell groups, formed by extensions of the central lateral and central medial nuclei, referred to as a single rhomboid or central nucleus or collectively called the midline nuclei. The nuclei just mentioned form the anterior or rostral group of intralaminar nuclei (Berman and Jones, 1982).

Towards the posterior end of the internal medullary lamina, contained within a splitting of the lamina and extending to the posterior surface of the thalamus, are the parafascicular and centre médian nuclei which constitute the posterior or caudal group of intralaminar nuclei (Le Gros Clark, 1932; Berman and Jones, 1982).

The central medial, paracentral, central lateral, and central or rhomboid nuclei form an extensive, central mass (the central medial and midline components) with thin lateral wings (the paracentral and central lateral components) stretching through much of the anteroposterior extent of the thalamus. The rhomboid or central nucleus at the midline joins up with the central medial nucleus and extends over the anterodorsal aspect of the mediodorsal nucleus to join up with the central lateral nucleus. The central lateral nucleus extends posteriorly over the posterior surface of the mediodorsal nucleus (Fig. 2.17A). The mediodorsal nucleus of each side is almost entirely enclosed by the anterior

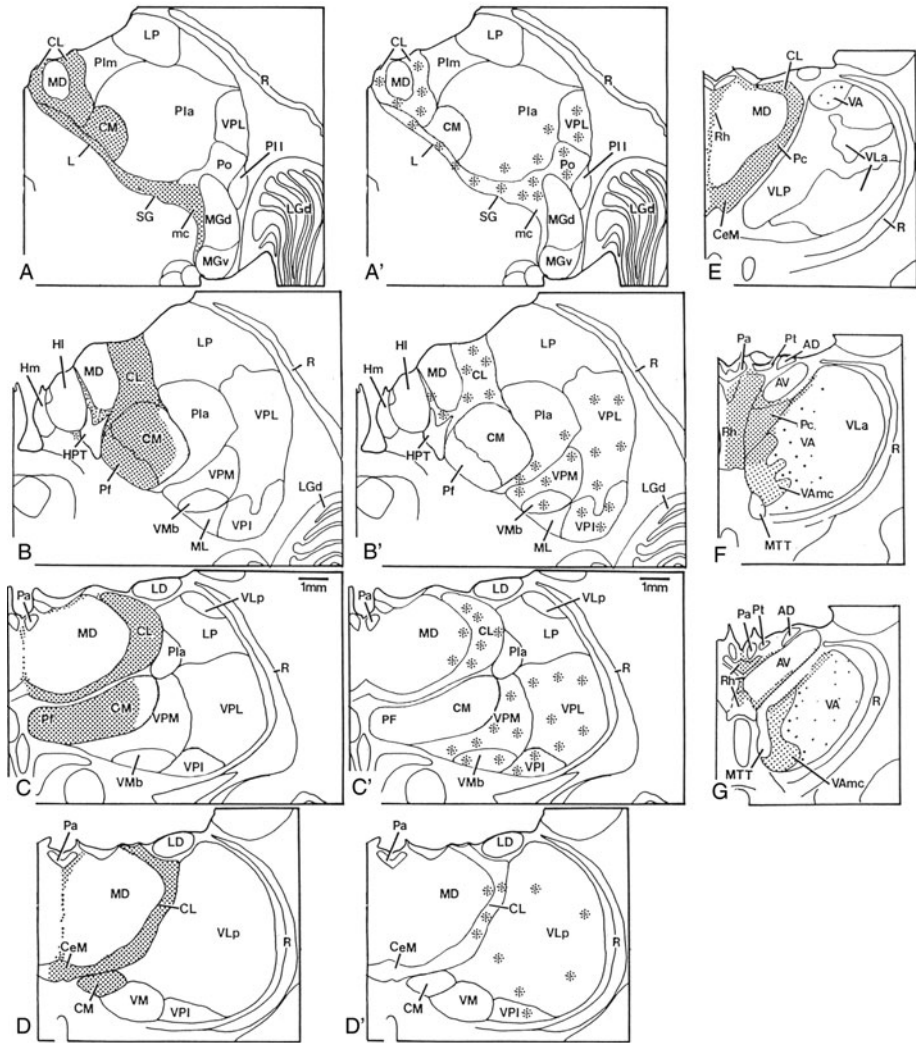


Fig. 2.31. (A–G) Camera lucida drawings in posterior (A) to anterior (G) order showing the overall distribution of neurons retrogradely labeled in the thalamus of macaque monkeys in which tracers were injected in different parts of the ipsilateral caudate nucleus and putamen. Based on work of Hunt and Jones (1988). (A'–D') Camera lucida drawings of the same sections upon which has been schematically illustrated the distribution of terminals of the spinothalamic and spinal trigeminothalamic pathways.

group of intralaminar nuclei (Figs 2.23, 2.31). In monkeys, apes and humans, a large extension of the central medial nucleus around the mamillothalamic tract as it joins the internal medullary lamina is known as the magnocellular ventral anterior nucleus (VAmc) (Jones, 2007).

The central lateral nucleus consists for the most part of large, densely stained cells. Posteriorly, the cells become larger and even more deeply stained, but because the internal medullary lamina is here broken up and less distinct, the boundaries between the central lateral, lateral posterior and mediodorsal nuclei become less obvious. In its most posterior part, the central lateral nucleus consists of scattered, large cells lying at the lateral and ventrolateral edges of the mediodorsal nucleus. These large cells of the central lateral nucleus persist to levels more posterior than the central medial or paracentral nuclei. In primates, the large, deeply staining cells in this location are sometimes called a paralamellar or densocellular component of the mediodorsal nucleus. These large, deeply staining cells extend around the posterior surface of the mediodorsal nucleus where they fuse with the underlying parafascicular nucleus and nucleus limitans (Figs 2.17A, B). The limitans nucleus runs down along the border of the thalamus and pretectum to become in turn continuous with the suprageniculate nucleus. The limitans-suprageniculate nucleus is now regarded as an extension of the anterior group of intralaminar nuclei (Jones, 2007).

Of the two members of the posterior group of intralaminar nuclei, the centre médian nucleus reaches its largest size in monkeys, apes and humans. It is enclosed by a splitting of the posterior part of the internal medullary lamina intercalated mainly between the central lateral nucleus and the ventral posterior medial nucleus and separated from the mediodorsal nucleus by the large-celled posterior extension of the central lateral nucleus (Niimi *et al.*, 1960; Mehler, 1966a; Jones, 1985, 2007), called in the human by Vogt and Vogt (1941) and Hassler (1959) a magnocellular division of the centre médian nucleus. At about the level of the habenulopeduncular tract, the parafascicular nucleus, made up of more tightly packed and more densely staining cells, abuts upon the centre médian nucleus (Fig. 2.17B, C). It is pierced by the habenulopeduncular tract and medially it lies against the anterior end of the periaqueductal gray matter. Laterally, cells of similar characteristics descend along the external medullary lamina ventral to the centre médian nucleus as the limitans-suprageniculate nucleus.

In monkeys, the greater part of the anterior group of intralaminar nuclei, including its midline components, is dominated by calbindin immunoreactive cells but there are a number of parvalbumin cells within the same territory, especially in the dorsolateral part of the central lateral nucleus (Jones, 2007). Posterior parts of the central lateral and central medial nuclei are largely devoid of calbindin cells; a few patches of calbindin immunoreactive cells can be found in the part of the central lateral nucleus that extends around the posterior pole of the mediodorsal nucleus and in the capsule of the centre médian nucleus. The centre médian nucleus itself displays remarkably few calbindin cells, widely scattered singly or in small patches (Fig. 2.29). These coincide with similar cells

immunoreactive for 29 kDa calretinin. The parafascicular nucleus is distinguished by a moderately densely calbindin immunoreactive neuropil but only a few immunoreactive cells. Where calbindin immunoreactive cells are few or absent in the intralaminar nuclei, they are replaced by parvalbumin immunoreactive cells and neuropil. Thus those parts of the central lateral and central medial nuclei that possess few calbindin cells have many parvalbumin cells and the centre médian and parafascicular nuclei are densely filled with parvalbumin cells lying in a densely immunoreactive neuropil. Posteriorly, there are complementary patches or stripes of calbindin and parvalbumin immunoreactive cells extending downwards in the limitans-suprageniculate nucleus towards the magnocellular medial geniculate and posterior nuclei.

The submedial nucleus (Sm) in rodents forms a distinctly rounded nucleus surrounding the mamillothalamic tract as this enters the thalamus. In cats it lies at the anterior pole of the centre médian nucleus enclosed in a sling of the internal medullary lamina. An equivalent submedial nucleus has not usually been identified in monkeys, except in the squirrel monkey by Emmers and Akert (1963), and fortuitous sections in other monkeys will sometimes suggest a similar small island of loosely dispersed cells at the anterior pole of the centre médian nucleus, underlying the posterior part of the paracentral or central lateral nuclei.

Thalamic terminations of spinothalamic and spinal trigeminothalamic projections

Posterior nuclei and ventral posterior complex

When traced en masse, spinothalamic and spinal trigeminothalamic fibers deposit the first of their thalamic terminal ramifications in bursts within the posterior nucleus. In monkeys, and in humans, these terminations commence in the region adjacent to the suprageniculate nucleus (Figs 2.16, 2.25–2.27, 2.31) where they were once mistakenly believed to be in the magnocellular medial geniculate nucleus (Chapter 1; Mehler, 1966a, 1966b, 1969; Kerr, 1975a, 1975b; Boivie, 1979; Burton and Craig, 1979; Berkley, 1980; Asanuma *et al.*, 1983b; Burton and Craig, 1983; Mantyh, 1983). The terminations extend forwards in the posterior nucleus, into the VPI and VMb nuclei and around the posterior pole of the ventral posterior nucleus following the matrix regions of the ventral posterior complex into the anterior pulvinar nucleus medially and into the VLP nucleus anteriorly (Rausell and Jones, 1991b; Rausell *et al.*, 1992a; Graziano and Jones, 2004). Within VPM, spinal trigeminothalamic fiber terminations are concentrated in the calbindin-dense, CO-weak zones that form the s region along the medial border of VPM and in the matrix regions intercalated between the parvalbumin-rich, CO-rich rods of VPM (Figs 2.25, 2.26). Within VPL, the typical

burst-like spinothalamic fiber terminations are concentrated in calbindin-rich, CO-weak zones that are interspersed among the clusters of parvalbumin-rich, CO-rich VPL cells (Fig. 2.26). Similar burst-like patches characterize the terminations in the calbindin-rich, CO-weak posterior, VPI, VMb and anterior pulvinar nuclei. The clusters that extend from VPL into VLP are also typically associated with CO-weak, parvalbumin negative and calbindin-rich zones in that nucleus.

Medial and trigeminal lemniscal terminals, by contrast with those of spinothalamic and spinal trigeminothalamic terminals, are restricted to VPL or VPM and focused on parvalbumin-rich cell clusters or rods (Rausell *et al.*, 1992a) (Fig. 2.24). The terminal clusters of spinothalamic fiber terminations are significantly smaller than those of medial lemniscal fibers (Ralston and Ralston, 1993). When examined electron microscopically, however, the terminals resemble those of medial lemniscal fibers and ~80% of these end only on relay cell dendrites, with far fewer ending on the presynaptic dendrites of relay neurons (Ralston and Ralston, 1993). Within the zones of spinothalamic and spinal trigeminothalamic terminations, as within the lemniscal terminal zones, many thalamocortical relay cells are present (Gingold *et al.*, 1991; Rausell *et al.*, 1992a; Stepniewska *et al.*, 2003). Spinothalamic and medial lemniscal terminals have not been seen ending on the same relay cell dendrites in VPL of monkeys (Ralston and Ralston, 1993, 1994). It has not been definitively determined, however, if this indicates terminations on different relay cells, as implied by the non-overlapping nature of the terminations as seen light microscopically, or spatially segregated terminations on the same relay cell. Although the concentration of spinothalamic and spinal trigeminothalamic terminations in regions of weak cytochrome oxidase staining and those of lemniscal terminations in cytochrome oxidase-rich zones implies a considerable degree of gross segregation, dendrites of relay cells could clearly extend from one zone into the other.

Intralaminar terminations

Medially directed spinothalamic fibers reach the central lateral nucleus of the intralaminar complex, the small submedial nucleus and adjacent variably identified regions (Fig. 2.16). Although the exact locations of the terminations of fibers within the intralaminar system are still a matter of some debate, it can be confidently asserted that, contrary to reports in the early literature (Chapter 1), no spinothalamic or spinal trigeminothalamic fibers terminate in the centre médian nucleus (Figs 2.31, 2.32).

Spinothalamic and spinal trigeminothalamic fibers reach the caudal part of the internal medullary lamina by ascending along the border between the thalamus and anterior pretectal nucleus, many of them located within the limitans part of the limitans-suprageniculate nucleus. They enter the caudal

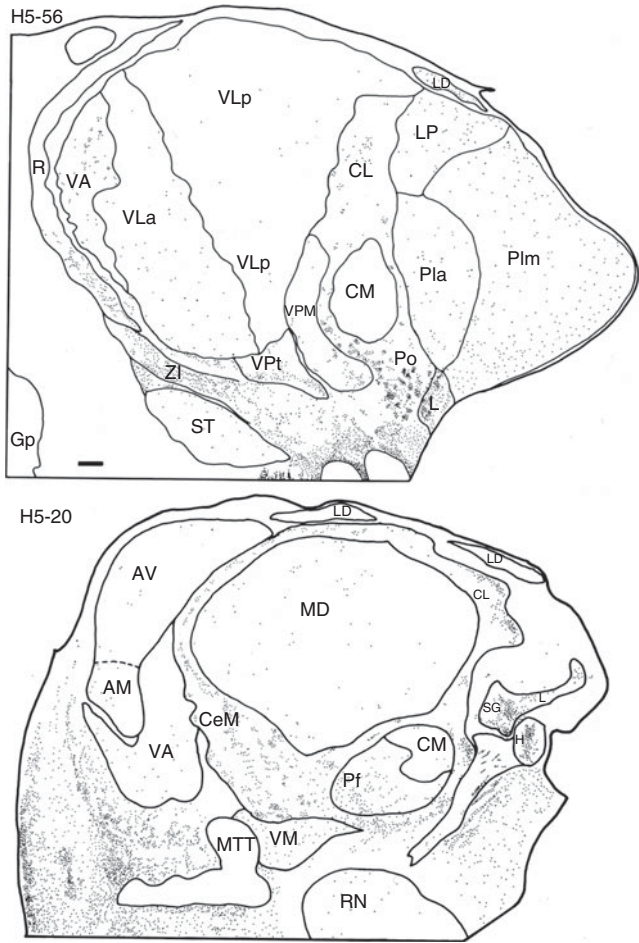


Fig. 2.32. Camera lucida drawings of parasagittal sections (upper is lateral to lower) of a human thalamus, showing the distribution of tachykinin-immunoreactive fibers. Note concentration in the intralaminar nuclei and in the region posterior (Po) to the caudal pole of the ventral posterior nucleus. Bar: 1 mm. From Hirai and Jones (1989b).

pole of the central lateral nucleus where it wraps around the posterior pole of the mediodorsal nucleus and many terminations are found among the large, deeply staining cells that characterize this part of the central lateral nucleus (Figs 2.16, 2.31). Although once considered to be largely confined to the large cells of the central lateral nucleus and of the so-called densocellular division of the mediodorsal nucleus, which is formed by these cells (Mehler *et al.*, 1960; Mehler, 1966a, 1966b, 1969; Boivie 1971), later work with more sensitive anatomical tracers has revealed that the terminations extend further anteriorly into more anterior parts of the central lateral nucleus, the paracentral nucleus and

paralaminae regions of the mediodorsal nucleus (Craig and Burton, 1981; Asanuma *et al.*, 1983c; Burton and Craig, 1983; Mantyh, 1983; Craig and Burton, 1985; Hirai and Jones, 1988; Apkarian and Shi, 1994; Craig, 2003).

Fibers to the intralaminar nuclei arise mainly in deeper laminae of the spinal and trigeminal dorsal horns (Trevino, 1976; Willis *et al.*, 1979; Giesler *et al.*, 1981; Craig *et al.*, 1989; Stevens *et al.*, 1989), but lamina I cells can also contribute (Craig, 2003). Some are branches of those directed towards the ventral posterior nucleus (Giesler *et al.*, 1981).

The submedial nucleus

The submedial nucleus (Sm) of rats and cats, and a putatively equivalent nucleus in monkeys receives a comparatively modest input from the contralateral spinal cord and caudal spinal trigeminal nucleus (Craig and Burton, 1981, 1985; Burton and Craig, 1983; Mantyh, 1983; Robertson *et al.*, 1983; Peschanski, 1984; Ma *et al.*, 1988; Dado and Giesler, 1990; Yoshida *et al.*, 1991; Blomqvist *et al.*, 1992; Iwata *et al.*, 1992; Ericson *et al.*, 1996; Craig, 2003). The fibers terminate mainly in a dorsal, acetyl cholinesterase-rich part of the nucleus, although there may be some species differences. In rats, there is also a small ipsilateral projection (Yoshida *et al.*, 1991). In the cat and rat many of the fibers arise from cells in the marginal layer of the dorsal horn of the spinal cord and of the caudal nucleus of the spinal trigeminal complex (Craig and Kniffki, 1985; Craig and Dostrovsky, 1991; Iwata *et al.*, 1992) but the terminations of the axons of these cells are by no means confined to Sm, extending into it from all the other adjacent nuclei that receive spinothalamic terminations (Iwata *et al.*, 1992; Craig and Dostrovsky, 2001; Craig, 2003). In rats, deeper dorsal horn cells are the major contributors to the submedial projection and projecting cells are also found in the interpolar nucleus of the caudal trigeminal complex (Yoshida *et al.*, 1991). The lamina I spinal terminations in Sm led Craig and Burton (1981) to represent Sm as a major thalamic pain center, although interest in this has now declined. Neurons responding to noxious stimulation have been reported in Sm of the rat, although other Sm neurons respond to thermal and to innocuous stimuli (Dostrovsky and Guilbaud, 1988; Miletic and Coffield, 1989; Craig and Dostrovsky, 1991; Kawakita *et al.*, 1993). There are some suggestions of a body topography in the nucleus although the nociceptive neurons have large, commonly bilateral receptive fields.

The submedial nucleus is by no means an exclusive pain relay. A ventral acetyl cholinesterase-weak part receives olfactory inputs from a region of olfactory cortex close to the anterior olfactory tubercle (Price and Slotnick, 1983; Russchen *et al.*, 1987; Yoshida *et al.*, 1992) and other fibers are reported to come from the lateral hypothalamus, subiculum and the brainstem sources of non-specific thalamic afferents (Witter *et al.*, 1990).

A separate thalamic relay for high-threshold neurons of lamina I of the dorsal horn?

Spinal and medullary dorsal horn cells located in both lamina I and in deeper laminae and cells with both noci- and thermoceptive and wide dynamic range properties are reported to project to both the ventral posterior complex and to the other thalamic sites, some of them quite far-flung in the intralaminar and posterior complexes (see previous sections). There are neurons with specific responses to noxious and/or thermal stimuli in most of the thalamic nuclei in which the fibers terminate ([Chapter 3](#)) and functional imaging and evoked potential studies reveal activation of many cortical areas such as the anterior cingulate and dorsal insular regions to which these nuclei project during exposure of humans to painful stimuli ([Chapters 5, 8](#)) (Craig *et al.*, 1996; Derbyshire and Jones, 1998; Lenz *et al.*, 1998a, 1998c; Ohara *et al.*, 2004a, 2004b). In VPL and VPM there are neurons with pain- and temperature-specific stimulus-response properties and small localized receptive fields that betoken a topographically organized, modality-specific projection upon the primary somatosensory area of the cortex and thus a basis for localization and discrimination of painful stimuli in animals (Kenshalo and Isensee, 1983; Chudler *et al.*, 1990; Kenshalo and Willis, 1991) and humans (Ohara *et al.*, 2004a, 2004c).

A recent attempt to overthrow this time-honored position has been based upon a claim by Craig and co-workers to be able selectively to label nociceptive-specific fibers arising in lamina I of the dorsal horn, to plot them throughout the neuraxis, and to identify their terminations in the monkey and human thalamus with a specificity of immunocytochemical staining unattainable by other investigators (Craig *et al.*, 1994, 2002; Blomqvist *et al.*, 2000; Craig, 2003). According to these authors, axons arising from high-threshold lamina I cells throughout the spinal and medullary dorsal horns are characterized by calbindin immunoreactivity and their thalamic terminations are restricted to a very small focal area outside the confines of VPL and VPM and characterized by strong immunoreactivity for calbindin. This focal region they regarded as a new thalamic nucleus and called it the posterior ventral medial nucleus or VMpo. According to the authors, calbindin immunostaining specifically labels spinothalamic and spinal trigeminothalamic terminations and selectively delineates VMpo with little immunostaining of other thalamic nuclei. They also claimed that VMpo relays lamina I-specific inputs to cingulate and insular cortex and to area 3a rather than to primary somatosensory cortex. Pain perception would thus depend upon areas of the cortex not hitherto recognized as having the capacity for discriminative operations on sensory inputs. They attributed the more selective character of their immunostaining for calbindin, in comparison with other studies upon which the descriptions of the two previous sections are based, to the use of a different monoclonal antibody obtained from a commercial source.

The simplicity of a calbindin-specific labeled line extending from lamina I to an independent nucleus of the thalamus was for a time quite attractive but it has not stood up to critical examination (Jones, 2002; Willis *et al.*, 2002; Ralston, 2003; Graziano and Jones, 2004; Jones, 2007). A review of lamina I inputs and of the distributions of high-threshold neurons in the thalamus, more critical immunostaining of the thalamus and repetition of the tracing experiments upon which the idea was based, have all discounted it (Fig. 2.27). When the thalamus is adequately stained immunocytochemically for calbindin, the densest zone of calbindin immunoreactivity is revealed to consist of the medial tip region of VPM embedded in the larger zone of calbindin immunostaining described in the previous two sections (Jones *et al.*, 2001; Jones, 2007) (Fig. 2.29). In the densest zone neurons and fibers stain intensely for calbindin and the region of densest staining within it coincides with the most medial rods of VPM; this zone co-stains for cytochrome oxidase and parvalbumin (Figs 2.20, 2.21, 2.29B–E). In weakly immunostained single sections and in preparations in which the boundaries of VPM were not evident, this would stand out as an apparently separate entity, but adequate staining and the systematic staining of adjacent sections for other markers, as described earlier and shown in Fig. 2.29, reveals the densest zone to be an integral part of VPM (Rausell and Jones, 1991a; Jones *et al.*, 2001). In this part, ipsilateral intraoral structures are represented (Jones *et al.*, 1986b; Rausell and Jones, 1991a) (Fig. 2.33). Around it, however, and extending posteriorly is the posterior complex and adjacent nuclei that also rather specifically immunostain for calbindin. It is in this region that there is a concentration of spinothalamic fiber terminals. In response to criticisms of the type outlined above, the Craig group now seem to have relocated “VMpo” to this region (Craig, 2006). The use of anti-calbindin antibodies or antisera from different sources gives the same pattern of immunostaining, and western blotting of the two antibodies in question reveals, not unexpectedly, that they recognize the same epitopes (Graziano and Jones, 2004), so differences in descriptions of the calbindin immunoreactive posterior region cannot depend on this factor. Tracing the calbindin-rich medial tip of VPM anteriorly and posteriorly (Jones *et al.*, 2001; Fig. 2.29) shows that it never extends beyond the confines of the VPM nucleus. It is an unusual region, nevertheless, for it is the only region in the ventral posterior nucleus to show coincidence of parvalbumin and calbindin expression; elsewhere their expression is complementary.

Repetition of the tracing experiments upon which the idea of lamina I-specific inputs to the so-called VMpo region were based, involving injections of anterograde tracer into the superficial medullary dorsal horn, reveal that the labeled fibers terminate within calbindin-positive regions of the thalamus but in a much more far-flung series of bursts than within the medial tip region of VPM or within any comparably restricted focus (Graziano and Jones, 2004; Fig. 2.27).

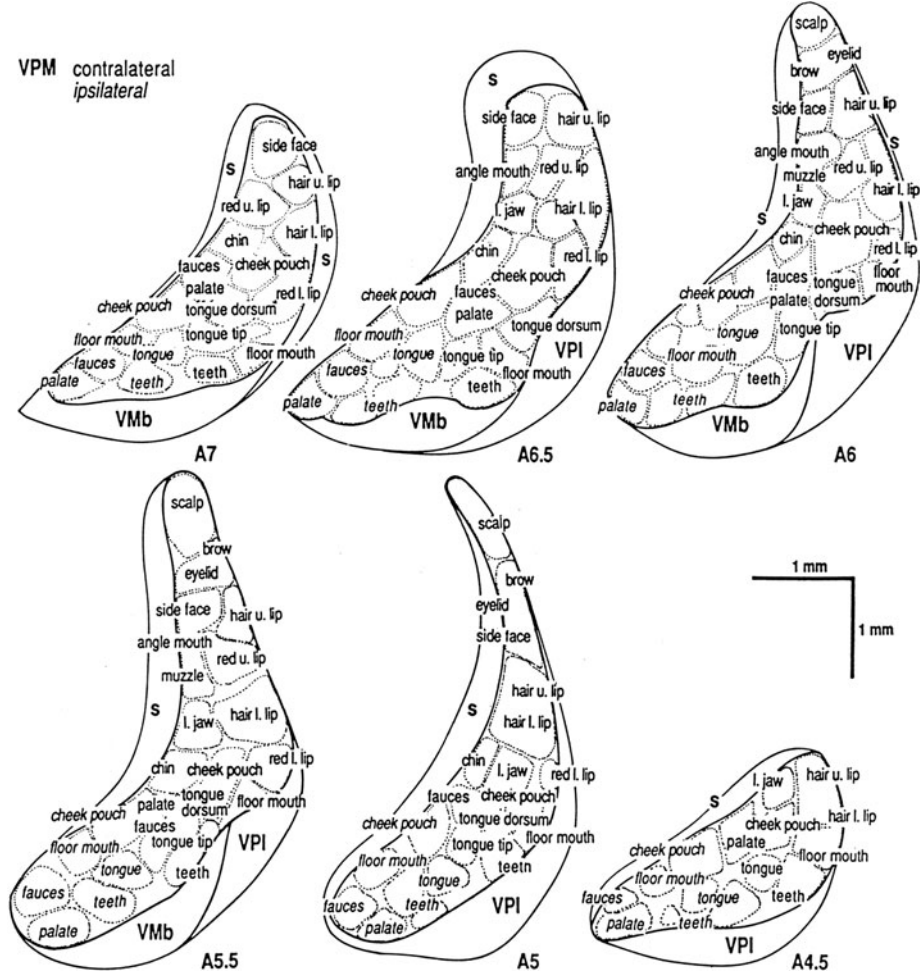


Fig. 2.33. Frontal sections at 0.5 mm intervals through the VPM nucleus of a macaque monkey, with stereotaxic coordinates added, showing details of the pattern of peripheral representation in relation to the cytochrome oxidase-stained rods (dotted outlines). Based on Rausell and Jones (1991a).

A dense cluster of terminations was invariably concentrated towards the medial tip of VPM but located well within the boundaries of the nucleus as outlined by its delimiting fiber lamina. When the densest clusters of terminations were superimposed upon images of the cytochrome oxidase-stained sections, the clusters, while definitely located within regions in which the calbindin matrix was concentrated, were by no means located in the medial tip or “VMpo” region. Although it is possible that injections located at other lamina I locations in the medullary or spinal dorsal horns would give fiber labeling in the medial tip region, the results of the experiments just described rule out the belief that

lamina I cells at all levels of the spinal and medullary dorsal horns and representing all parts of the body surface project solely to the zone of densest calbindin immunoreactivity at the medial tip of VPM. It is difficult to believe in any case that, as stated by Craig, lamina I fibers arising throughout the full length of the medullary and spinal dorsal horns could converge, without any topographic order upon such a small nucleus as that envisioned as VMpo.

Although a retrograde tracing study by Craig and Zhang (2006) reported that injections of tracer in the region called VMpo retrogradely labeled spinothalamic tract neurons specifically in lamina I, the injections were of such large extent that they clearly involved parts of the posterior, anterior pulvinar, VPL, VPM and VPM nuclei as well, so they can only be taken as evidence for nociceptive inputs to a much wider territory than that construed as VMpo. Moreover, other retrograde tracing studies make it clear that the terminals of axons arising from lamina I cells are not restricted to the relatively tiny medial tip of VPM. Injections of tracer into VPL and VPM that did not involve the medial tip region resulted in retrograde labeling of projection neurons in laminae I and IV–VI at all levels of the spinal and medullary dorsal horns (Willis *et al.*, 2001). Neurons in both lamina I and in the deeper laminae could also be antidromically activated by weak electrical stimuli applied to VPL or VPM outside the medial tip region (Price *et al.*, 1976; Applebaum *et al.*, 1979; Zhang *et al.*, 2000a, 2000b). Although similar stimulation aimed at the medial tip region of VPM elicited antidromic responses in lamina I cells that had cooling-specific, multimodal or nociceptive stimulus-response characteristics (Dostrovsky and Craig, 1996), this does not prove that all lamina I cells with such properties project to the region in and around the medial tip of VPM. Many cells throughout VPL and VPM, as well as those located in the central lateral nucleus, possess nociceptive stimulus-response properties. This also argues strongly against the idea of the tiny medial tip/VMpo region being the exclusive relay for noci- and thermoceptive influences passing through the thalamus. The relay of lamina I projections in VPL and VPM continues to argue strongly in favor of the primary somatosensory area to which these nuclei project being involved in discriminative pain perception (Willis *et al.*, 2002). Terminations in the posterior nucleus and other regions outside VPL and VPM may preferentially contact cells projecting to para- and postinsular regions of cerebral cortex that are involved in signaling a sense of the affective qualities of a painful stimuli (Lenz *et al.*, 1997).

The view that all fibers ascending from lamina I of the dorsal horn are calbindin immunoreactive (Craig *et al.*, 1994) has also not held up in the face of critical examination. Dense bundles of calbindin immunoreactive fibers lie ventral to the medial tip region of VPM within the medial end of the thalamic fasciculus. Many of these fibers are ascending from the brainstem and enter the

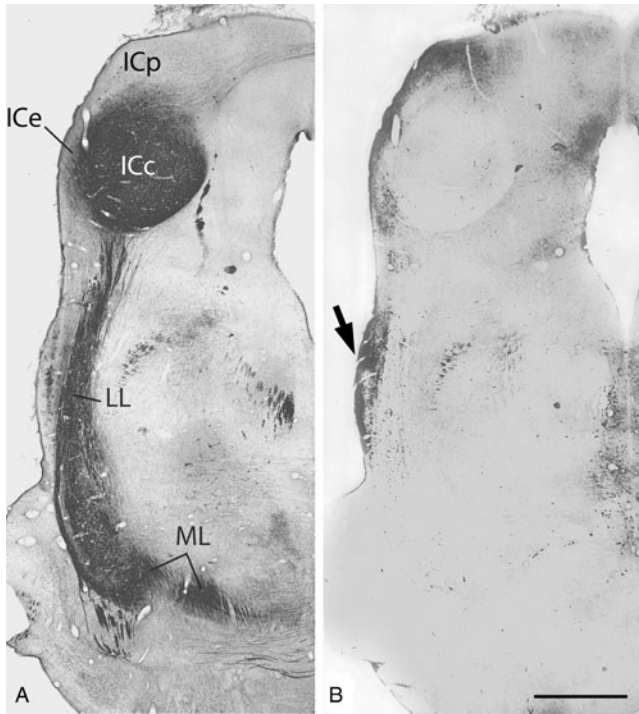


Fig. 2.34. Photomicrographs of the brainstem of a young macaque monkey, stained immunocytochemically for parvalbumin (A) or calbindin (B), showing the differential expression of the two calcium binding proteins in the medial and lateral lemniscal (ML, LL) and lateral tegmental pathways (arrow). Spinothalamic fibers ascend in the vicinity of the arrow (Fig. 2.35). From Jones (2007). Bar: 1 mm. ICc, ICe, ICp, central, external and pericentral nuclei of the inferior colliculus.

various nuclei of the ventral posterior complex but they are by no means limited in their distribution to the calbindin-rich medial tip of VPM or any adjacent calbindin-rich region. The majority of the calbindin immunoreactive fibers in and around the medial tip region are the thalamocortical axons of calbindin cells projecting to the cerebral cortex, not fibers ascending from the spinal cord and brainstem.

The high level of calbindin immunoreactivity in lamina I (and II) of the dorsal horn, the presence of calbindin immunoreactive fiber bundles ascending in the vicinity of the classical spinothalamic tract (Fig. 2.34) and the presence of dense calbindin immunoreactivity in the posterior thalamic region has invited the speculation that the lamina I projection to the thalamus is made up exclusively of calbindin immunoreactive fibers. However, concerted attempts to double-stain labeled spinothalamic or spinal trigeminothalamic fibers for calbindin immunoreactivity have never been successful (Rausell *et al.*, 1992a; Graziano

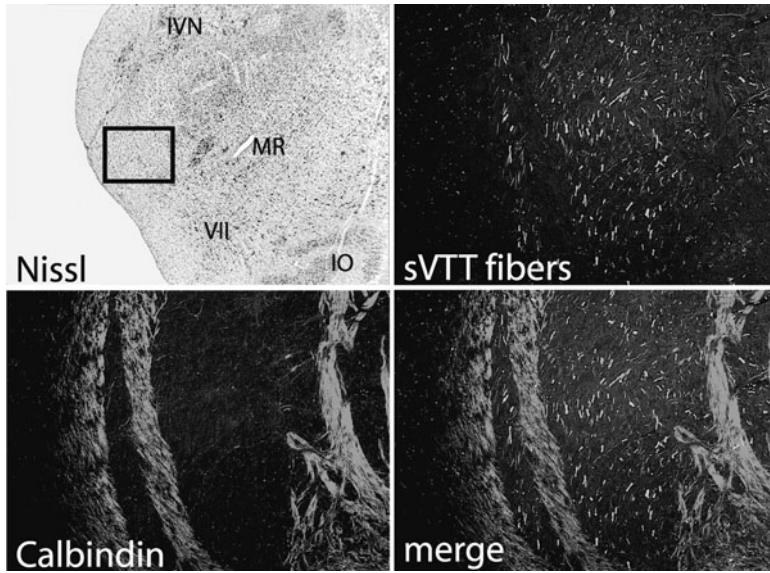


Fig. 2.35. Frontal section from the brain shown in Fig. 2.27. Boxed area, from approximately the same region as that arrowed in Fig. 2.34, is shown in the other three panels at higher magnification and from an adjacent section stained immunocytochemically for calbindin and scanned by laser confocal microscopy for both calbindin immunoreactivity and for fluorescein dextran labeled spinal trigeminothalamic fibers (sVTT). In the merged image it can be seen that the labeled fibers are not immunoreactive for calbindin. From Graziano and Jones (2004).

and Jones, 2004) (Fig. 2.35). Fibers arising in the superficial dorsal horn and ascending through the brainstem to the thalamus commonly lie in close contiguity to calbindin immunoreactive fiber bundles but they cannot be co-stained for calbindin immunoreactivity (Fig. 2.35).

Cortical projections of thalamic nuclei in which spinothalamic and spinal trigeminothalamic fibers terminate

The primary somatosensory cortex

The principal cortical target of the ventral posterior nucleus is the first somatosensory area (SI; Fig. 2.22) (Jones and Powell, 1970; Burton and Jones, 1976; Jones *et al.*, 1979, 1982; Lin *et al.*, 1979; Nelson *et al.*, 1980; Jones and Friedman, 1982; Pons and Kaas, 1985; Brysch *et al.*, 1990; Gingold *et al.*, 1991; Krubitzer and Kaas, 1992; Rausell *et al.*, 1992a; Stevens *et al.*, 1993; Burton *et al.*, 1995; Manger *et al.*, 1995, 1996; Zhang *et al.*, 2001a, 2001b; Coq *et al.*, 2004). There is a parallel projection to the second somatosensory area (SII) but this is not agreed to by all recent investigators mainly because of differences in the manner

in which the cortex of the peri-insular regions has been subdivided and because of failure to take into account the differential projections of the core and matrix cells of the ventral posterior complex.

The SI area of primates is traditionally divided into four cytoarchitectonic fields: from anterior to posterior these are areas 3a, 3b, 1 and 2 (Fig. 2.22). There is a more or less complete representation of the contralateral half body in each field (Paul *et al.*, 1972; Merzenich *et al.*, 1978; Kaas *et al.*, 1979; Nelson *et al.*, 1980; Iwamura *et al.*, 1983a, 1983b). Single- and multi-unit studies in monkeys have shown that neurons in area 3a are responsive primarily to stimuli applied to deep tissues, especially muscle; neurons in areas 3b and 1 are responsive to low-threshold cutaneous stimuli; those in area 2 are responsive to deep stimuli, mainly movements of joints (Powell and Mountcastle, 1959; Phillips *et al.*, 1971). Area 3b receives inputs from both slowly adapting and rapidly adapting mechanoreceptors, the inputs gaining access to different modular territories of that area (Sur *et al.*, 1981, 1984).

Anterograde labeling studies have revealed that different parts of the ventral posterior nucleus project to the separate fields of SI (Friedman and Jones, 1981; Jones *et al.*, 1982; Jones and Friedman, 1982) (Fig. 2.22). The central core region of VP, comparable to the VPLp nucleus of the human thalamus (the V.c.p.e nucleus of Hassler, 1959) has its predominant subcortical input from low-threshold cutaneous mechanoreceptors and projects to areas 3b and 1; central and peripheral parts of the core project to one or both of these areas. An anterodorsal shell region, comparable to the VPLa nucleus of the human thalamus (the V.c.a.e nucleus of Hassler, 1959), is dominated by low-threshold inputs from muscle and joint receptors and projects to areas 3a and 2; the anterior part of this shell is the thalamic relay for Group IA afferents and projects specifically to area 3a while the dorsal part receives less well-defined muscle and joint inputs and projects to areas 3a and 2 (Friedman and Jones, 1981; Jones and Friedman, 1982; Burton *et al.*, 1995). Virtually no cells in regions projecting to two fields have branched axons ending in the two fields (Jones, 1983).

The area-specific projections of the ventral posterior nucleus are formed by the axons of parvalbumin positive neurons located in the core regions of the VPL and VPM nuclei (Rausell and Jones, 1991a, 1991b; Rausell *et al.* 1992a; Jones, 1998b, 1998c, 2001, 2007). These axons terminate in middle layers of the relevant area of SI in a highly ordered topographic array and their terminations do not extend over the cytoarchitectonic borders of the area to which they project. The calbindin neurons of the matrix regions of VPL and VPM, by contrast, send their axons to terminate in superficial layers (I, II and upper III) of the cortex and these axons can spread over the borders of architectonic fields (Fig. 2.24).

Area 2, in addition to its input from the ventral posterior nucleus, receives a significant input from the anterior pulvinar nucleus (Fig. 2.22), which also projects

to wider areas of the parietal and parainsular cortex (Jones *et al.*, 1979; Mesulam and Mufson, 1985; Pons and Kaas, 1985; Cusick and Gould, 1990). This input, like that from the ventral posterior nucleus itself, arises primarily from the calbindin cells of the thalamic matrix; the matrix is enriched in the anterior pulvinar nucleus.

The differential engagement of core and matrix cells by the lemniscal and spinothalamic systems respectively (Fig. 2.24) and their separate projections to the somatosensory cortex forms the basis of two distinct parallel pathways through the ventral posterior complex, one dominated by inputs from low-threshold mechanoreceptors and the other by spinothalamic inputs from nociceptors and thermoceptors.

The second somatic sensory and adjacent areas

The second somatosensory area (SII), which in monkeys occupies a large part of the parietal operculum, has been subjected to repeated parcellations. Originally identified by evoked potential recording as a single area (Woolsey, 1958), the area, when re-investigated with modern multiunit mapping studies, commonly allied with tracing of corticocortical connections from SI, has been shown to be made up of two complete contralateral body representations. These are located anterior and posterior on the parietal operculum, and extend slightly onto the insula. The two body representations are mirror images of one another in monkeys (Fig. 2.36) and similar representations have been identified in humans (Disbrow *et al.*, 2000). The two divisions were called SIIc (posteriorly) and SIIf (anteriorly) by Whitsel *et al.* (1969b), Robinson and Burton (1980a, 1980b, 1980c) and Burton *et al.* (1995) but in repeat studies of the macaque, areas SIIc and SIIf have been renamed SII and PV respectively (Disbrow *et al.*, 2003) (Krubitzer and Kaas, 1990; Qi *et al.*, 2002; Coq *et al.*, 2004). Somatosensory responses can also be evoked, without clear evidence of a body topographic representation, in other regions in the vicinity of the lateral sulcus of primates. These include the granular insular field, the retroinsular field, area 7B and a ventral area (VS) adjacent to gustatory and visceral representations whose input comes predominantly from the VMb nucleus (Robinson and Burton, 1980a, 1980b, 1980c; Krubitzer and Kaas, 1990; Schneider *et al.*, 1993; Burton *et al.*, 1995; Krubitzer *et al.*, 1995; Qi *et al.*, 2002).

Many studies demonstrated that the SII region receives thalamic input from the VPL and VPM nuclei. Some have emphasized that the predominant input to SII comes, instead, from the VPI nucleus (Friedman and Murray, 1986; Krubitzer and Kaas, 1990; Disbrow *et al.*, 2002; Qi *et al.*, 2002). Others continue to locate cells projecting to SII in VPL proper as well as in VPI (Robinson and Burton, 1980c; Burton, 1984; Brysch *et al.*, 1990; Stevens *et al.*, 1993; Zhang *et al.*, 2001a, 2001b). SII-projecting cells in VPL occupy regions of VPL in which cytochrome oxidase staining is weak; that is to say they lie in the fingers of weak staining that

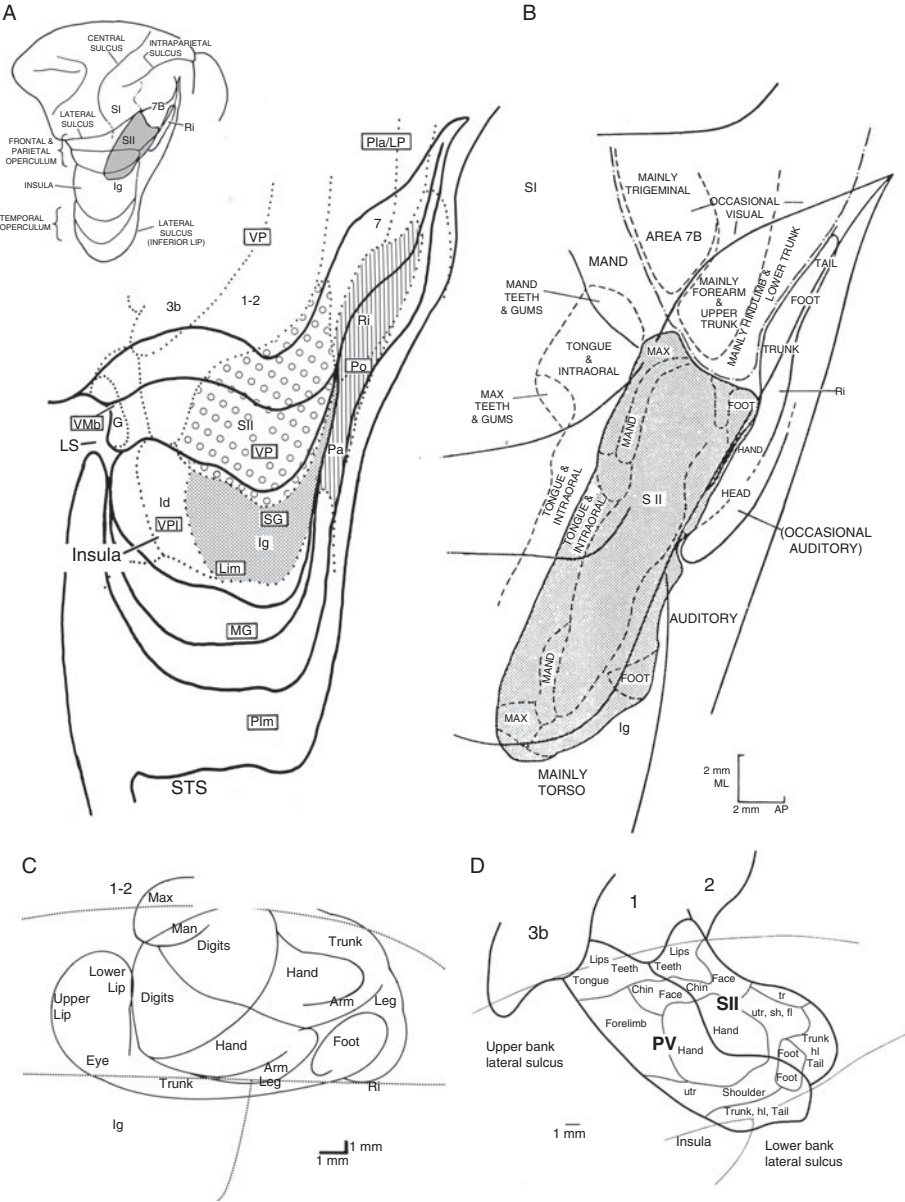


Fig. 2.36. The SII somatosensory region in the upper bank of the lateral sulcus of macaque monkeys. Anterior is to the left in all cases. (A), redrawn from Jones and Burton (1976), shows a reconstructed lateral sulcus (LS) drawn as though opened out to reveal the insula. STS is superior temporal sulcus. Granular insular area (Ig) receives fibers from the limitans-suprageniculate nucleus (Li-SG); retroinsular area (Ri) receives fibers from the posterior nucleus (Po). Adjacent fields receive fibers from the ventral posterior complex, with major projections from the VmB nucleus to the gustatory area (G), from VPI to the dysgranular insular area (Id) and from the VPM and VPL nuclei to SI

insinuate their way upwards from VPI into VPL, especially in the zone between the upper and lower limb representations in VPL. VPI and these finger regions are regions in which calbindin immunoreactive cells of the thalamic matrix are concentrated. The areas of the parietal operculum, when examined immunocytochemically, resemble areas surrounding the primary auditory cortex that are dominated by inputs from calbindin matrix cells of the dorsal nuclei of the medial geniculate complex (Hashikawa *et al.*, 1995; Jones *et al.*, 1995; Molinari *et al.*, 1995; Jones, 2003). They lack the dense parvalbumin immunoreactive fiber plexuses typical of the primary auditory, somatosensory and visual sensory areas and show well-stained calbindin immunoreactive cells but no staining of fiber plexuses (Jones, 2007). Currently, it appears that SIIc area and PV areas receive their principal thalamic input from VPI and adjacent matrix regions of VPL, along with the calbindin-rich anterior pulvinar nucleus. There are hints also of inputs from the anterodorsal deep shell region of VPL. Other inputs to PV may come from what is described as the mediodorsal nucleus (Disbrow *et al.*, 2002) but which is primarily the central lateral nucleus.

Thalamic cells projecting to SII, when identified by antidromic activation in New World monkeys rather than by anatomical tracing, were widely distributed within the ventral posterior nucleus and co-located with SI-projecting cells (Zhang *et al.*, 2001a, 2001b). Both SI- and SII-projecting cells possessed low-threshold, cutaneous or deep receptive fields. A small number of wide dynamic range neurons and a smaller number of high-threshold neurons located in VPL proper were found to project to the SI cortex (Kenshalo *et al.*, 1980), but it has not been specifically determined that wide dynamic range or high-threshold neurons in VPL or VPM project to SII. In monkeys, some spinothalamic tract axons end in relation to VPI cells which can be expected to project to SII (Stevens *et al.*, 1993) and nociceptive responsive neurons have been recorded in the SII region of monkeys (Chudler *et al.*, 1986; Dong *et al.*, 1989). Painful experiences were reported by patients in whom cortical regions that included the SII region were stimulated (Penfield and Perot, 1963; Gloor *et al.*, 1982). The selective innervation of diffusely projecting matrix cells of VPI by spinothalamic and spinal trigeminothalamic

Caption for Fig. 2.36. (cont.)

and SII. For diffuse projections from matrix cells within VPI and other nuclei to the SII, insular and retroinsular fields see Fig. 2.37. Inset: the general orientation of figures (A–D). From Robinson and Burton (1980b). B, from Robinson and Burton (1980a), shows a single SII area with extended representations of the digits of the hand and a split representation of the foot. C, from Burton *et al.* (1995), is rotated with respect to (A) and shows two mirror image representations of the contralateral body surface. (D), from Disbrow *et al.* (2002), labels the posterodorsal of these representations SII and the anteroventral one PV.

fibers and their projection to the opercular-insular region that includes SII may, therefore, make an important contribution to the experience of pain but similar innervation of the SI-projecting matrix cells of VPL and VPM makes it impossible to rule out the SI area as well.

We should not forget that the terminations of spinothalamic fibers, unlike those of lemniscal fibers, are not constrained by the ventral posterior nucleus or posterior complex. The typical burst-like terminal ramifications of the spinothalamic fibers extend well into the adjoining ventral lateral posterior nucleus (VLp) where they alternate with the terminations of cerebellothalamic fibers (Tracey *et al.*, 1980; Asanuma *et al.*, 1983b, 1983c; Stepniewska *et al.*, 2003; Jones, 2007) (Figs 1.31, 2.16). This implies that influences mediated by the spinothalamic fibers will be projected upon the motor cortex which is the principal target of the VLp nucleus (Jones, 2007).

Cortical targets of the posterior nucleus and adjacent regions

In studies of the cortical projections of the posterior complex of rhesus monkeys and squirrel monkeys, Burton and Jones (1976) concluded that its overall cortical target commenced on the insula and extended posteriorly around the second somatosensory area (SII) and the first auditory field (AI) into the retroinsular cortex of the lateral sulcus (Figs 2.36, 2.37). The limitans-supragenigulate nucleus clearly projected to the granular insular field, the medial part of the posterior nucleus, extending back along the medial border of the medial geniculate complex and largely co-extensive with that receiving spinothalamic afferents, projected to the retroinsular field (Ri) between SII and AI, and a lateral, presumed auditory part, incorporating what would now be regarded as the anterodorsal nucleus of the medial geniculate complex, projected to the postauditory field adjacent to Ri and posterior to AI. Mufson and Mesulam (1984) and Mesulam and Mufson (1985) reached similar conclusions, showing that the anterior insula fields were primarily connected with VPI and posterior fields with the limitans-supragenigulate and anterior pulvinar nuclei as well as with the centre médian and parafascicular nuclei.

In the cortical target of the limitans-supragenigulate nucleus, the granular insular area (Burton and Jones, 1976; Mufson and Mesulam, 1984; Mesulam and Mufson, 1985), most neurons are reported to be driven by innocuous somatic stimuli and to have large receptive fields (Robinson and Burton, 1980c).

The principal cortical area to which the posterior nucleus projects, the retroinsular area (Burton and Jones, 1976; Fig. 2.36), does not contain neurons uniquely sensitive to noxious stimuli, although many have large, convergent receptive fields (Robinson and Burton, 1980b). The postauditory area, shown by Robinson and Burton (1980a, 1980b, 1980c) to exhibit low-threshold neuronal responses to auditory stimuli, has since been renamed the posteromedial

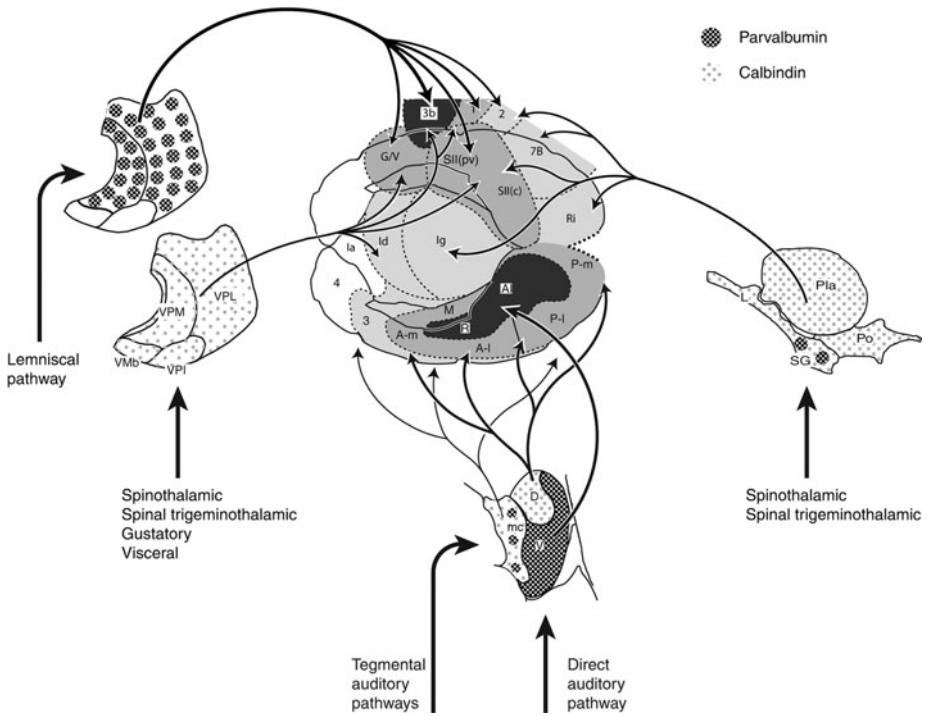


Fig. 2.37. Central figure shows the parietal and temporal opercula of a macaque monkey opened out to reveal the insula. The opercula are drawn to scale but the insula, in being “flattened” is somewhat “stretched.” Different densities of shading indicate cortical areas with heavy (dark shading) to lightest (no shading) densities of parvalbumin immunoreactive fiber plexuses. Outlying figures show sections of the ventral posterior complex (left), posterior complex (right) and medial geniculate complex (below) with the major densities of parvalbumin core cells and calbindin matrix cells along with their differential innervation by ascending fiber pathways. The cortical projections of the core and matrix cells are indicated by arrows. AI, primary auditory field; A-l, anterolateral auditory field; A-m, anteromedial auditory field; P-l, posterolateral auditory field; P-m, posteromedial auditory field.

auditory field (Morel and Kaas, 1992; Jones *et al.*, 1995; Kosaki *et al.*, 1997) (Fig. 2.37). It has a tonotopic organization that reverses from the primary AI field.

The human parainsular regions

Functional imaging studies reveal that painful sensory events are associated with activation not only of the first and second somatic sensory areas but also of anterior cingulate and para-insular regions of the cerebral cortex (Coghill *et al.*, 1994; Casey *et al.*, 1996; Gelnar *et al.*, 1999; Peyron *et al.*, 1999; Ploner *et al.*, 1999, 2002; Craig *et al.*, 2000; Timmermann *et al.*, 2001; Chen *et al.*, 2002; Ohara *et al.*, 2004a) (Chapter 8). As we have just seen, SII and the parainsular regions have connections with the posterior nucleus region of the thalamus and in

humans, as in monkeys, spinothalamic and spinal trigeminothalamic fibers have an extensive zone of terminations that corresponds almost exactly to the posterior nucleus as defined earlier in this chapter and in [Chapter 1](#) (Mehler, 1966a, 1966b, 1969; Jones, 2007). Neurosurgical experience tells us that stimulation in regions near the posterior pole of the ventral posterior nucleus elicits sensations of pain, and that lesions placed there can alleviate painful sensations ([Chapter 7](#)). Microstimulation posterior and inferior to VPL elicits painful mechanical and thermal sensations that are projected to peripheral receptive fields (Hassler, 1970; Lenz *et al.*, 1993a, 1993b, 1994a, 1994b, 1995, 1996, 1998b; Lin and Lenz, 1994; Davis *et al.*, 1996, 1999; Ohara and Lenz, 2003). Microstimulation in the core of VPL, by contrast, more commonly elicits paresthesiae and non-painful thermal sensations (Ohara *et al.*, 2004d). The effective site for influencing pain sensation by microstimulation has usually been equated with what Hassler (1959) called the parvocellular part of the ventral posterior complex (nucleus ventralis caudalis, pars parvocellularis or V.c.pc). This is largely co-extensive with the VPI and VMb nuclei and their continuations into the posterior nucleus (Po). The Po nucleus is essentially the same as Hassler's nucleus limitans portae (Li.por). According to Hassler (1960), stimulation of the nucleus limitans portae in humans also elicits painful sensations and lesions centered on it can alleviate painful conditions. Such effects could be produced by stimulation or destruction of the cells of the region which receive specific terminations of spinothalamic and spinal trigeminothalamic fibers but effects on spinothalamic fibers that pass through the posterior nucleus en route to other thalamic nuclei cannot be ruled out.

Electrical stimulation of the human SII and adjacent regions of cortex that are the targets of the posterior nuclear complex in some reports did not elicit sensations of pain (White and Sweet, 1969; Lende *et al.*, 1971), but in others painful sensations were reported when the insula was stimulated (Ostrowsky *et al.*, 2002). Deep undercutting or excision of the parietotemporal operculum posterior to the insula reportedly can alleviate painful conditions (Talairach *et al.*, 1949; Lende *et al.*, 1971) and small infarctions of the opercular-insular region have been associated with hyperpathia or hemi-hypalgesia (Biernond, 1956; Greenspan *et al.*, 1999).

From the extensive review contained in the preceding sections and in other chapters of this book, the peri-insular region is by no means the only terminus of the ascending pain pathway so it is unlikely to be the sole area of the cerebral cortex concerned with the appreciation of pain ([Chapter 8](#)). Similarly, the parvocellular parts of the ventral posterior complex and their extension back into the posterior nucleus are unlikely to be the exclusive route for conveyance of pain messages to the cerebral cortex. The ventral posterior nucleus and its target, the SI cortex, cannot be dismissed ([Chapter 3](#)); nor can the intralaminar thalamic nuclei and their cortical targets.

Cortical and striatal projections of the intralaminar nuclei

The distribution of spinothalamic and spinal trigeminothalamic fibers in relation to the intralaminar nuclei has been described earlier and are schematized in Fig. 2.31A. The intralaminar nuclei and their extensions, the limitans-suprageniculate and magnocellular medial geniculate nuclei, give rise to the greater part of the extensive thalamostriatal projection (Fig. 2.31B). Spinothalamic and spinal trigeminothalamic fibers definitely terminate in relation to striatally projecting cells. Some striatally projecting axons have branches that also pass to the cortex (Jones and Leavitt, 1974; Beckstead, 1984; Macchi and Bentivoglio, 1986; Jones, 1989, 1998b; Fenelon *et al.*, 1991; Sadikot *et al.*, 1992; de las Heras *et al.*, 1998; Erro *et al.*, 2002; Van der Werf *et al.*, 2002).

There have been few studies of the cortical projections of the intralaminar nuclei in monkeys. The cortical branches of axons of single centre médian nucleus cells projecting to the striatum in monkeys end rather sparsely in layers I and VI (Parent and Parent, 2002). In other species, the cortical projection of the intralaminar nuclei is neither diffuse nor non-specific; each intralaminar nucleus projects to a particular region although this can be quite extensive and not delimited by cytoarchitecture (Macchi *et al.*, 1975, 1977, 1984; Royce and Mourey, 1985; Macchi and Bentivoglio, 1986; Royce *et al.*, 1989; Berendse and Groenewegen, 1991).

The anterior intralaminar nuclei (the central medial, paracentral, central lateral and their midline extension) project to prefrontal, cingulate, parietotemporal, entorhinal and prepiriform cortex. The central medial projection is heaviest to medial and basal areas of the cortex while the paracentral and central lateral projection is heaviest to lateral areas. The central lateral nucleus and thus neurons located there that receive inputs from spinothalamic fibers, projects mainly to primary sensory-motor and anterior parietal areas. The projection to the somatosensory areas is weaker than that to the motor areas and much weaker than that to the anterior parietal areas (Royce and Mourey, 1985; Royce *et al.*, 1989). Small but significant numbers of cells in the centre médian nucleus also project to the primary motor cortex. The parafascicular nucleus projects to deeply placed areas around the rhinal sulcus but also to the insular region and to the cingulate gyrus (Jones and Leavitt, 1974; Mufson and Mesulam, 1984; Royce and Mourey, 1985; Groenewegen *et al.*, 1999). The magnocellular medial geniculate nucleus and the limitans-suprageniculate nucleus are the sources of an equivalent intralaminar projection to the auditory areas of the cerebral cortex (Jones, 1985, 1989; Hashikawa *et al.*, 1995). Temporal and insular areas of the monkey cortex also receive inputs from the limitans-suprageniculate nucleus (Burton and Jones, 1976; Pearson *et al.*, 1978; Mufson and Mesulam, 1984; Asanuma *et al.*, 1985).

Some authors describe intralaminar axons ending only in layer I of the cortex while others report them in layer VI only or in both layers I and VI (Jones, 1975; Kaufman and Rosenquist, 1985; Rieck and Carey, 1985; Royce and Mourey, 1985; Cunningham and LeVay, 1986; Royce *et al.*, 1989; Towns *et al.*, 1990; Berendse and Groenewegen, 1991; Marini *et al.*, 1996). Molinari *et al.* (1994), in cats, suggested that one class of intralaminar cells projected to superficial layers and a second to deeper layers. This also seems to be the case for nuclei such as the magnocellular medial geniculate nucleus that are organized like the intralaminar nuclei (Hashikawa *et al.*, 1995). In the cat, both cortically projecting types are calbindin immunoreactive and calbindin immunoreactive cells also form the population that projects to the striatum (Molinari *et al.*, 1994).

Cortical projections of the submedial nucleus

The submedial nucleus (Sm) is not always identified in the primate brain. In rats it projects to ventral-lateral orbital cortex in the vicinity of the frontal pole (Jones and Leavitt, 1974; Price and Slotnick, 1983; Coffield *et al.*, 1992; Reep *et al.*, 1996), and in cats to a region in the medial bank of the presylvian sulcus (Craig *et al.*, 1982). This cortical region in cats lies medial to the projection zone of gustatory/visceral afferents relayed through the VMB nucleus (Beckstead, 1978; Craig *et al.*, 1982; Yoshida *et al.*, 1992). An equivalent region in monkeys and humans should, therefore, lie in the junctional region between the insula, orbital surface of the frontal lobe and the frontal operculum (Carmichael and Price, 1994; Öngür *et al.*, 2003). In rats the projection field of the Sm nucleus abuts on and probably overlaps the projection of the mediodorsal and parataenial nuclei (Krettek and Price, 1977; Reep and Winans, 1982; Price and Slotnick, 1983; Groenewegen, 1988; Coffield *et al.*, 1992; Reep *et al.*, 1996).

Cortical projections of the basal ventral medial nucleus: gustatory and visceral pathways

The principal afferent input to the VMB nucleus comes from the gustatory division of the parabrachial nucleus of the pons (Norgren and Leonard, 1971, 1973; Norgren, 1976; Ricardo and Koh, 1978; Saper, 2002). In primates there is also a direct gustatory pathway from the nucleus of the solitary tract (Beckstead *et al.*, 1980; Norgren, 1990; Pritchard *et al.*, 2000) but this is contested (Saper, 2002). Medial or anterior divisions of the parabrachial nucleus project bilaterally to VMB, the ipsi- and contralateral projections being of equal density in monkeys (Norgren and Wolf, 1975; Norgren, 1976, 1983; Beckstead *et al.*, 1980; Saper and Loewy, 1980; Block and Schwartzbaum, 1983; Yasui *et al.*, 1983; Fulwiler and Saper, 1984; Nomura and Ogawa, 1985; Cechetto and Saper, 1987; Hayama and Ogawa, 1987; Ogawa *et al.*, 1987; Halsell, 1992; Karimnamazi and Travers, 1998; Pritchard

et al., 2000; Saper, 2000). Parabrachial neurons projecting to VMb in rats also send axon branches to more rostral and ventral forebrain areas such as the amygdala (Norgren, 1976; Voshart and Van der Kooy, 1981; Halsell, 1992; Pritchard *et al.*, 2000). The solitary tract nucleus-parabrachial nucleus-VMb pathway is relatively rich in fibers containing neuroactive peptides and there are a few peptide-containing cells in VMb itself (Mantyh and Hunt, 1984).

VMb of the rat is divided into medial and lateral divisions. The medial division is the primary terminus of second-order taste afferents while the lateral division is innervated by visceral afferents coming from cardiac, arterial and gastric baroreceptors, chemoreceptors and mechanoreceptors (Cechetto and Saper, 1987). Many of these afferents may be included in the spinothalamic and spinal trigeminothalamic pathways and in monkeys form the diffuse patches of terminations extending from VPI and adjacent nuclei into VMb (Craig and Burton, 1985; Iwata *et al.*, 1992; Rausell *et al.*, 1992a; Apkarian and Shi, 1994; Apkarian *et al.*, 2000; Craig, 2003; Graziano and Jones, 2004). Some neurons in VMb show convergent cutaneous, muscular and noxious visceral inputs (Monconduit *et al.*, 2003). In the monkey VMb nucleus, the non-gustatory and gustatory division are located anteriorly and posteriorly respectively (Pritchard *et al.*, 2000).

VMb projects to a cortical area located between the first somatosensory and insular areas (Fig. 2.37). Stimulation of the vagus, glossopharyngeal, chorda tympani or lingual nerves elicits neuronal responses in regions anterior to the insular cortex in many species including monkeys (Dell and Olson, 1951; Dell, 1952; Benjamin and Pfaffman, 1955; Benjamin and Akert, 1959; Emmers, 1966; Ganchrow and Erickson, 1972; Norgren and Wolf, 1975; Yamamoto *et al.*, 1980, 1981a, 1981b, 1988, 1989; Pritchard *et al.*, 1986; Niimi *et al.*, 1989; Yaxley *et al.*, 1990; Baylis *et al.*, 1995; Ito *et al.*, 2001). Stimulation or injections of anatomical tracers in these cortical regions antidromically activates or retrogradely labels cells in VMb (Ganchrow and Erickson, 1972; Yamamoto *et al.*, 1981a, 1981b). There is a primary taste responsive area at the junction of the orbitofrontal and insular cortex in monkeys and a secondary area located more anteriorly in the orbitofrontal cortex (Benjamin and Burton, 1968; Ogawa *et al.*, 1985; Scott *et al.*, 1986; Rolls *et al.*, 1990; Yaxley *et al.*, 1990; Ito and Ogawa, 1991; Baylis *et al.*, 1995; Scott and Plata-Salaman, 1999; Ito *et al.*, 2001; Rolls, 2001), both connected with VMb (Burton and Jones, 1976; Pritchard *et al.*, 1986; Baylis *et al.*, 1995).

Stimulation of the VMb region in humans elicits sensations of taste and gastric fullness plus painful and non-painful somatic sensations (Lenz *et al.*, 1997), while visceral stimuli lead to activation of the anterior insular region in humans (King *et al.*, 1999; Banzett *et al.*, 2000; Harper *et al.*, 2000). Thermal stimuli activate a slightly more posterior region (Craig *et al.*, 2000).

Summing up

Peripheral nociceptors and the Aδ and C fibers in whose endings they are located form a series of labeled lines that enter the spinal cord in the lateral divisions of the dorsal roots. In the dorsal horn, the fibers have terminations on neurons located in superficial laminae and on the dendrites of those located in deeper laminae. GABAergic and enkephalinergic cells form potent modulators of the traffic through the dorsal horn. There are two main classes of spinothalamic tract neuron involved in the central pain pathways: those that are noci- or thermoceptive specific and those that possess wide dynamic range properties. The spinothalamic and spinal trigeminothalamic tracts are the principal ascending pathways leading to cortical centers involved in the conscious appreciation of pain. The spinocervicothalamic and postsynaptic dorsal column pathways also contribute, the latter especially in relation to visceral pain. The positions of the ascending pain pathways in the brainstem and their sites of brainstem terminations in the medulla, pons and midbrain are now well-defined. Few of these brainstem sites, which include large regions of the reticular formation as well as other nuclei, project to the thalamus; those that do are mainly concerned with visceral or gustatory sensations rather than pain. The spinothalamic and spinal trigeminothalamic fibers have widespread terminations in the thalamus. Thalamic nuclei in which the fibers terminate include the ventral lateral, ventral posterior, posterior, limitans/suprageniculate and posterior intralaminar nuclei. The terminations have a predilection for ending in relation to the calbindin immunoreactive neurons that form the thalamic matrix and which tend to have more diffuse cortical projections than the parvalbumin immunoreactive neurons on which lemniscal terminations are focused. There is a particular concentration of fibers that may include a predominant population arising from cells in lamina I of the dorsal horn, in regions around the posterior pole of the ventral posterior nucleus, regions that have received various names. Attempts, however, to force all lamina I arising fibers into a narrowly restricted terminal zone are unjustified. Cortical projections of the thalamic nuclei in which pain fibers end include the primary and secondary somatosensory cortex as well as para-insular and anterior cingulate regions, all of which have been implicated by imaging and other observations in the appreciation of pain.

Endnote

1 This part of the lateral funi- culus has come to be called the “dorsolateral funiculus,”	which is confusing since this is, more correctly, the stand- ard anatomical term for	Lissauer’s tract (e.g. Haines, 2008).

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Physiology of cells of origin of spinal cord and brainstem projections

Introduction

As discussed in [Chapter 2](#), several of the sensory pathways that ascend from the spinal cord or brainstem to higher levels of the monkey central nervous system have a nociceptive component and thus may contribute to pain sensation. Spinal cord projections with nociceptive components that ascend to the brain in the anterolateral quadrant of the spinal cord include the spinothalamic, spinoreticular, spinomesencephalic and spinohypothalamic tracts; nociceptive projections that ascend in the dorsolateral or dorsal funiculus are the spinocervical tract and the postsynaptic dorsal column pathway (see Willis and Coggeshall, [2004](#)). Brainstem projections include the trigeminothalamic tract (Price *et al.*, [1976](#)).

To investigate the physiology of an individual spinal cord or brainstem neuron that belongs to one of the ascending nociceptive pathways, it is important to “identify” the neuron by showing that the axon of the individual neuron under investigation actually projects to the appropriate target (Willis and Coggeshall, [2004](#)). Recordings from a neuron unidentified in terms of its projection can be misleading, since many unidentified neurons are likely to be interneurons, and these could be excitatory or inhibitory and might or might not influence the activity of sensory projection neurons. For instance, many spinal cord interneurons belong to neural circuits that function to control motor output (Jankowska *et al.*, [1981](#); Rudomin *et al.*, [1987](#)).

Identification of a projection neuron is typically accomplished by demonstrating that the neuron can be activated antidromically in response to electrical stimulation in a region in which the axon of that projection neuron synapses (Trevino *et al.*, [1973](#); Bryan *et al.*, [1974](#); Haber *et al.*, [1982](#); see Willis and Coggeshall, [2004](#)). An alternative approach that might be considered is the injection of

a marker substance into the region containing the recorded neuron, followed by its anterograde transport and subsequent histochemical identification in synaptic terminals. However, such an approach is likely to yield ambiguous results and cannot be accomplished quickly, since anterograde axonal transport involves a delay. Furthermore, injection of anterograde tracer into the extracellular environment of an individual neuron under investigation using an extracellular recording technique would not provide convincing evidence that a neuron that picked up the label was the one from which recordings were made. Furthermore, intracellular injection of an anterograde tracer is often unlikely successfully to label the distant terminals of the long axons of many projection neurons.

Monkey spinothalamic tract neurons

The following section will describe the physiological properties of identified spinothalamic tract (STT) neurons in monkeys. However, the approach used in the investigation of STT cells applies as well to other types of ascending sensory projection neurons. Details about the techniques used for examining STT cells will be presented here, but similar techniques would be used for the study of other types of projection neurons.

Antidromic identification

Figures 3.1 and 3.2 illustrate criteria that allow the recognition of antidromic activation of an STT neuron (Fuller and Schlag, 1976; Lipski, 1981). These criteria include: (1) an action potential that is recorded from the soma-dendritic region of a candidate neuron (as shown by a prominent negative component of the spike; axons generally have entirely positive monophasic action potentials) at a constant latency on repeated stimulus trials; (2) the action potential has a distinct threshold, which is actually the threshold of the axon to the electrical stimulus applied in the target structure; and (3) orthodromic action potentials will collide with and block an antidromic action potential when they precede the antidromic action potential within a defined time frame, which is equal to or less than twice the antidromic latency plus the duration of the axon's absolute refractory period (about 0.5 ms).

Antidromic microstimulation has been utilized to map the area in which the terminals of individual STT neurons end within the monkey thalamus (Zhang *et al.*, 2000a). After positioning a stimulating electrode in the thalamus to activate STT cells antidromically, a roving microelectrode is used to apply very small current pulses in a series of parallel tracks at several different rostro-caudal levels to determine the thalamic region from which an STT cell could be activated antidromically using a very low stimulus intensity (such as 30 μ A;

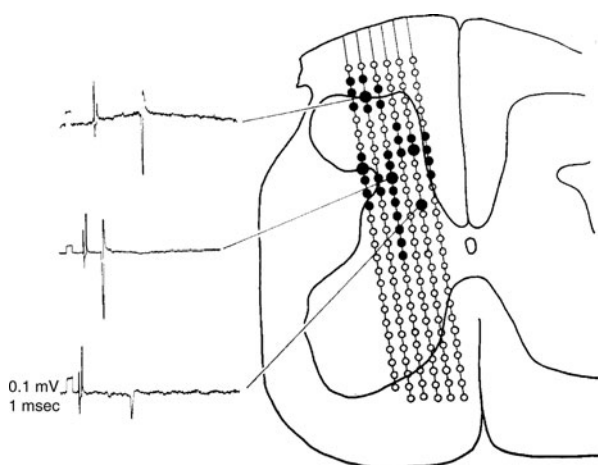


Fig. 3.1. Antidromic activation of spinothalamic tract (STT) neurons following stimulation in the ventral posterior lateral (VPL) nucleus of the thalamus on the side contralateral to the recorded neuronal activity. The locations of six microelectrode recording tracks separated by $150\ \mu\text{m}$ are shown superimposed on a drawing of a section through the lumbosacral spinal cord of a rhesus monkey. Signal-averaged recordings were made at $150\ \mu\text{m}$ intervals along each track. The open circles indicate recording sites at which no antidromic activity was detected, whereas the filled circles are locations where an antidromic action potential was recorded (the largest symbol in each cluster represents the point where the action potential of a given STT cell was of maximal size). The averaged antidromic action potentials of three of the five STT cells detected are shown at the left. The temporal compactness of the averaged action potentials reflects the fact that the action potentials had a constant latency. From Trevino *et al.* (1973).

Zhang *et al.*, 2000a). Figures 3.3A and B show the locations of sites from which low-intensity stimuli activated 20 different STT neurons. Of these, 19 sites were in the ventral posterior lateral (VPL) nucleus and 1 in the suprageniculate nucleus. Recording sites for neurons that projected to the VPL nucleus were located in either the superficial dorsal horn (SDH) or the deep dorsal horn (DDH).

In Fig. 3.3C are the positions of lesions marking the sites from which recordings were made from these 20 STT neurons. The recording sites are shown on a drawing of a section through the L5–7 region of a monkey spinal cord. The gray matter of the spinal cord can be subdivided grossly into a dorsal horn, intermediate region, ventral horn and central gray. However, a more commonly used subdivision is based on the ten spinal cord laminae described by Rexed (1952, 1954; see Chapter 2 of this volume). The only lamina of Rexed shown in Fig. 3.3C is lamina I, which is located in the most superficial part of the dorsal horn. The recording sites for many of the STT neurons in the experiments of

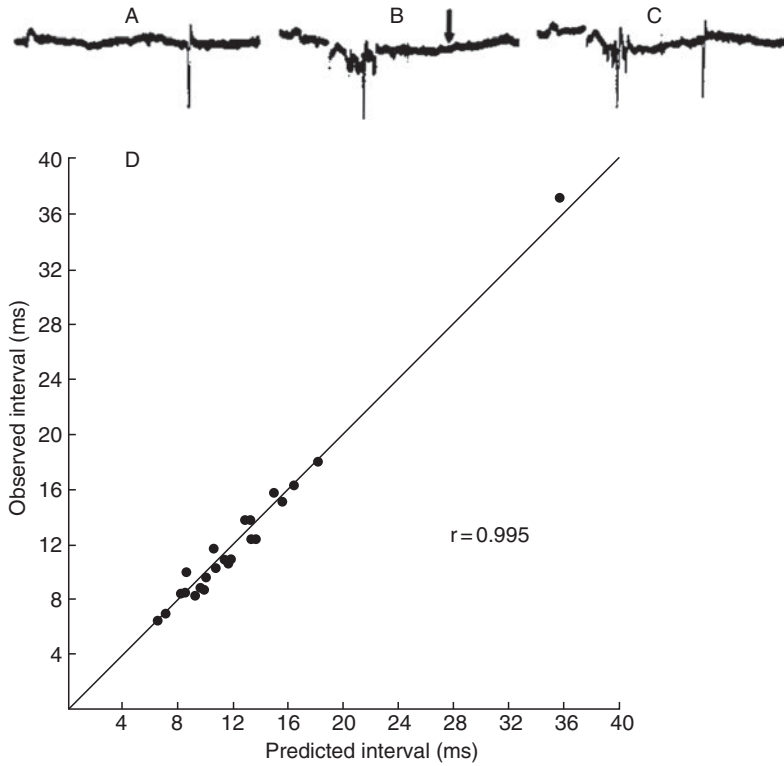


Fig. 3.2. Demonstration of the collision of an orthodromic with the antidromic action potential of a spinothalamic tract (STT) neuron. In (A) is shown a presumed antidromic action potential recorded from a dorsal horn neuron in response to stimulation in the contralateral VPL nucleus. In (B) is shown an orthodromic action potential recorded from the same neuron in response to electrical stimulation of the skin within the receptive field of the neuron. In the same recording, the thalamic stimulus failed to result in the appearance of an antidromic action potential at the expected time (arrow). The reason for this is that the orthodromic action potential occurred within the interval during which collision would be expected (twice the antidromic latency plus an absolute refractory period of about 0.5 ms). In (C) there was a greater interval between the cutaneous stimulus and the stimulus applied in the VPL nucleus, and so there was no collision and both the orthodromic and the antidromic action potentials could be recorded. The graph in (D) shows the critical intervals at which collision would be predicted to occur plotted against the observed intervals for collision in recordings from 22 different STT cells. The correlation coefficient is indicated. From Trevino *et al.* (1973).

Zhang *et al.* (2000a) were in lamina I. Other STT cells were in laminae III–V, which are deeper within the dorsal horn (Fig. 3.3C).

Spinothalamic tract neurons were classified as “low threshold” (LT), “high threshold” (HT) or “wide dynamic range” (WDR) neurons (see Mendell, 1966;

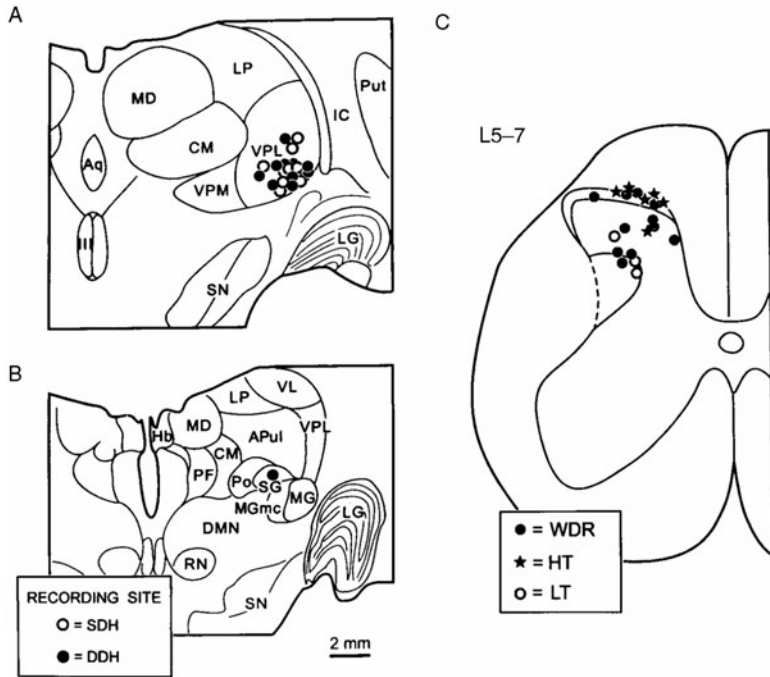


Fig. 3.3. Projections of monkey spinothalamic tract (STT) neurons to the thalamus, as determined by antidromic microstimulation. In (A) and (B) are shown low-intensity stimulus sites from which individual STT cells could be activated antidromically from stimulation in the ventral posterior lateral (VPL) nucleus or, in one case, the supragenulate (SG) nucleus. The open circles indicate neurons that were located in the superficial dorsal horn (SDH), and the filled circles neurons of the deep dorsal horn (DDH). In (C) the sites in the dorsal horn at which the STT cells could be recorded are shown in a drawing of a transverse section made at the L5-7 level. Filled circles indicate the locations of wide dynamic range (WDR) neurons, asterisks high-threshold (HT) neurons and open circles low-threshold (LT) neurons. From Zhang *et al.* (2000a).

Chung *et al.*, 1979). Low-threshold STT neurons respond to weak tactile stimuli, but their responses do not increase when strong mechanical stimuli are used. High-threshold STT neurons fail to respond to weak mechanical stimuli, but do respond in a graded fashion to strong mechanical stimuli that extend well into the noxious range. Wide dynamic range STT cells are activated by both weak and intense mechanical stimuli. Most of the high-threshold STT neurons in the sample recorded by Zhang *et al.* (2000a; Fig. 3.3C, HT = asterisks) were in lamina I, whereas many wide dynamic range neurons (Fig. 3.3C, WDR = filled circles) and several low-threshold (Fig. 3.3C, LT = open circles) STT neurons were in deeper dorsal horn laminae (see the section below on Receptive Fields for a further

description of the criteria used for classifying dorsal horn neurons and for illustrations of the responses of different classes of STT neurons).

The emphasis here will be on the physiological properties of projection neurons from which recordings were made in monkeys. Monkey STT cells have been described in several series of investigations by different laboratories (Trevino *et al.*, 1973; Albe-Fessard *et al.*, 1974a, 1974b; Willis *et al.*, 1974; Blair *et al.*, 1981, 1982, 1984; Giesler *et al.*, 1981; Milne *et al.*, 1981; Ammons *et al.*, 1984, 1985a, 1985b; Ammons, 1989; Brennan *et al.*, 1989; Zhang *et al.*, 2000a, 2000b). Antidromically identified STT cells have also been studied in rats (Dilly *et al.*, 1968; Giesler *et al.*, 1976; Men  tre  y *et al.*, 1984; Palecek *et al.*, 1992; Dado *et al.*, 1994a, 1994b) and cats (Dilly *et al.*, 1968; Trevino *et al.*, 1972; Albe-Fessard *et al.*, 1974a; Craig and Kniffki, 1985).

Axonal conduction velocities

When monkey STT cells are activated antidromically, it is an easy matter to determine the conduction velocities of their axons if the distance between the location of the tip of the stimulating electrode placed in the thalamus to the recording site in the spinal cord can be estimated. The conduction distance from the entry point of the recording microelectrode into the spinal cord to a surface feature in the brainstem, such as the obex, can be directly measured post-mortem. The stereotaxic position of the obex can be obtained directly or from an atlas of the monkey brain. The conduction distance within the brain is then estimated by determining the difference between the stereotaxic position of the thalamic stimulus site and that of the obex. The total conduction distance is the sum of the distance from the recording site in the spinal cord to the obex plus the distance from the latter to the VPL thalamic nucleus. The total conduction distance can then be divided by the latency of the antidromic action potential, to yield a value of conduction velocity in mm/ms, which is numerically equivalent to m/s.

In the study by Trevino *et al.* (1973), the mean axonal conduction velocity for 118 STT neurons in monkeys was 33.4 m/s. Axons with the fastest mean conduction velocities were located in the neck of the dorsal horn (38.7 m/s for STT cells in lamina IV and 45.5 m/s for those in lamina V), whereas STT neurons with the slowest mean axonal conduction velocities were in lamina I (20.3 m/s) and laminae VI–VIII (28.0, 26.5 and 22.7 m/s for STT cells in laminae VI, VII and VIII, respectively).

Albe-Fessard *et al.* (1974a) also recorded from monkey STT neurons that were identified by antidromic activation. They recorded from 23 such neurons in the area of lamina V activated antidromically by thalamic stimuli applied in the VPL_c, VPL_o or VL_o nuclei (nomenclature of Olszewski, 1952). One STT cell was backfired from the parafascicular nucleus, and it was located in lamina VIII.

No monkey STT cells have so far been reported to have axons that conduct at velocities slow enough to signify that the axons were unmyelinated (however,

see Albe-Fessard *et al.*, 1974b). By contrast, some lamina I STT cells in cats appear to have unmyelinated axons (Craig and Kniffki, 1985). The lack of unmyelinated axons in monkey STT cells implies that the time of arrival of information in the thalamus by way of the STT is more dependent on the peripheral conduction time for action potentials in nociceptors to reach the spinal cord gray matter than on the central delay due to conduction along the spinothalamic tract to the thalamus. For example, if the conduction distance from a peripheral receptive field to the spinal cord were 200 mm and the conduction velocity of unmyelinated nociceptive afferent fibers averaged 1 m/s, the latency for the arrival of afferent activity in these afferents at the spinal cord would be about 200 ms. However, if the conduction distance from STT neurons to the thalamus were 200 mm, the conduction time for information to reach the thalamus would be only about 6 ms, plus the several ms required for the afferent volley to evoke discharges in STT neurons.

Receptive fields

After documenting that a neuron under study can be activated antidromically from a projection target, such as a thalamic nucleus in the case of an STT cell, the effects on the neuron of stimulating its receptive field are then determined. Identification of the receptive field of a central sensory neuron generally involves the application of natural forms of stimuli to an appropriate region of the body, such as the skin or muscle (Price and Mayer, 1974; Willis *et al.*, 1974; Applebaum *et al.*, 1975; Price *et al.*, 1978; Foreman *et al.*, 1979b), although useful information can be also obtained from recordings of the responses of the neuron to electrical stimulation of peripheral nerves (Price and Wagman, 1970; Foreman *et al.*, 1975, 1979a; Beall *et al.*, 1977). The natural stimuli (Fig. 3.4IA) that are generally used are relatively weak ones to avoid the sensitization of nociceptors that may result from very intense stimuli (Meyer and Campbell, 1981; LaMotte *et al.*, 1983; see Willis and Coggeshall, 2004). However, some central neurons (called high-threshold or “nociceptive-specific” neurons) respond preferentially to intense stimuli, and so mapping of the receptive field of such neurons requires the use of strong stimuli (Fig. 3.4II; Willis *et al.*, 1974; Price *et al.*, 1978; see Price and Dubner, 1977; Willis and Coggeshall, 2004). In this case, the stimuli should be in the lowest part of the noxious range and applied a minimum number of times.

Dorsal horn neurons, including monkey STT cells, are often grouped according to the range of mechanical stimulus intensities that are required for their activation (Mendell, 1966; Chung *et al.*, 1979). Only an occasional STT neuron can be classified as a “low-threshold” neuron; such cells are excited just by innocuous mechanical stimuli. Many STT cells are “wide dynamic range” neurons, which are cells activated by both innocuous and noxious intensities of stimuli (Mendell,

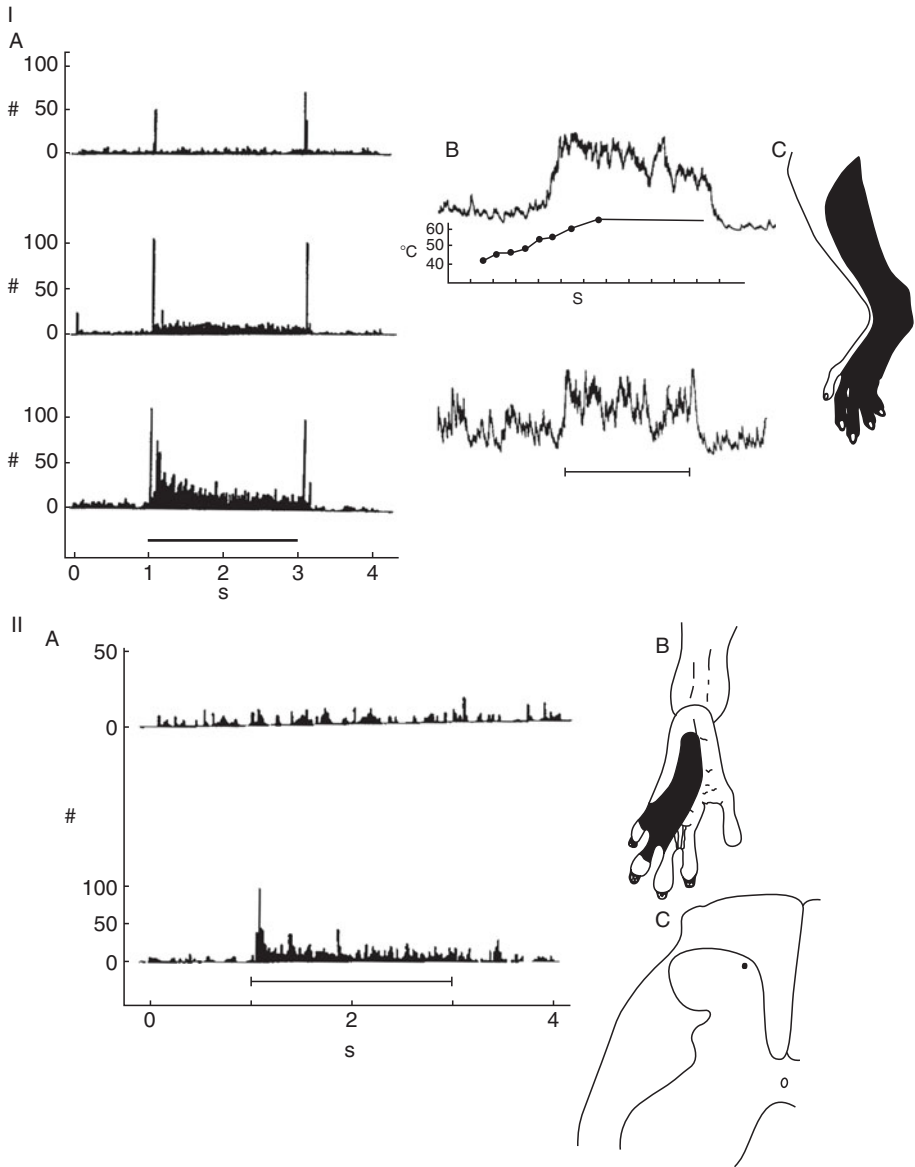


Fig. 3.4. Receptive fields of monkey spinothalamic tract (STT) neurons. I, recordings from a wide dynamic range STT cell. The uppermost histogram in (A) shows the response of the neuron to movement of a single hair within the receptive field on the hairy skin of the leg and foot shown in (C). The hair was deflected 0.5 mm by a mechanical stimulating device and then returned to its original position after 2 s (see horizontal bar below A). The other two histograms show the responses of the neuron when the skin was indented by the stimulator using two successively more intense stimuli. The rapidly adapting responses are presumably due to the innocuous

1966). The responses of these neurons to noxious mechanical stimuli increase as stimulus intensity is increased within the noxious range (Fig. 3.4IA; Price and Dubner, 1977; Ferrington *et al.*, 1987). High-threshold (HT) or nociceptive-specific STT neurons are excited by noxious, but not by innocuous mechanical stimuli (Fig. 3.4II). High-threshold and wide dynamic range STT cells can generally also be activated by noxious thermal and chemical stimulation of the skin (Fig. 3.4IB; Price and Mayer, 1974; Willis *et al.*, 1974; Price *et al.*, 1978; Kenshalo *et al.*, 1979; Surmeier *et al.*, 1986a, 1986b; Ferrington *et al.*, 1987; Simone *et al.*, 1991), and they may respond to strong stimulation of afferent fibers that supply deep somatic tissues (muscle, joints) and/or of visceral organs (Fig. 3.5; Willis *et al.*, 1974; Foreman *et al.*, 1979b; Foreman, 1989; Milne *et al.*, 1981; Dougherty *et al.*, 1992).

It should be noted that there is a correspondence between the distribution of the somatic and visceral receptive fields of STT neurons and the areas of referred pain that accompany visceral diseases as reported by patients (Head, 1893). For example, the SST cell in Fig. 3.5 could be activated both by mechanical stimulation of the skin and underlying muscle and also by stimulation of cardiopulmonary afferents. The somatic receptive field was in the area of the pain of angina pectoris that is often experienced by patients with coronary artery disease.

An alternative system for classification of monkey STT cells (and other somatosensory neurons) based on cluster analysis has been proposed (Chung *et al.*, 1986; Surmeier *et al.*, 1988; Owens *et al.*, 1992). Cluster analysis is a statistical technique (one example is “k-means cluster analysis”) that can group neurons based on their responses, for example, to mechanical stimuli. The responses of a substantial population of neurons must be recorded to establish criteria for clustering (e.g. the responses of 128 STT neurons were used in the sample analyzed by Chung *et al.*, 1986, and of 221 STT neurons in that analyzed by Surmeier *et al.*, 1988). The responses were grouped into a limited number of clusters (3 or 4).

Caption for Fig. 3.4. (cont.)

movement of hair, whereas the sustained responses were attributed to strong mechanical displacement of the skin. The uppermost tracing in (B) shows the increasing firing rate of the cell as the skin temperature was raised above about 47°C by a thermal probe (see monitor below the histogram), and the lower trace shows the response to cooling during the period indicated by the horizontal bar. II, recordings from a high-threshold or nociceptive-specific STT cell. In (A) the upper histogram shows the lack of response to an indentation of the skin of 0.5 mm, applied by the stimulating device using a force of less than 100 g. The lower histogram shows there was a response when the force was increased to 1000 g. Note that the activity outlasted the 2 s stimulus. In (B) is shown the receptive field on the glabrous skin of the plantar foot, and (C) shows the recording site near lamina I of the dorsal horn. From Willis *et al.* (1974).

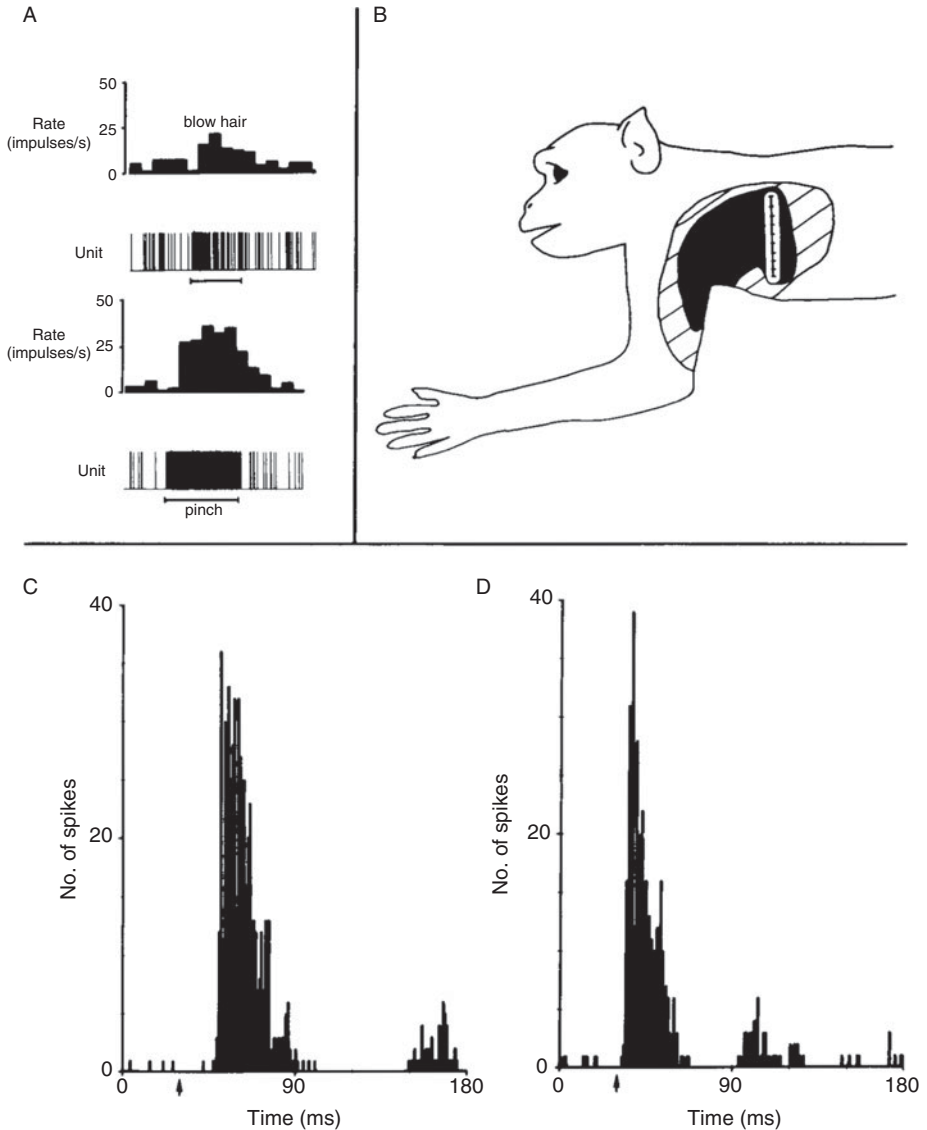


Fig. 3.5. Responses of a monkey wide dynamic range spinothalamic tract (STT) neuron to stimulation of somatic and visceral afferents. In (A) are shown the responses of the STT cell to an innocuous cutaneous stimulus (hair movement) and to pinching the skin and underlying muscle in the chest. Firing rates are shown by histograms and individual action potentials by unit recordings. In (B) is drawn the somatic receptive field on the left side of the chest. The solid black area includes the region from which hair movements elicited responses. This area plus the surrounding region indicated by the stripes was that from which activity was evoked by noxious mechanical stimulation. (C) shows a poststimulus histogram of the response of the neuron to electrical stimulation of the splanchnic nerve, and (D) the response to stimulation of cardiopulmonary sympathetic afferents. From Foreman (1989).

The responses of newly recorded neurons could later be grouped into one of the previously established clusters by calculating the Euclidian distances of the responses of the newly recorded neurons from the mean value for each cluster. The cluster chosen for a new neuron is that which is at the shortest Euclidian distance from the responses of the new neuron. The main advantage of cluster analysis is its objectivity. Disadvantages include the necessity of first collecting a large sample of neuronal responses on which to base a judgment of the proper number of clusters and how best to analyze the data to determine the cluster values (see Owens *et al.*, 1992). Cluster analysis has so far not been widely adopted for the identification of somatosensory neurons.

Some monkey and feline STT cells, as well as interneurons, in or near lamina I respond to innocuous thermal stimuli (Ferrington *et al.*, 1987; cf. Christensen and Perl, 1970; Price and Mayer, 1974; Iggo and Ramsey, 1976; Kumazawa and Perl, 1978; Craig *et al.*, 2001). The cells may also be activated by noxious thermal stimuli. Presumably, the responses of monkey and feline STT neurons and interneurons located in the superficial dorsal horn to innocuous thermal stimuli play a role in thermal sensations, including warm and cool.

Inhibition of monkey STT cells has been demonstrated during stimulation of peripheral receptive fields, peripheral nerves or the spinal cord dorsal columns (Willis *et al.*, 1974; Foreman *et al.*, 1976; Gerhart *et al.*, 1981; Chung *et al.*, 1984a, 1984b, 1985; Lee *et al.*, 1985; Brennan *et al.*, 1989). It is likely that inhibition of STT neurons (Fig. 3.6) helps explain the effectiveness of peripheral nerve stimulation, transcutaneous electrical nerve stimulation (TENS) or of dorsal column stimulation in alleviating pain in patients (Wall and Sweet, 1967; Shealy *et al.*, 1970; Nashold and Friedman, 1972; Loeser *et al.*, 1975; Woolf, 1979; see Willis, 1982).

Somatotopic organization

Monkey STT cells located in the superficial dorsal horn (Rexed's laminae I–II; Rexed, 1952, 1954) (see Chapter 2) have a somatotopic arrangement which reflects that of dorsal horn neurons in general. For example, STT neurons with receptive fields on the extensor surface of the hindlimb are located laterally and those with receptive fields on the flexor surface are positioned more medially in the superficial dorsal horn (Fig. 3.7I; Willis *et al.*, 1974; cf. Brown and Fuchs, 1975; Sorkin *et al.*, 1986). Curiously, STT neurons in Rexed's laminae V and VI, the deepest layers of the dorsal horn (see Rexed, 1952, 1954) (see also Chapter 2) do not seem to have this somatotopic arrangement (Fig. 3.7II). Perhaps this is because their receptive fields are on average much larger than are those of more superficial STT cells (Fig. 3.8; Willis, 1989). Furthermore, the dendritic trees of STT cells in lamina V are oriented in the transverse plane (Surmeier *et al.*, 1988), whereas those of STT cells and other neurons in the superficial dorsal horn are oriented

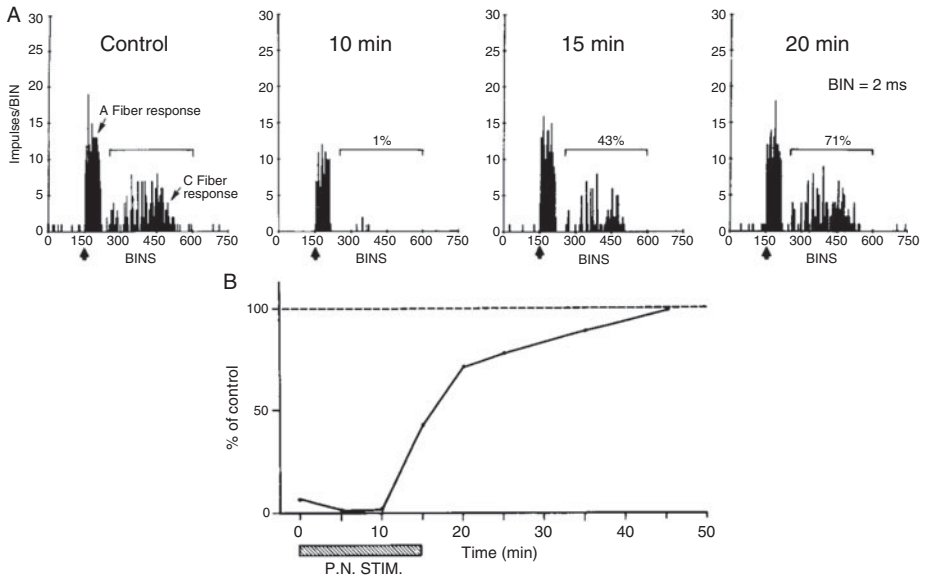


Fig. 3.6. Prolonged inhibition of a spinothalamic tract (STT) cell following peripheral nerve stimulation. In (A) are poststimulus time histograms of the cell's responses to A and C fiber volleys in the sural nerve. The histograms sum the effects of a series of ten stimuli. Conditioning stimulation of the common peroneal nerve was by repeated trains of pulses lasting 7 s at 2 Hz and above threshold for C fibers repeated every 10 s for 15 min. (B) shows the time course of the inhibition of the responses to C fiber volleys evoked by sural nerve stimulation. From Chung *et al.* (1984a).

longitudinally (Zhang and Craig, 1997) (see Chapter 2). This arrangement would be consistent with a somatotopic afferent input to the dendrites of lamina I STT cells but an input from widespread sources to the dendrites of lamina V STT cells.

The axons of monkey STT cells are arranged somatotopically within the lateral and ventral funiculi (Fig. 3.9C; Applebaum *et al.*, 1975). A similar arrangement has been reported in clinical studies in which anterolateral cordotomies have been made for the relief of pain (Fig. 3.9A, B; Hyndman and Van Epps, 1939; Walker, 1940). Axons conveying information that represents input from sacral segments are located laterally to axons representing input from more rostral parts of the body.

Spinothalamic tract neurons can be activated antidromically from just the lateral thalamus (e.g. from the VPL nucleus), from just the medial thalamus (e.g. from the central lateral nucleus), or from both lateral and medial nuclear regions of the thalamus (Giesler *et al.*, 1981). Spinothalamic tract cells that project to the VPL nucleus in the lateral thalamus or to both lateral and medial thalamus have similar response properties. Most are wide dynamic range neurons,

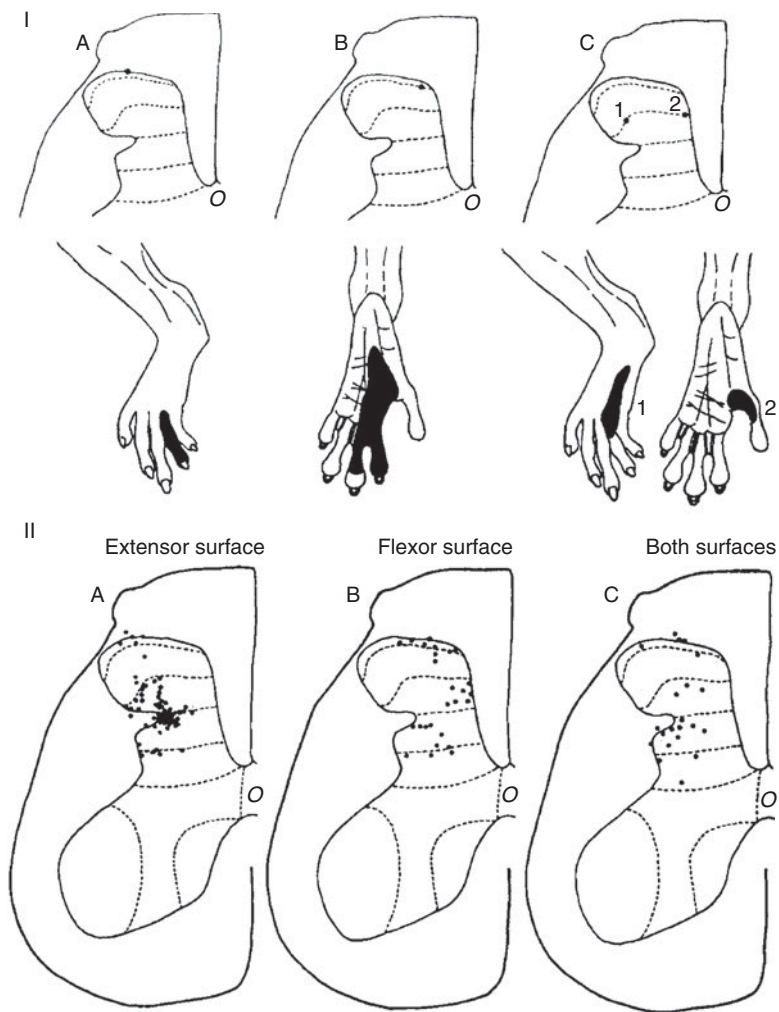


Fig. 3.7. Somatotopic organization of the receptive fields of spinothalamic tract (STT) neurons in the superficial dorsal horn. In (IA–C) are shown the sites at which recordings were made from STT cells in the superficial dorsal horn in three different experiments. Receptive fields were on the extensor (A, C) or flexor (B, C) surface of the hindlimb, depending on the lateral/medial location of the neuron. In IIA–C the locations of STT cells having receptive fields in these areas are plotted on drawings of transverse sections of the lumbar spinal cord. From Willis *et al.* (1974).

although some are high-threshold neurons. They are located in the dorsal horn and have receptive fields of restricted size. By contrast, STT cells that project just to the central lateral nucleus in the medial thalamus are located in the intermediate region or ventral horn, are mostly high-threshold neurons, and

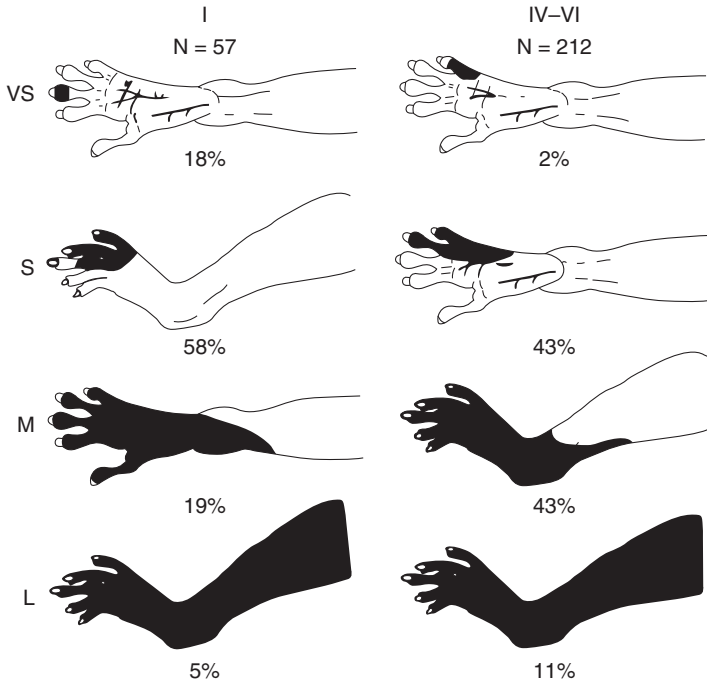


Fig. 3.8. Sizes of the cutaneous receptive fields of spinothalamic tract (STT) cells located in lamina I or in laminae IV-VI of the monkey spinal cord. The numbers of STT cells examined in each laminar region are indicated. Very small (VS) fields were of an area equivalent to or less than a digit. Small (S) fields covered a surface the size of the foot or less. Medium (M) fields were larger than the foot but smaller than the combination of leg and foot. Large (L) fields had an area greater than the foot plus leg. The percentages indicate the proportion of STT cells in different parts of the dorsal horn that had the corresponding sizes of receptive fields. From Willis (1989).

have receptive fields on several limbs or even very large receptive fields covering essentially the entire body surface, including the face (Fig. 3.10I). The conduction velocities of the axons of these neurons are slower than those of STT cells that project to the lateral thalamus. A lesion of the lateral funiculus at an upper cervical level reduces the excitatory receptive fields of STT cells that project to the medial thalamus to just the ipsilateral hindlimb, and electrical stimulation within the medial pontomedullary reticular formation can produce a prolonged and intense excitation of these STT neurons (Fig. 3.10II). Such observations suggest that the large excitatory receptive fields of STT cells that project to the medial thalamus depend on the activation of reticular formation neurons through an ascending spinoreticular pathway, and that these reticular neurons

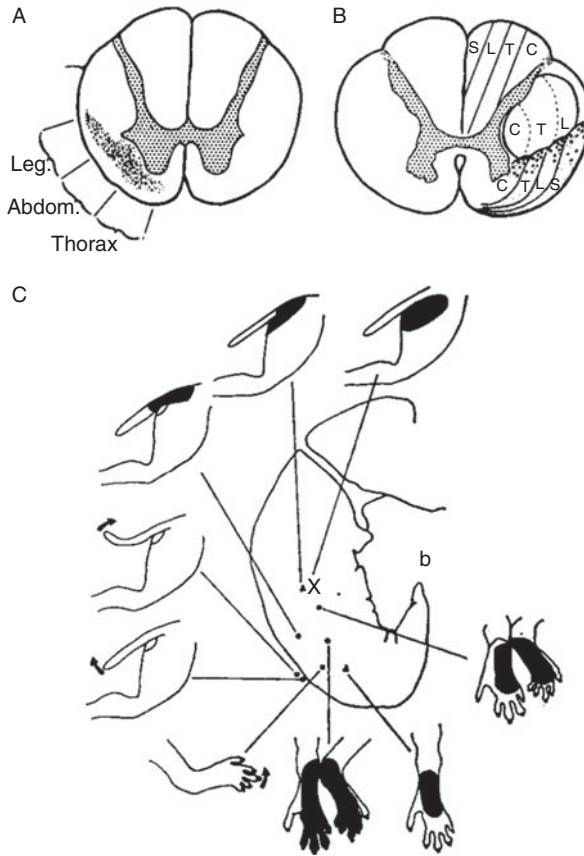


Fig. 3.9. Areas of the anterolateral quadrant that when sectioned result in analgesia in the regions indicated (leg, abdomen or thorax in (A) and cervical (C), thoracic (T), lumbar (L) and sacral (S) in (B). Note the opposite organization in the dorsal funiculus. The locations of the axons of several monkey spinothalamic tract (STT) neurons had somatotopically arranged receptive fields, as shown in the drawings in (C). From Willis (1985).

then excite the medially projecting STT cells through a reticulospinal projection (Giesler *et al.*, 1981).

Monkey spinoreticular neurons

Antidromic identification

Recordings have been made from a limited sample of monkey spino-reticular tract (SRT) neurons that were identified by antidromic activation (Albe-Fessard *et al.*, 1974a; Haber *et al.*, 1982; cf. studies in cat and rat by Fields *et al.*, 1975, 1977; Maunz *et al.*, 1978; Men  trety *et al.*, 1980; Foreman *et al.*, 1984; Thies, 1985).

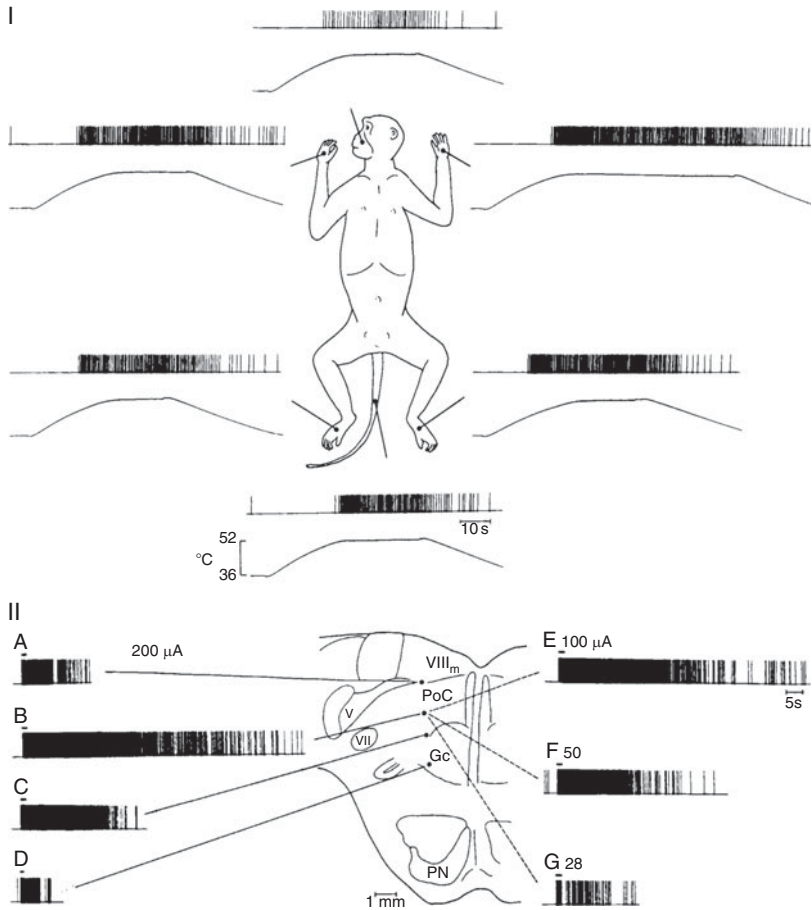


Fig. 3.10. (I) shows the responses of a medially projecting monkey spinothalamic tract (STT) neuron to the application of noxious heat stimuli to various parts of the surface of the body and face. Temperature monitor traces are shown below recordings of window discriminator pulses triggered by action potentials of the neuron. The background temperature of the skin was 36°C, and the heat pulses raised the skin temperature to 52°C. (II) illustrates the activation of a medially projecting STT cell by electrical stimulation in the pontine reticular formation. Stimulation sites are indicated by filled circles shown on a drawing of a transverse section through the brainstem at the level of nucleus pontis centralis caudalis (PoC) and the nucleus gigantocellularis (Gc). In (A–D), the stimulus strength was 200 μ A (0.1 ms pulses applied at 333 Hz); in (E–G), the stimuli were at the lower intensities indicated. From Giesler *et al.* (1981).

In the study by Haber *et al.* (1982), all of the monkey SRT neurons recorded were tested for responses to natural stimulation of the fore- and hindlimbs, trunk and face. Nearly half failed to respond to any of the stimuli tried. All of these unresponsive neurons were in laminae VI–VIII, mostly in VII. Many of these

neurons had spontaneous activity, allowing the collision test to be used to demonstrate antidromic activation. However, other neurons lacked either spontaneous or evoked activity, and so collision could not be demonstrated. However, these neurons did meet the other criteria for antidromic activation. More than two-thirds of the monkey SRT neurons recorded from were activated antidromically from the contralateral brainstem. Several were also activated antidromically from the contralateral diencephalon, and these were considered to be STT cells with collaterals to the medial brainstem (Haber *et al.*, 1982). Most monkey SRT neurons were located in laminae VI–VIII, especially in VII; none were found in laminae I–III.

Axonal conduction velocities

The conduction velocities of the axons of 29 monkey SRT neurons varied from 9–54 m/s, with a mean conduction velocity of 25.6 m/s (Haber *et al.*, 1982). Neurons that projected to both the brainstem and the thalamus had axons with somewhat faster conduction velocities (mean of 37 m/s).

Receptive fields

In the sample of monkey SRT neurons reported by Haber *et al.* (1982), only one SRT neuron was classified as a low-threshold cell. This neuron was located in lamina IV. Three SRT neurons were wide dynamic range neurons that projected to both the medial brainstem and to the contralateral diencephalon. Other SRT neurons were high-threshold neurons, and these often had input from deep tissues, as well as from the skin. Two SRT cells had receptive fields that were restricted to deep tissue.

The SRT neuron in Fig. 3.11 had symmetrical, bilateral receptive fields in the skin overlying the biceps muscles. The cell was activated antidromically from the region of the nucleus gigantocellularis (Fig. 3.11C). It was excited by pinching the skin in the receptive fields. It was also excited when the contralateral triceps muscle was squeezed, but inhibited when a similar stimulus was applied to the ipsilateral triceps muscle (Fig. 3.11A). The neuron was classified as a high-threshold neuron with a convergent excitatory input from cutaneous and deep receptors. The neuron was located in lamina VII of the cervical enlargement (Fig. 3.11B).

Monkey and cat SRT neurons in the upper thoracic spinal cord could be activated by occlusion of a coronary artery or injection of bradykinin into the coronary circulation (Blair *et al.*, 1984). Such SRT neurons (at least in cats) are inhibited by distension of the urinary bladder (Hobbs *et al.*, 1990), similarly to monkey STT cells of the upper thoracic spinal cord that respond to input from cardiopulmonary afferent fibers (Brennan *et al.*, 1989).

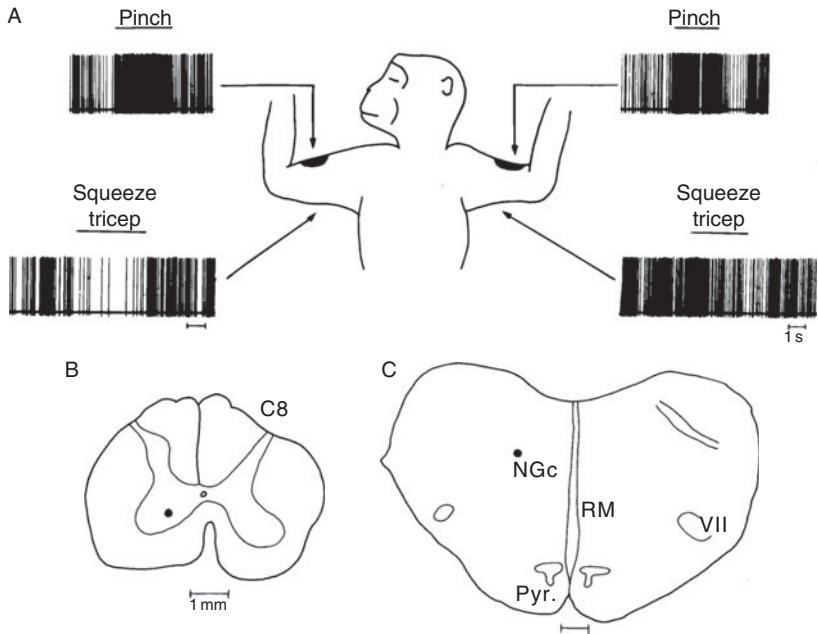


Fig. 3.11. In (A) are shown the responses of a spinoreticular tract (SRT) neuron to pinching the skin over the biceps muscles and to squeezing the triceps muscles bilaterally. The drawing in (B) indicates the recording site for the neuron in the cervical enlargement. The neuron was activated antidromically from the location shown by the filled circle in (C) in the nucleus gigantocellularis of the medulla. From Haber *et al.* (1982).

Somatotopic organization and axonal projections

Monkey SRT neurons and their projections do not have a somatotopic organization (Willis and Coggeshall, 2004). The axons cross the midline near the cell bodies of the SRT neurons and they ascend in the ventral part of the spinal cord white matter to terminate in several reticular formation nuclei, including the nucleus medullae oblongatae centralis, lateral reticular nucleus, nucleus reticularis gigantocellularis, nucleus reticularis pontis caudalis and oralis, nucleus paragigantocellularis dorsalis and lateralis, and nucleus subcoeruleus (see Willis and Coggeshall, 2004 for references).

Monkey spinomesencephalic neurons

There are several systems of ascending axons that originate in the spinal cord and terminate in the mesencephalon. These are often termed collectively as spinomesencephalic neurons. The neurons of origin in the spinal cord end in a number of different target structures in the midbrain, including the nucleus

cuneiformis, parabrachial nucleus, periaqueductal gray, intercollicular nucleus, deep layers of the superior colliculus, nucleus of Darkschewitsch, anterior and posterior pretectal nuclei, red nucleus, Edinger Westphal nucleus and interstitial nucleus of Cajal (reviewed by Willis and Coggeshall, 2004). Projections are heavier on the side contralateral to the cell bodies of origin. Several of these projections have been assigned separate names, e.g. the spinotectal tract (to the superior colliculus), the spinoannular tract (to the periaqueductal gray) and the spinoparabrachial tract (to parabrachial nuclei) (Willis and Coggeshall, 2004).

Antidromic identification

Spinoannular tract neurons have been identified by antidromic activation from the periaqueductal gray in monkeys (Price *et al.*, 1978; Yeziarski *et al.*, 1987). These neurons were located in the superficial and deep layers of the dorsal horn. Some of these same neurons also projected to the VPL thalamic nucleus. Antidromically identified spinomesencephalic cells have also been recorded from in cats (Hylden *et al.*, 1985, 1986; Yeziarski and Schwartz, 1986) and rats (Men  trety *et al.*, 1980). The spinomesencephalic neurons in the study in rats by Men  trety *et al.* (1980) were located in the marginal zone (lamina I), the neck of the dorsal horn and the lateral spinal nucleus. Most of these neurons were contralateral to the site of stimulation, although those in the lateral spinal nucleus had bilateral axonal projections. The spinomesencephalic neurons in the studies in cats by Yeziarski and Schwartz (1986) and by Hylden *et al.* (1985, 1986) were widely distributed, many being located in laminae I–VIII, and some could be activated antidromically from more than one midbrain site. The axons of spinomesencephalic neurons generally ascend to the brain by way of the ventral white matter of the spinal cord, along with the STT and SRT.

The conduction velocities of spinomesencephalic axons vary widely. In monkeys, the mean conduction velocity of a sample of 24 spinomesencephalic axons was 47.8 m/s (Yeziarski *et al.*, 1987). Spinoreticular neurons, including spinomesencephalic cells, investigated by Men  trety *et al.* (1980) in rats had conduction velocities that ranged from 3.6–40 m/s, and axons arising from neurons of the lateral spinal nucleus conducted at 0.6–20 m/s, indicating that some of these axons were unmyelinated. The axons of spinomesencephalic cells in the cat conducted at 7.8–102.8 m/s (Yeziarski and Schwartz, 1986). Feline spinoparabrachial axons have slowly conducting axons, 1–18 m/s (Hylden *et al.*, 1985).

Receptive fields

In monkeys, the terminals of spinomesencephalic neurons have a roughly somatotopic organization. The projections from the lumbosacral enlargement end in the caudal and middle zones of the midbrain, more caudally than

projections from the cervical enlargement. Trigeminal projections are to still more rostral levels (Wiberg *et al.*, 1987).

Monkey spinomesencephalic neurons that also project to the thalamus have restricted excitatory receptive fields (Yezierski *et al.*, 1987). However, those that project just to the midbrain have complex receptive fields. Intradermal injection of capsaicin has been shown to produce a prolonged excitation of both wide dynamic range and nociceptive-specific spinomesencephalic neurons (Dougherty *et al.*, 1999). After capsaicin injection, spinal cord neurons that project to the dorsal periaqueductal gray showed increased responses to mechanical stimuli and enlarged receptive fields. Responses to iontophoretically released excitatory amino acids also increased. However, following capsaicin injection, there were no enhanced responses in spinal neurons that project to the ventral periaqueductal gray, and low-threshold spinomesencephalic neurons were inhibited.

The monkey spinohypothalamic tract

The cells of origin of the spinohypothalamic tract have been mapped anatomically in rats (e.g. Burstein *et al.*, 1990, 1996) and by antidromic activation in rats (Burstein *et al.*, 1991) and monkeys (Zhang *et al.*, 1999). Antidromically identified monkey spinohypothalamic neurons are found in the superficial and deep layers of the dorsal horn and also in the intermediate region (Zhang *et al.*, 1999). Collaterals are given off by the rostrally ascending axons of rat spinohypothalamic tract neurons to the deep dorsal horn of the C1 spinal cord, as well as to the pontomedullary reticular formation, several midbrain structures and the thalamus (Kostarczyk *et al.*, 1997).

The axons of rat spinohypothalamic tract cells project bilaterally to the hypothalamus, and some have collaterals that also end in the thalamus (Zhang *et al.*, 1995). Many of the same axons turn caudally and descend within the brainstem and end in the midbrain; some continue still more caudally and terminate in the pons or rostral medulla. Monkey spinohypothalamic neurons in the lumbar enlargement have receptive fields on the ipsilateral hindlimb, and those from which recordings have been made are all exclusively or preferentially nociceptive (Zhang *et al.*, 1999). Most spinohypothalamic tract cells in rats have been classified as wide dynamic range or high-threshold neurons, although a few were low-threshold neurons (Burstein *et al.*, 1991).

Several other spinolimbic pathways have been described in rats, including a spino-parabrachio-amygdalar pathway (Bernard and Besson, 1990; see review by Willis and Westlund, 1997), a direct spinoamygdalar pathway (Cliffer *et al.*, 1991), and spinotelencephalic pathways that project to the septal nuclei, nucleus accumbens and other limbic structures (Burstein *et al.*, 1987; Burstein and

Giesler, 1989; Cliffer *et al.*, 1991). It is unclear as yet if these pathways also occur in primates.

Monkey spinocervical tract neurons

Most studies of the spino-cervico-thalamic pathway, which was first recognized by Morin in 1955, have been done using cats. These include numerous physiological studies of feline spinocervical tract (SCT) neurons (Taub and Bishop, 1965; Brown and Franz, 1969, 1970; Bryan *et al.*, 1973a and b; Cervero *et al.*, 1977; Brown *et al.*, 1980, 1986, 1987a, 1987b, 1987c; Brown and Noble, 1982; Kunze *et al.*, 1987; Short *et al.*, 1990) or of neurons in the lateral cervical nucleus (LCN), which is located in the upper cervical spinal cord (Morin *et al.*, 1963; Oswaldo-Cruz and Kidd, 1964; Horrobin, 1966; Craig and Tapper, 1978; Kajander and Giesler, 1987a, 1987b). Some studies have also been done on raccoons (Ha *et al.*, 1965; Hirata and Pubols, 1989; Simone and Pubols, 1991) or rats (Giesler *et al.*, 1979). However, there have been only a few investigations of the spino-cervico-thalamic pathway in monkeys (Bryan *et al.*, 1974; Downie *et al.*, 1988). There is inconsistent evidence concerning the possible presence of an LCN in the human spinal cord (cf. Truex *et al.*, 1965; Kircher and Ha, 1968; see Willis and Coggeshall, 2004).

Antidromic identification

Bryan *et al.* (1974) were able to activate 80 SCT cells antidromically in monkeys. The concentric bipolar steel stimulating electrode used for this purpose was inserted slightly below the surface of the spinal cord at the C3 segmental level and just lateral to the dorsal root entry zone. Another stimulating electrode was placed in the lower medulla to test whether or not it was possible also to activate the neurons antidromically from a more rostral level than the upper cervical spinal cord, i.e. at a level above that of the lateral cervical nucleus. Such neurons would not be considered to belong to the SCT. The neurons observed did not project above the level of the lateral cervical nucleus. Monkey SCT neurons were concentrated in laminae IV and V, although a few were in deeper parts of the gray matter and one was in lamina I.

Downie *et al.* (1988) recorded from 12 monkey SCT neurons that were activated antidromically from C3 but not from a level above C1. The locations of two of these neurons are shown in Fig. 3.12IF. The results of the collision test for one of the SCT neurons are seen in Fig. 3.12IA. The cell had a restricted excitatory receptive field on the foot and toes (Fig. 3.12ID) and the cell was classified as a wide dynamic range neuron (Fig. 3.12IE).

Axonal conduction velocities

In the experiments of Bryan *et al.* (1974), the conduction velocities of the axons of monkey SCT cells ranged from 7.1–60 m/s (mean 27.8 m/s).

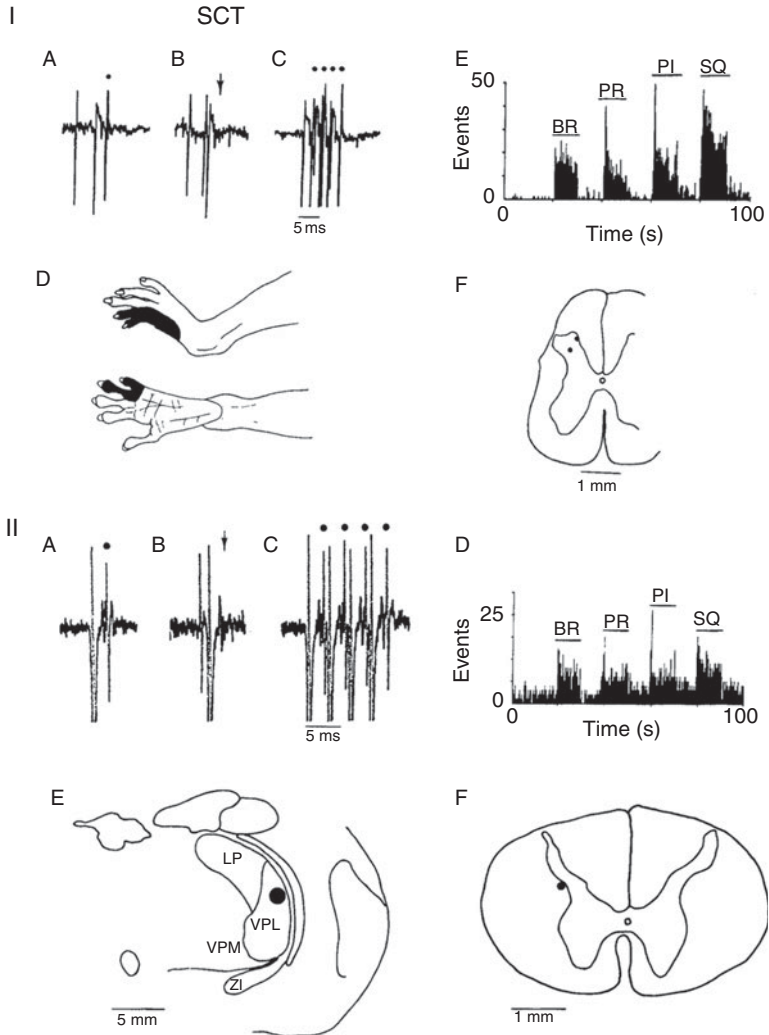


Fig. 3.12. (IA–E) show properties of a wide dynamic range monkey spinocervical tract (SCT) neuron and (F) the location of two SCT neurons in the dorsal horn. In (A), an antidromic action potential was evoked following stimulation of the dorsal part of the lateral funiculus at the C3 segmental level. In (B), the antidromic action potential was blocked because of collision with an orthodromic spike that occurred within the critical interval. (C) shows that the antidromic action potential could follow four stimuli repeated at 3 ms intervals. (D) shows the receptive field. The responses in the histogram in (E) were to a series of graded mechanical stimuli applied in the receptive field. The filled circles in (F) indicate the locations of two SCT neurons in the dorsal horn. The properties of neurons in the monkey lateral cervical nucleus (LCN) are illustrated in (IIA–F). An antidromic action potential in the neuron is shown in (A), collision in (B) and high frequency following in (C). Responses to mechanical

The spinocervical cells in the deepest part of the spinal gray matter (laminae VII and VIII) had the fastest conducting axons (mean of 44 m/s), and the SCT neuron in lamina I had the slowest (13 m/s). The conduction velocities of the axons of monkey SCT cells in the study by Downie *et al.* (1988) were in the range of 13–71 m/s (mean 36 m/s).

Receptive fields

The receptive fields of 32 monkey spinocervical tract neurons were evaluated by Bryan *et al.* (1974). There were 13 low-threshold cells and 12 wide dynamic range cells in the sample. One cell was a high-threshold neuron. No receptive fields were found for four cells, and two had large inhibitory receptive fields, covering most of the lower extremity, but no detectable excitatory field. Some of the neurons (six of 16 tested) were activated by noxious heat stimuli. Downie *et al.* (1988) classified nine SCT cells based on their responses to mechanical stimuli. The sample included four low-threshold cells, four wide dynamic range cells (see Fig. 3.12I), and one high-threshold cell. Eight of the nine SCT cells responded to noxious heat stimuli.

Somatotopic organization

Bryan *et al.* (1974) observed that monkey spinocervical tract neurons in the lateral part of the dorsal horn had receptive fields on the dorsal surface of the limb (extensor surface), whereas medially placed cells had receptive fields on the ventral (flexor) surface. This arrangement is similar to that described previously for monkey STT cells.

Monkey lateral cervical nucleus neurons

Antidromic identification

In two monkeys, Bryan *et al.* (1974) made recordings from three neurons that were considered to be in the lateral cervical nucleus (LCN) in the upper cervical spinal cord. These cells could be activated antidromically from the contralateral rostral medial lemniscus. In 12 monkeys, Downie *et al.* (1988) recorded from 49 neurons of the lateral cervical nucleus. These cells were in segments C1–C2.

Caption for Fig. 3.12. (cont.)

stimulation of the receptive field are shown by the histogram in (D). The cell was activated antidromically from the contralateral VPL thalamic nucleus at the site indicated by the filled circle in (E). The location of the neuron in the LCN is shown in (F). From Downie *et al.* (1988).

The latencies of antidromic action potentials evoked in LCN neurons by stimulation in the rostral medial lemniscus averaged 2.3 ms, which corresponds to a conduction velocity of 17 m/s (assuming a conduction distance of 38 mm). The overall conduction velocity of the monkey spino-cervico-thalamic pathway from the periphery to the thalamus was about 29 m/s (Downie *et al.*, 1988).

Receptive fields

The neurons considered by Bryan *et al.* (1974) to be in the LCN of monkeys could be excited by innocuous mechanical stimuli applied to the hindlimb or body wall or by stimulation of the cord dorsum at L7. However, they were not responsive to stimulation of the face or neck and so they clearly did not belong to the spinal nucleus of the trigeminal nerve.

In the study by Downie *et al.* (1988), cells in the LCN had receptive fields on the skin in various parts of the body, including the hindlimb (28 cases), the forelimb (ten cases), the trunk (four cases) or the tail (five cases). The over-representation of hindlimb receptive fields was attributed to the bias introduced by insertion of the antidromic stimulating electrode into the hindlimb region of the VPL nucleus. Most of the neurons investigated had cutaneous receptive fields, but two had fields in deep structures. The sizes of the receptive fields varied from very small (area equivalent to that of a digit or part of a digit) to large (area including parts of the distal and proximal limb). Most fields were medium sized (area comparable to the foot plus the area below the knee).

Downie *et al.* (1988) were able to classify 40 cells of the lateral cervical nucleus according to their responses to innocuous and noxious mechanical stimuli. There were 18 low-threshold cells (45%), 19 wide dynamic range cells (47.5%; Fig. 3.12II) and only three high-threshold cells (7.5%). Low-threshold cells had smaller receptive fields than did the wide dynamic range cells. Many of the low-threshold and wide dynamic range neurons also responded to noxious heat stimuli. Steady indentation of the skin at an innocuous intensity failed to activate LCN neurons, suggesting that these cells do not receive an input from slowly adapting mechanoreceptors. However, sinusoidal vibratory stimuli resulted in repetitive discharges of about 10–30 Hz in most LCN neurons. There was no indication that the neurons had an input from Pacinian corpuscles.

Monkey postsynaptic dorsal column neurons

The dorsal columns of the spinal cord contain numerous axons that are collaterals of primary afferent neurons whose cell bodies are in dorsal root ganglia. In addition to these are other axons that arise from neurons most of whose cell bodies are in the dorsal horn. The latter neurons with axons in the

dorsal columns were named postsynaptic dorsal column (PSDC) neurons because of the synapse that occurs between primary afferents and the neurons that project their axons into the dorsal columns (Uddenberg, 1968; Angaut-Petit, 1975a, 1975b). Postsynaptic dorsal column neurons in turn synapse on neurons in the dorsal column nuclei that project to the contralateral VPL thalamic nucleus (Angaut-Petit, 1975b).

Antidromic identification

Postsynaptic dorsal column neurons have been identified by antidromic activation from the dorsal column nuclei or from the dorsal columns as they approach the dorsal column nuclei in several investigations in rats (Giesler and Cliffer, 1985; Al-Chaer *et al.*, 1996a, 1996b, 1997) and cats (Uddenberg, 1968; Angaut-Petit, 1975a, 1975b; Jankowska *et al.*, 1979; Brown & Fyffe, 1981; Brown *et al.*, 1983; Lu *et al.*, 1983; Bennett *et al.*, 1984; Kamogawa and Bennett, 1986; Noble and Riddell, 1988). There has been only a single study of PSDC neurons in monkeys (Al-Chaer *et al.*, 1999). In addition there has been an investigation in monkeys of the effect of a dorsal column lesion on the responses of neurons in the VPL thalamic nucleus to visceral and somatic stimulation (Al-Chaer *et al.*, 1998).

In the experiments by Al-Chaer *et al.* (1999), monkey PSDC neurons at the L6–S1 segmental level of the spinal cord were identified by antidromic activation from either the dorsal column at an upper cervical spinal cord level or from the nucleus gracilis. The same neurons were also tested for antidromic activation from the VPL nucleus and were found not to respond. A total of 48 PSDC neurons were activated antidromically from the rostral dorsal column and nine from the nucleus gracilis. The conduction velocities of the axons of these PSDC neurons were not determined.

Receptive fields

Both cutaneous and visceral receptive fields of the monkey PSDC neurons were examined (Al-Chaer *et al.*, 1999). Cutaneous stimuli included brushing the skin and graded mechanical compression of a fold of skin; the visceral stimuli were graded colorectal distensions (CRD). Postsynaptic dorsal column neurons that were located superficially in the dorsal horn were not responsive to CRD, whereas other PSDC neurons that were deep in the spinal cord gray matter were either excited (21 neurons) or inhibited (three neurons) by CRD. Of the 24 PSDC neurons that were excited by CRD, 22 had cutaneous receptive fields on the thigh, rump or scrotum; two did not respond to cutaneous stimulation. Of the 24 PSDC neurons that did not respond to CRD, 12 had receptive fields on the leg, upper thigh and the rump, and 12 could not be excited by somatic stimulation. Figure 3.13 shows the responses of a monkey

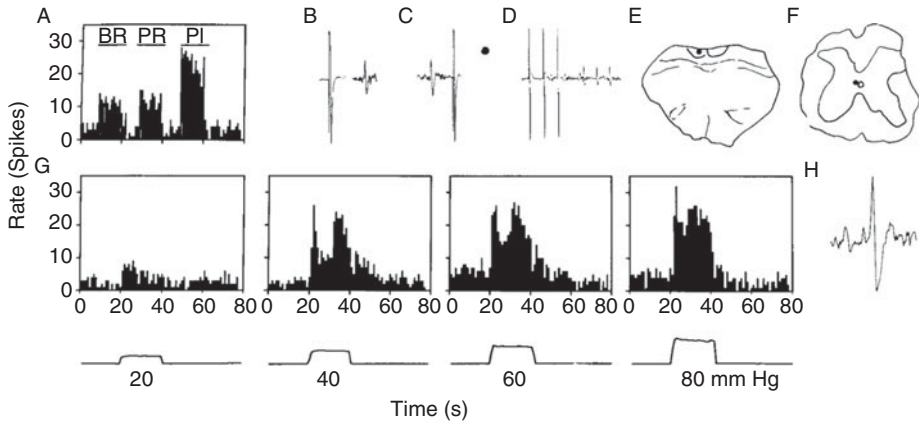


Fig. 3.13. (A) is a rate histogram of the responses of a postsynaptic dorsal column (PSDC) neuron to cutaneous stimuli. (B) is the antidromic action potential evoked by stimulation in the dorsal column nuclei. (C) shows collision and (D) high frequency following the antidromic spike. (E) is a drawing of a transverse section through the caudal medulla at the level of the gracile nuclei. The filled circle shows the location of the stimulation site for antidromic activation of the neuron. (F) is a drawing of a transverse section of the spinal cord at SI showing the recording site for the PSDC neuron. The rate histograms in (G) are the responses of the neuron to graded colorectal distensions (CRDs); the monitor records show the timing of the distensions and the intensity in mm Hg. (H) is the action potential of the neuron. From Al-Chaer *et al.* (1999).

PSDC neuron to graded intensities of cutaneous stimulation (Fig. 3.13A) and of CRD (Fig. 3.13G). Evidence for antidromic activation (Fig. 3.13B–D), the stimulation site in the nucleus gracilis (Fig. 3.13E) and the recording site near the central canal (Fig. 3.13F) are also shown.

Somatotopic organization and axonal projections

The somatic receptive fields of the PSDC neurons that also responded to CRD were appropriate to the spinal cord segmental level in which the neurons were located, L6–SI. These neurons were located medially in the spinal cord gray matter, whereas PSDC neurons that failed to respond to CRD were generally located more laterally (Al-Chaer *et al.*, 1999). The cutaneous receptive fields of the PSDC neurons that had responses to CRD were near the midline of the monkey's body. Noxious visceral stimulation, using distention of the ureter, or noxious cutaneous stimulation, using intradermal injection of capsaicin, were able to evoke Fos expression in both PSDC and STT neurons in rats (Palecek *et al.*, 2003).

The axons of the PSDC neurons examined were presumed to have ascended to the brain by way of the dorsal columns, since a lesion of the dorsal columns

reduced or eliminated the responses of neurons in the monkey VPL thalamic nucleus to CRD (Al-Chaer *et al.*, 1998). Similar observations had been made previously in rats (Hirshberg *et al.*, 1996; Al-Chaer *et al.*, 1996a, 1996b, 1997). An antero-grade tracing study in rats demonstrated a projection from the central region of the lumbar spinal cord to the gracile nucleus and from the thoracic cord to the junction between the gracile and cuneate nuclei (Wang *et al.*, 1999). Behavioral studies showed that visceral pain in animal models can be disrupted by a lesion of the dorsal column (Houghton *et al.*, 1997; Feng *et al.*, 1998; Ness, 2000; cf. Amassian, 1951; Palecek and Willis, 2003; see also Houghton *et al.*, 2001). This is consistent with the clinical studies in human patients that have shown a substantial reduction in the pain of pelvic cancer following a midline myelotomy (Gildenberg and Hirshberg, 1984; Nauta *et al.*, 1997, 2000; Becker *et al.*, 1999; Kim and Kwon, 2000).

Monkey trigeminothalamic tract neurons

Pain and temperature sensations from the oral-facial region are transmitted to neurons in the caudal part of the spinal nucleus of the trigeminal nerve, also referred to as the nucleus caudalis or the medullary dorsal horn, by way of the spinal tract of the trigeminal nerve. Some tactile sensation is also mediated through mechanoreceptive afferents with collaterals in the spinal tract. The nucleus caudalis in turn projects to the contralateral ventral posterior medial (VPM) nucleus of the thalamus by way of the trigeminothalamic tract (see Chapter 2). Thus, it has been suggested that this pathway functions for the oro-facial region in a manner parallel to the spinothalamic tract for the body (Sjöqvist, 1938; Kerr *et al.*, 1968; see review by Dubner and Bennett, 1983). However, Denny-Brown and Yanagisawa (1973) found that cutaneous facial analgesia after trigeminal tractotomy in monkeys could be reversed following the systemic injection of strychnine, indicating that an alternative projection was available. Young *et al.* (1981) observed that interruption of the spinal tract of the trigeminal nerve in macaques results in hypalgesia to ipsilateral noxious cutaneous stimuli, especially in peripheral parts of the face, but that this procedure did not produce dental analgesia.

Antidromic identification

In a study by Price *et al.* (1976), 113 trigeminothalamic neurons were identified in the nucleus caudalis of anesthetized monkeys by antidromic activation from the contralateral ventral posterior medial (VPM) or posterior thalamic nuclei. Bushnell *et al.* (1984) recorded from 51 trigeminothalamic projection neurons identified by antidromic activation from the VPM thalamic nucleus in awake, behaving monkeys.

Axonal conduction velocities

The axons of the trigeminothalamic tract neurons recorded by Price *et al.* (1976) in monkeys had conduction velocities that varied from 2–24 m/s (mean 12 m/s). Neurons with the slowest conducting axons had the highest threshold to mechanical stimuli. Bushnell *et al.* (1984) found that monkey WDR trigeminothalamic neurons had only slightly shorter antidromic latencies than did NS neurons. The conduction velocities of neurons in their sample ranged from 8.5–23 m/s.

Receptive fields

Kerr *et al.* (1968) evaluated the receptive fields of neurons in the trigeminal complex in monkeys (*Macaca nemistrina*). The neurons were not identified by antidromic activation. Recordings were made from single units whose action potentials were characteristic of those attributable to the somadendritic region of neurons. Graded intensities of mechanical stimuli were used to activate the neurons. Thermal stimuli were not emphasized. The receptive fields were generally small and discrete at all levels of the trigeminal complex. For example, receptive fields were small on the lip, eyelids and cornea, although receptive fields on the scalp were large. Some neurons were very sensitive to the movement of a single vibrissa. Others were activated by stimuli applied to one or more teeth. Units that responded to hair displacement tended to be more lateral and those responsive to touch-pressure stimuli more medial. Nociceptive-specific units were difficult to find within the trigeminal complex proper, although some were observed in the adjacent reticular formation and in the trigeminal and facial motor nuclei and may have had a motor function. However, units that responded to both innocuous and noxious stimuli (“wide dynamic range” neurons) were apparently common (cf. the study in cats by Kruger and Michel, 1962a).

Price *et al.* (1976) investigated the receptive field properties of antidromically identified trigeminothalamic tract neurons in the monkey subnucleus caudalis (as well as caudalis neurons that could not be so identified). They subdivided the trigeminal neurons into five classes.

Class 1 was comprised of neurons that responded in a rapid fashion to hair movement or light stroking of the skin. A total of 35 neurons of this class were activated antidromically from the VPM thalamic nucleus. The cells did not respond to thermal stimuli. Receptive fields were usually less than 2 cm² in size and had distinct borders. Class 2 units also responded to weak mechanical stimuli, but in a slowly adapting fashion. A total of 24 neurons of this type could be activated antidromically from the thalamus. Neurons that belonged to class 1 or 2 were generally located in the superficial part of the magnocellular layer.

Of the class 3 units examined, 29 were identified by antidromic activation from the VPM thalamic nucleus. Class 3 neurons were also activated by weak mechanical stimuli, but their responses increased with stimulus strength and were greatest when the skin was pinched with serrated forceps. Electrical stimulation of the skin showed that most of these neurons received input from unmyelinated afferents. Such neurons were excited by noxious heat stimuli. Receptive fields varied in size from about 1 cm^2 to nearly half the area of the face. The neurons tended to be located in the deep magnocellular layer or in the underlying lateral reticular formation. Some class 3 neurons had small receptive fields and were in the superficial magnocellular layer or the marginal layer.

Fourteen class 4 units were antidromically identified following stimulation in the VPM nucleus. These neurons did not respond to innocuous mechanical stimuli. They were found to have excitatory input from A δ -sized afferent fibers, and their response thresholds for mechanical stimuli were in a range that does not elicit pain. However, these neurons responded maximally to noxious pinching with serrated forceps, and they had input from C fibers. They could be activated by noxious heat stimuli but not by cooling. Receptive fields were usually small (less than 2 cm^2), although some were medium-sized or large.

Ten class 5 neurons were identified by antidromic activation. They were not excited by non-painful mechanical stimuli but did discharge following pinching with serrated forceps. They received input from A δ afferents, but not from C fibers. Generally, there were no responses to noxious heat or to cooling. Receptive fields were less than 2 cm^2 . Class 4 and 5 neurons with small receptive fields tended to be located in the marginal layer, whereas those with medium to large receptive fields were in the magnocellular layer or the lateral reticular formation.

Price *et al.* (1976) also found five neurons that responded selectively to innocuous cooling. Four of these were located in the marginal zone and the other in the lateral reticular formation. One of the marginal neurons was antidromically identified as a trigeminothalamic neuron (see also Dostrovsky and Hellon, 1978).

Hoffman *et al.* (1981) recorded responses to noxious heat stimuli from 65 neurons in the medullary dorsal horn (trigeminal nucleus caudalis) in awake, behaving monkeys (*Macaca mulatta*). As in the anesthetized monkeys examined by Price *et al.* (1976), the neurons could be classified as low-threshold, wide dynamic range (WDR) or nociceptive-specific (NS) cells, based on their responses to graded intensities of mechanical stimuli. Stimulus-response curves of the responses of 16 WDR and 7 NS neurons to graded heat stimuli were compared. The curves for the WDR neurons consistently increased monotonically over the noxious range ($45\text{--}49^\circ\text{C}$), whereas the NS neurons were less consistently affected by noxious heat stimuli and some discharged when warm stimuli were given. The WDR

neurons had large receptive fields, involving 2–3 divisions of the trigeminal innervation, whereas NS neurons had smaller receptive fields, less than 1 trigeminal division.

The stimulus–response curves were steeper for WDR cells than for NS cells, and so the responses of WDR cells were more suitable than those of NS cells for encoding the magnitude of noxious thermal stimuli. By contrast, the small receptive fields of NS cells made them more suitable for encoding stimulus location. The NS cells were usually located in the superficial layers of the medullary dorsal horn, whereas WDR neurons were usually in the deep layers. No attempt was made to identify the neurons according to their projection target.

Related behavioral studies were also done on the same unanesthetized monkeys in which single unit activity was recorded from neurons in the medullary dorsal horn (Dubner *et al.*, 1981; Hayes *et al.*, 1981). An important finding was that a subpopulation of WDR neurons in the medullary dorsal horn had responses to small increases in noxious stimuli with detection speeds that were comparable to those of the behaving monkeys (Maixner *et al.*, 1986, 1989; Dubner *et al.*, 1989; Kenshalo *et al.*, 1989), whereas other WDR neurons and also NS trigeminal neurons did not. It was concluded that a subpopulation of DR neurons encodes the intensity of noxious heat stimuli. It was further suggested that NS trigeminal neurons may evoke emotional reactions and/or may contribute to the activation of descending pain-modulating pathways.

Somatotopic organization

Kerr *et al.* (1968) investigated the somatotopic organization of the trigeminal complex of monkeys. Recordings were made of the responses of 1142 units activated by stimulation of the ipsilateral face or oral cavity. Neurons with receptive fields in the mandibular division were dorsal to those with fields in the ophthalmic division. The oral cavity representation was located medially. The somatotopy was similar at different rostro-caudal levels of the trigeminal complex (cf. the study of somatotopy in the cat trigeminal complex by Kruger and Michel, 1962b).

Price *et al.* (1976) also observed that neurons in the marginal layer and in the superficial part of the magnocellular layer of the nucleus caudalis have a distinct somatotopic organization. Cells located dorsomedially in the nucleus caudalis had receptive fields in the mandibular division of the trigeminal nerve. More lateral neurons had receptive fields in the maxillary division. Finally, cells that were ventrolateral to those with maxillary fields had receptive fields in the ophthalmic division. The same somatotopic arrangement was present at transverse levels from 0–4 mm caudal to the obex. Neurons in the deep part of the magnocellular layer or in the underlying reticular formation had large receptive

fields that were not clearly somatotopically organized (cf. the somatotopic organization of spinothalamic tract neurons in the superficial and deep dorsal horn; see section on monkey spinothalamic tract neurons, Fig. 3.7 and Willis *et al.*, 1974).

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Physiology of supraspinal pain-related structures

Introduction

It is well understood that there are different components to the sensation of pain (Melzack and Casey, 1968). The sensory-discriminative aspect of pain refers to the location, intensity and quality of the sensory experience of pain. The affective-motivational aspect of pain refers to the unpleasantness of the pain and how likely it is that it will motivate the animal to escape the pain. We refer to these different components of the pain sensation throughout this review as we examine the possibility that these different components are mediated by different structures in the brain.

The spinothalamic tract (STT) is the spinal tract projecting toward the brain which is most often associated with the sensation of pain (Price and Dubner, 1977; Willis, 1985; Price *et al.*, 2003). Cells of origin of the STT can be divided into those which respond to low-threshold stimuli (LT cells), those which respond to stimuli across the intensive continuum into the noxious range (wide dynamic range, WDR), and those that respond only to noxious stimuli (nociceptive specific, NS). Evidence that any structure mediates the sensory aspect of pain is grouped into four lines: that the structure is connected to other structures known to demonstrate pain-related activity; that neural elements in that structure respond to noxious stimuli; that stimulation of that structure produces pain; and that interventions which interfere with the function of that structure interfere with the sensation of pain evoked by noxious stimuli (Price and Dubner, 1977). This chapter will review the evidence that structures located in the brainstem, thalamus and cortex meet these four lines of evidence of the sensory-discriminative aspect of pain.

Brainstem

Terminal fields of inputs from the spinal cord

In humans the terminal zones of spinal projection neurons are found not only in the thalamus, but also in the parabrachial nucleus, lateral periaqueductal gray matter (PAG), lateral reticular nucleus, paramedian reticular nuclei (interfasciculus hypoglossi), medial gigantoreticular core, nucleus subcoeruleus, subnucleus compactus Kölliker and nucleus intercollicularis (Mehler, 1962). In monkeys the most dense terminal zones of spinal projection neurons are found in the parabrachial nucleus and the PAG, with less dense terminations in the brainstem reticular formation, the posterior pretectal nucleus, the intercollicular nucleus, and nuclei of the brainstem adrenergic group including locus coeruleus and subcoeruleus, Kölliker–Fuse nucleus, nucleus of the solitary tract (NST) and ventral lateral medulla (Wiberg *et al.*, 1987; Westlund and Craig, 1996).

In monkeys the PAG is composed of longitudinal, columnar structures that receive input from different levels of the spinal cord (Bandler and Shipley, 1994a). In particular, inputs from lumbar, cervical lamina I and trigeminal sensory nuclei are found in progressively more rostral levels of the lateral column of the PAG, with considerable overlap of the representations of body parts (Wiberg *et al.*, 1987; Yeziarski, 1988). This input to the PAG arises largely from contralateral lamina I, although there is weaker input from lamina V in the cat and monkey (Wiberg *et al.*, 1987; Yeziarski, 1988). In monkeys injections into the trigeminal principal sensory nucleus labeled terminals primarily in the superior colliculus and those into the spinal trigeminal nucleus terminate in the parabrachial nucleus and PAG.

Injections of small amounts of labeled leucine into the PAG labeled terminations in the medial dorsal nucleus of thalamus (MD), midline thalamic nuclei, intralaminar thalamic nuclei, preoptic area and anterior, dorsal, periventricular nucleus and lateral and posterior hypothalamic nuclei (Mantyh, 1983a). This study may be consistent with connections seen in diffusion tractography in humans which show extensive thalamic connections (Sillery *et al.*, 2005).

Nociceptive cells projecting to or located within brainstem and midbrain

Spinal neurons responding to non-noxious and noxious stimuli and projecting to the brainstem have often been observed. In a number of species these spinal neurons have been classified by their terminations as follows: spinoreticular neurons (Fields *et al.*, 1977; Haber *et al.*, 1982; Blair *et al.*, 1984) and spinomesencephalic neurons (Hylden *et al.*, 1986; Yeziarski and Schwartz, 1986; Yeziarski *et al.*, 1987). Spinal neurons that project to the rostral brainstem

include those that have terminals in the PAG (Casey, 1971; Eickhoff *et al.*, 1978), hypothalamus (Burstein *et al.*, 1991; Katter *et al.*, 1996), parabrachial nucleus (Bernard and Besson, 1990) and thalamus (Surmeier *et al.*, 1988; Craig and Hunsley, 1991; Palecek *et al.*, 1992a, 1992b). However, there are a few reports of the properties of these neurons in monkeys.

In one study in monkeys, spinobulbar neurons were identified by antidromic activation from the medial aspect of the pontomedullary RF ($n = 29$) (Haber *et al.*, 1982). One half of these cells responded to noxious stimuli applied in RFs ranging from small digital to bilateral trunk RFs within cutaneous and deep structures. These neurons were more commonly in laminae IV to VI. Three of these cells were also antidromically activated from the thalamus, suggesting that the axon to the reticular formation is collateral of an STT axon (Haber *et al.*, 1982).

In another study, isolated STT neurons were identified as terminating in the thalamus and midbrain of monkeys, based on antidromic activation from both of these structures (Yeziarski *et al.*, 1987). Many of the neurons activated from the midbrain had large complex/bilateral excitatory RFs involving more than one limb. Neuronal somata were equally divided between spinal lamina I and laminae VI/V. Receptive fields (RFs) were smaller and conduction velocities faster among neurons projecting to the midbrain and thalamus than among those projecting only to the midbrain. Some neurons in each group had complex inhibitory RFs. There are few studies of the response of primate brainstem and midbrain neurons to noxious/painful stimuli.

One study reported responses of monkey spinomesencephalic neurons to mechanical stimuli. Two-thirds could be classified, based upon antidromic invasion, as STT cells terminating in the ventroposterolateral nucleus (VPL) with a mesencephalic collateral (STT/MST). The remainder could only be activated antidromically from the midbrain and were classified as spinomesencephalic cells (Dougherty *et al.*, 1999). In comparison with STT/SMT cells STT cells were more superficial in the dorsal horn (III to V vs. V to VII), and had lower thresholds and faster conduction velocities. Among SMT neurons six were classified as WDR, three as NS and two as LT cells, while STT/SMT neurons included 14 WDR, three NS and four LT cells.

Wide dynamic range cells had RFs as small as part of a digit to as large as the dorsal aspect of the whole leg, while NS neurons had low spontaneous firing rates and small RFs, such as the dorsum of a single digit (Dougherty *et al.*, 1999). Stimulus-evoked responses of NS, WDR and LT neurons were not significantly different between SMT and STT/SMT neurons. Reconstruction of optimal sites for producing antidromic invasion revealed that both SMT and STT/SMT sites were located in the ventrolateral or dorsolateral column of PAG, and in the pretectal

area. On the basis of limited evidence, spinal neurons projecting to the brainstem are found throughout the dorsal horn laminae, and often have large complex RFs, cutaneous or deep receptive fields.

There are few reports of neurons in the primate brainstem or midbrain responding to noxious stimuli. An early study, in lightly anesthetized squirrel monkeys, isolated midbrain neurons were classified into those responding to noxious stimuli and those responding to somatic, visual or auditory stimulation (Casey, 1966). One hundred and forty-two cells responded to innocuous somatic stimulation, while 34 responded to both innocuous and noxious stimulation, and so were classified as WDR units. No cells responded specifically to noxious stimuli (nociceptive specific). Receptive fields were "widespread" except in the case of neurons recorded in the ventral posterior (VP) region.

Most cells had excitatory responses to stimulation (28/34) whereas the remainder had inhibitory responses (Casey, 1966). The response latencies were estimated to be in the range of 300–350 ms. The anatomic location of these neurons was determined by histologic reconstruction of recording sites. Recorded neurons were designated as neurons responding to noxious stimuli or responding to other stimuli such as somatic, visual or auditory stimulation/total units by the following ratios in parentheses (noxious stimuli/other stimuli/total). For example, if among cells located in mesencephalic structures the number of cells in the anterior pretectal nucleus responding to noxious stimuli was 5, to any stimulus was 10, and the total studied was 11; then this was expressed as anterior pretectal (5/10/11). In the mesencephalic reticular formation the numbers of responsive cells were expressed (1/2/4). Cells responsive to noxious stimuli were not found in PAG (0/4/7), brachium superior colliculus and superior colliculus (0/14/18), or tractus retroflexus (0/2/2). No evidence of somatotopic organization was found.

The properties of neurons have been studied in the medullary reticular formation below the level of the obex in anesthetized monkeys (Villanueva *et al.*, 1990). These cells responded only to noxious cutaneous mechanical stimulation, with A δ latencies. Receptive fields were large and bilateral. Responses to stimulation of a contralateral limb were of low threshold, long latency and large magnitude. The low spatial and intensity resolution of these neurons suggest that they are involved in processes which do not require a response to noxious stimuli. These neurons may encode the features of the painful stimulus, such as the autonomic, motivational or affective aspects of pain.

Nociceptive neurons have been reported in the human mesencephalon during stereotactic surgery for pain (Amano *et al.*, 1978). Nashold reported low-frequency electrographic activity in the PAG which was correlated with paroxysms of pain in a patient with chronic pain (Nashold, Jr. and Wilson, 1966).

Stimulation of the midbrain

Stimulation of the PAG produces different patterns of behavior, depending upon the site of stimulation in the dorsolateral and ventrolateral columns of the PAG. In a wide range of species, activation of the dorsolateral column of the PAG produces a behavioral response of vocalization, grimacing, attack or escape and a parallel tachycardia and pressor response (Lovick, 1993; Bandler and Shipley, 1994b), while activation of the ventrolateral column produces behavioral quiescence, bradycardia and hypotension (Depaulis *et al.*, 1994). Both of these response profiles have been observed in response to stimulation within the PAG of humans (Nashold, Jr. and Wilson, 1966; Young *et al.*, 1985; Young, 1989). A wide range of analgesic, autonomic and “emotional” responses can be evoked by stimulation of the hypothalamus.

There are relatively few reports of the neuronal effects of PAG in primates. An early study of freely moving monkeys found that both noxious and electrical stimulation of the PAG and tegmentum provoked a similar reaction consisting of vocalization, offensive or defensive behaviors, and autonomic changes (Delgado, 1955). Vocalizations were characterized as rhythmic, high-frequency, loud screeches. Autonomic effects included piloerection, pupillary dilation, and increased respiratory and heart rate. Some of these effects have also been found in awake humans (Rasche *et al.*, 2006).

Stimulation of PAG has effects upon somatic sensory transmission through spinothalamic pathways to the ventral posterior nucleus of the thalamus (Gerhart *et al.*, 1984). In this study 37 WDR neurons demonstrated inhibition by PAG stimulation; the strength and duration of the inhibition varied with the intensity of stimulation in the PAG or “the deep layers of the tectum.” These effects were abolished by lesions of the cervical cord in proportion to the extent of the lesion. These pathways seem to traverse the dorsal lateral funiculus, although ventral pathways are also involved.

The most recent report of stimulation in the human periventricular gray (PVG) described evoked sensations at the time of surgery to implant a deep brain stimulation (DBS) electrode for the treatment of chronic pain. The coordinates of stimulation were 2–3 mm in front of the posterior commissure, approximately 2 mm above to 2 mm below the posterior commissure, and 2 mm lateral to the wall of the third ventricle (Rasche *et al.*, 2006). Stimulation at sites above the anterior commissure–posterior commissure (AC–PC) line created a “feeling of warmth, floating, and dizziness” at threshold current (50 Hz, 0.2 s). As the current was increased a sensation of fear and anxiety was evoked which could be severe enough to be classified as panic. Ventral to the AC–PC line gaze deviation, paralysis or diplopia could be evoked (Rasche *et al.*, 2006). Increased pulse rate or

blood pressure was common at the target site selected for analgesic stimulation as a treatment of chronic pain. These intraoperative effects did not persist with chronic stimulation after implantation of a permanent stimulator.

It has been suggested that PAG-DBS analgesia may be due to opiates, since the PAG stimulation evokes analgesia which is naloxone reversible, and is associated with opiate immunoreactivity in the CSF (Hosobuchi *et al.*, 1977, 1979). These studies have been called into question by the observation that ventriculography with contrast media used to collect CSF for the latter studies can exert a powerful effect upon CSF opiate immunoreactivity (Fessler *et al.*, 1984).

A large study of patients with implanted stimulators in the PVG ($n = 45$) found evidence that PVG-induced analgesia is opiate independent (Young and Chambi, 1987). Three criteria were used to identify opioid dependence: (1) development of tolerance to stimulation, (2) demonstration of naloxone reversibility, and (3) cross-tolerance with respect to intravenous morphine. Among this group of patients tolerance developed in 37%, the same rate as for stimulation of the ventral caudal (Vc) region, which is presumably non-opioid dependent. Reversibility of analgesia by naloxone occurred at the same rate as placebo. Among patients with tolerance to PVG stimulation or to morphine, none demonstrated cross-tolerance for the other, e.g. patients tolerant of morphine did not respond to PVG stimulation. Therefore, clinical evidence suggests that stimulation of the PAG may be mediated through opioid dependent or independent mechanisms.

Thalamus

Medial and intralaminar nuclei of thalamus

The presence of cells responding to noxious stimuli in intralaminar nuclei is consistent with the significant STT termination in these nuclei. The major intralaminar terminals are found in the central lateral nucleus (CL) separate from the main STT fiber pathway directed toward the ventrocaudal nucleus (Vc) (Mehler, 1966a, 1966b). Hassler proposed that the pathway to the CL nucleus mediated the suffering of pain while that to the Vc mediated the sensory aspect (Hassler, 1959b, 1970; Tasker *et al.*, 1982). Spinothalamic tract fibers are found traversing the centr  median nucleus (CM) on their course towards terminations in the CL (Bowsher, 1960).

In primates, dense STT terminations are observed in the central lateral nucleus (Mehler *et al.*, 1960; Boivie, 1979; Berkley, 1980; Mantyh, 1983b) while a light projection is found in the central median (CM) and parafascicularis nuclei (Pf) (Mehler *et al.*, 1960; Kerr, 1975; Berkley, 1980; Burton and Craig, Jr., 1983; Apkarian and Hodge, 1989c). These intralaminar nuclei project to the striatum, including both caudate nucleus and putamen (Kalil, 1978; Smith and Parent,

1986; Nakano *et al.*, 1990; Sadikot *et al.*, 1990; Sadikot *et al.*, 1992a, 1992b) and to the cortex diffusely (Powell and Cowan, 1967; Strick, 1975; Macchi and Bentivoglio, 1986). Spinothalamic tract terminations are also found in the monkey sub-medius nucleus (Apkarian and Hodge, 1989c), particularly in the dorsal (Craig, Jr. and Burton, 1981) and rostral (Mantyh, 1983b; Craig, 1990b) portions. The medial dorsal nucleus receives STT input (Kerr, 1975; Apkarian and Hodge, 1989c) and projects to the dorsolateral prefrontal cortex (Kievit and Kuypers, 1975; Tobias, 1975; Goldman-Rakic and Porrino, 1985). Therefore, the pattern of STT terminations in monkeys largely confirms that described in humans.

Responses of neurons in the medial and intralaminar thalamic nuclei to noxious stimuli (Casey, 1966) have been studied in squirrel monkeys which were given “a sedative dose of pentobarbital” at the beginning of each recording session. In medial thalamus responsive cells were found in MD (neurons responding to noxious/other such as auditory, visual stimuli/total: 14/52/76), PF (3/3/6) and lateral habenula (4/8/16). In another study of monkeys under light barbiturate anesthesia six units localized histologically in the intralaminar nuclei responded exclusively to noxious stimuli, as judged by the sensation evoked by these stimuli in humans (Perl and Whitlock, 1961). These neurons all had large receptive fields and responses to noxious stimuli were characterized by long-onset latencies and prolonged after-discharges. Electrical stimulation of nerves and mechanical cutaneous stimulation of several limbs evoked responses in these units. Responses of medial and intralaminar neurons to noxious stimuli have also been studied in monkeys carrying out a behavioral task.

Awake rhesus monkeys were trained to detect a small increase in temperature of a thermode over peri-oral skin which occurred on the baseline of a large step to a noxious temperature. Figure 4.1 illustrates this method during recordings from a cell in the monkey ventral posterior nucleus. Significant changes in firing rates occurred in response to the small temperature steps, which were at or below norms for the threshold for detection of these temperatures (Bushnell *et al.*, 1985). Neurons had large poorly defined receptive fields. Neurons responding to noxious stimuli were found in PF (4 PF neurons out of 16 studied: 4/16), MD (2/16), and one was found at the MD-CM border, but none was among neurons in LD or CM. Monkeys carried out these tasks when attending temperature or a congruent light intensity discrimination task.

Attention to the stimulus increased the thalamic response to noxious stimuli in this study (Bushnell and Duncan, 1989) but not in VP (Bushnell *et al.*, 1993). Ketamine-induced “light anesthesia” led to a significant decrease in the response to the large temperature step, although the differences in responses to innocuous versus noxious temperatures were still significant. The effects of attention may be consistent with alerting responses evoked by electrical stimulation in

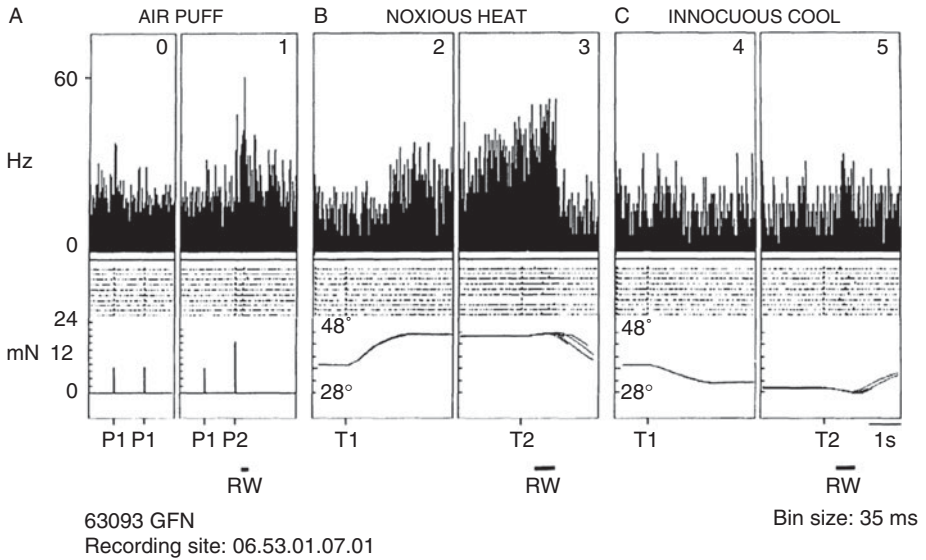


Fig. 4.1. Response of a neuron in an alert rhesus monkey to different cutaneous stimuli applied to the skin of the maxilla. (A) Raster and histogram (upper two traces) to four air puffs (lowest trace) which produced a small but significant response. (B, C) responses to noxious heating and innocuous cooling (C). The temperature stimulus shows an approximately 10 s (T1) from the adapting temperature with a smaller step (T2). There is a significant increase in activity during skin heating to T2 from the adapting temperature. There was a small, insignificant additional increase in response rate after T2. Reproduced from Bushnell *et al.* (1993), figure 3, with permission.

this area (Purpura and Housepian, 1961; Minamimoto and Kimura, 2002; Van der Werf *et al.*, 2002).

Repetitive low-frequency stimulation of this area will evoke widespread, stimulus locked, progressively increasing EEG waves from cortex (recruiting response) (Purpura and Housepian, 1961; Steriade *et al.*, 1997). Stimulation also evokes eye and head movements toward the opposite side, referred to as an orienting response (Van der Werf *et al.*, 2002). In trained monkeys, neurons in this area had a short-latency increase in activity in response to cues in the contralateral visual field, and a long-latency increase in activity to any directional stimulus (Minamimoto and Kimura, 2002). In the same study, injections of muscimol into this area were carried out to produce a transient lesion effect. These injections produced a decrease in the reaction time of eye movements to a cue in the contralateral but not ipsilateral field. These results and the study of responses to painful stimuli suggest that this region may have a significant role in directed attention to contralateral painful stimuli and may be related to

the attentional modulation of the neuronal response to noxious stimuli described above.

Nociceptive neurons have been identified in the human CM nucleus (Ishijima *et al.*, 1975; Tsubokawa and Moriyasu, 1975; Rinaldi *et al.*, 1991; Jeanmonod *et al.*, 1993, 1994). Ishijima *et al.* (1975) found that one-quarter (20/80) of the cells they recorded from the centre medial/parafascicularis complex of man responded to a noxious pinprick and two of these responded to application of noxious heat to the skin. None of these cells responded to non-noxious cutaneous stimuli. They identified two types of nociceptive cells: the first type responded at short latency to the application of stimuli, and terminated discharges shortly after discontinuation of the stimulus. The second type responded with a long latency and showed prolonged after-discharges. Both types of cells had receptive fields that were large, and often bilateral.

The two types of cells were distributed in different areas of the CM and PF nuclei. The first type of cell was found in the medial basal parts of CM, while the second type was scattered throughout the CM nucleus and the dorsal parts of PF. Tsubokawa and Moriyasu (1975) found a relatively large number of nociceptive neurons localized to the CM nucleus.

Recent studies by Rinaldi *et al.* (1991) ($n = 81$ cells) and Jeanmonod *et al.* (1993, 1994) ($n = 972$) in patients with deafferentation pain rarely found cells with receptive fields, in contrast to previous reports (Ishijima *et al.*, 1975; Tsubokawa and Moriyasu, 1975). Instead, cells with very high rates of spontaneous bursting discharge activity were reported (Rinaldi *et al.*, 1991; Jeanmonod *et al.*, 1993, 1994) – see below. The cells with receptive fields to innocuous tapping were found in two patients in whom bursting activity was absent (Rinaldi *et al.*, 1991). The receptive fields were very large and often bilateral. Jeanmonod and co-workers found two cells with large, bilateral cutaneous receptive fields to innocuous and noxious stimuli (Jeanmonod *et al.*, 1993, 1994). These cells were localized in the medial dorsal nucleus. Therefore, studies in monkeys demonstrate the presence of neurons in medial and intralaminar thalamus which respond to noxious stimuli. The results in humans are mixed with respect to the presence of cells in medial and intralaminar nuclei responding to noxious stimuli. Overall, these studies demonstrate the presence of neurons responding to both noxious and innocuous stimuli in large receptive fields. Responses occurred to small steps in temperature, consistent with the animal's discriminative performance (Bushnell *et al.*, 1985).

Electrical stimulation in the medial and intralaminar thalamus

Electrical stimulation in the medial and intralaminar thalamus has evoked a range of effects and sensations that are usually unpleasant

(Richardson, 1967). These effects included dyspnea and dizziness (Richardson, 1967; Richardson, 1974), pain and heat (Sugita and Doi, 1967), pupillary dilation and contraversive eye movements (Hassler and Reichert, 1959) and non-specific painful sensations (Fairman, 1966; Fairman and Llavallol, 1973).

The most detailed description of the effect of stimulation in these nuclei reported two types of sensation (Sano, 1979). The first type was a diffuse, burning pain referred to the contralateral half of the body, or the whole body. The sites at which these sensations were produced were usually concentrated near the posterior half of the internal medullary lamina, corresponding to the parvocellular regions of CM, plus PF and limitans. The first response to stimulation was exacerbation of the patient's spontaneous pain. The other type of sensation was a generalized "unpleasant" sensation, not localized to a particular body part. The sites at which these sensations were produced were concentrated in the very medial and anterior regions, possibly the medial dorsal and periventricular nuclei. Rinaldi and co-workers have also produced sensations by microstimulation in the medial thalamus, but these were not considered painful (Rinaldi *et al.*, 1991). Instead, a sensation of "pulling" was produced by stimulation in PF while throbbing was produced by stimulation in CM. These reports of the effect of electrical stimulation are consistent with neuronal responses which show poor spatial or modality resolution, but have a clear relation to noxious processing.

Lateral thalamus

A striking form of human thalamic neuronal activity is the response to light mechanical stimuli applied in small receptive fields on the face and hand. Receptive field locations for the cells in human thalamic Vc remain unchanged over distances of several millimeters in the anterior-posterior and dorsoventral directions but change markedly over similar distances in the mediolateral direction (Lenz *et al.*, 1988). A similar arrangement has been reported in monkeys (Mountcastle and Henneman, 1952; Jones *et al.*, 1982). From medial to lateral the sequence of neuronal cutaneous receptive fields progress from intra-oral through face, thumb, fingers (radial to ulnar), and arm to leg. Cells with deep receptive fields are usually located anterior and dorsal in the core but sometimes posterior to those with cutaneous receptive fields.

The region of the primate thalamic principal somatic sensory nucleus (human ventral caudal, Vc, or monkey ventral posterior, VP) is implicated in pain and temperature signaling pathways by anatomic studies (Walker, 1943; Bowsher, 1957; Mehler *et al.*, 1960; Mehler, 1962, 1966b) which indicate that the STT terminates in this region. The largest human thalamic termination of the STT is in the principal sensory nucleus, where it terminates as clusters (Mehler, 1962).

These clusters correspond to zones staining for the calcium binding protein, calbindin, in monkey VP (Rausell and Jones, 1991a). These zones are separate from the region of cytochrome oxidase positive terminals of the medial lemniscus, where the neuropil stains positive for the calcium binding protein parvalbumin (Rausell and Jones, 1991b).

Spinothalamic tract terminations occur in Vc and posterior to Vc in the magnocellular medial geniculate (Mehler, 1962, 1969), limitans, and ventral caudal portae (Vcpor) nuclei (Mehler, 1966b) and inferior to Vc in the ventral caudal parvocellular nucleus (Vcpc) (Mehler, 1966b). Monkey ventral medial posterior (VMpo), posterior to medial Vc, has a calbindin-staining terminal plexus which has also been identified in man (Craig *et al.*, 1994; Blomqvist *et al.*, 2000; see also Ralston, III, 2003; Graziano and Jones, 2004). It has been suggested that VMpo and the posterior nuclear group are specifically innervated by the dorsal STT (Craig and Zhang, 2006), although not all studies have been in agreement (Apkarian and Hodge, 1989a, 1989b; Ralston and Ralston, 1992; Zhang *et al.*, 2000). This is also discussed later in this chapter.

The region of the human principal sensory nucleus (Vc) (Hassler, 1959a) is divided into a core area (equivalent to monkey ventral posterior; see Fig. 4.2B) (Olszewski, 1952; Hirai and Jones, 1989), posterior and inferior regions. This area corresponds to the posterior and inferior subnuclei of Vc which are Vcpor, Vcpc (Mehler, 1966b), the posterior nucleus and the magnocellular medial geniculate (Mehler, 1962, 1966b; Lenz *et al.*, 1993b) (see Vc and Vcpor, Fig. 4.2A). Studies of patients at autopsy following lesions of the STT show terminations in all these nuclei (Bowsher, 1957; Mehler, 1966b, 1969).

This posterior inferior region includes the VMpo, which may receive lamina I STT inputs and may signal pain and temperature (location shown in Fig. 4.11) (Craig *et al.*, 1994; Blomqvist *et al.*, 2000; cf. Willis *et al.*, 2001; Graziano and Jones, 2004). These core and posterior inferior regions are defined relative to the most posterior and inferior cell with a response to non-painful, cutaneous stimuli (cell 57 in Fig. 4.2). In the core, the majority of cells respond to innocuous, mechanical, cutaneous stimulation.

Lateral thalamic nuclei: neuronal activity

In primates, some neurons responsive to noxious stimuli are found in the region of Vc including core, posterior and inferior regions, consistent with the anatomy of STT terminations in the lateral thalamus (see Chapter 2 and above). Figure 4.3 shows an example of a cell in the core of Vc with a differential response to painful thermal and mechanical stimuli (Lee *et al.*, 1999). The WDR cell shown in Fig. 4.3 showed responses to stimuli across the thermal series (Fig. 4.3D) and the mechanical series (Figs 4.3B, C). The graded response to

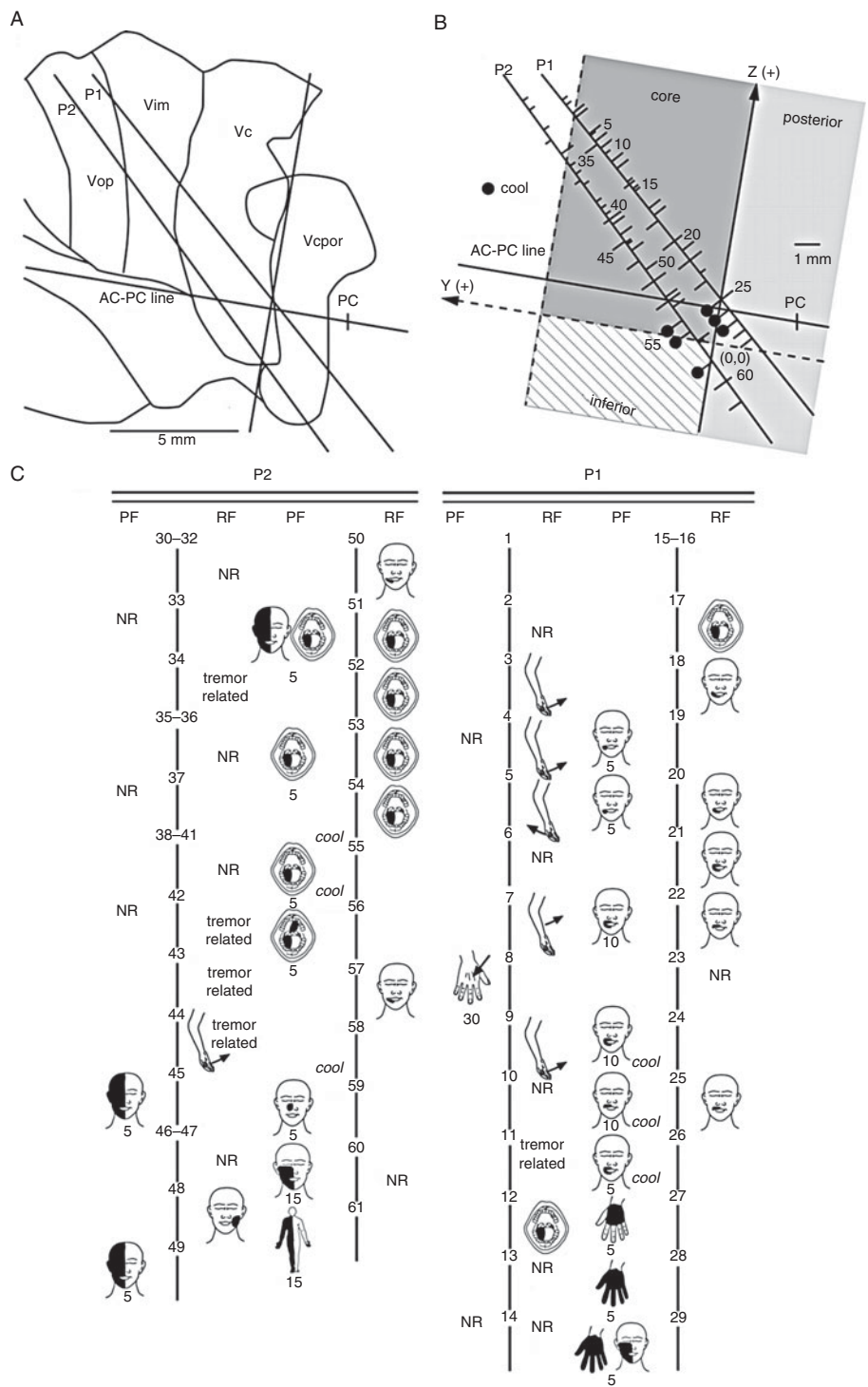


Fig. 4.2. (cont.)

mechanical stimuli was seen across the range from non-painful to painful (Fig. 4.3B) and within the painful range (Fig. 4.3C). The increase in firing rate spanned the range of stimuli into the painful range in the mechanical and thermal series. The increases between brush and large clip, large clip and medium clip, medium clip and small clip were significant. Comparison of firing rates produced by thermal stimuli and the background (firing rate with the Peltier at skin temperature) found that differences between these firing rates were significant.

Classification of cellular response type included multireceptive (MR) cells with responses to brush and compressive stimuli that were not graded into the painful range. Multiple-receptive cells respond to compressive stimuli, like WDR cells, and would have been included in the WDR class in some other studies (Chung *et al.*, 1986b; Bushnell *et al.*, 1993). Some of the compressive stimuli used in this series activate nociceptors even though they do not cause pain (Adriaensen *et al.*, 1984). Input from nociceptors might be transmitted to the thalamus through the dorsal column pathway since cells with similar properties have been reported in the dorsal column nuclei of anesthetized primates (Ferrington *et al.*, 1988). Similar responses have been recorded in the cells of origin of the STT (Willis *et al.*, 1974). Thus inputs from nociceptors may be transmitted to the thalamus through the dorsal column or the STT.

Overall, 15 cells studied had a graded response to mechanical stimuli extending into the painful range (WDR class of cells) among 57 cells studied in

Caption for Fig. 4.2. Map of receptive and projected fields for trajectories in the regions of the ventral caudal nucleus (Vc) in a patient with essential tremor. (A) Positions of the trajectories relative to nuclear boundaries as predicted radiologically from the position of the anterior commissure–posterior commissure (AC–PC) line. The AC–PC line is indicated by the approximately horizontal solid line in the panel. The trajectories are shown by the two oblique lines. (B) Location of the cells, stimulation sites, and trajectories (P1 and P2) relative to the AC–PC line indicated. The ventral border of the core of Vc is indicated by the dotted line parallel to AC–PC (y axis). The dotted and solid lines normal to the AC–PC line are the anterior and posterior (z axis) borders of the ventral caudal (Vc), respectively, as defined by the location of the most anterior and posterior cells with a cutaneous receptive field (RF). The locations of stimulation sites are indicated by ticks to the left of the trajectory; the locations of the cells are indicated by ticks to the right of the trajectory. Cells with RFs are indicated by long ticks; those without are indicated by short ticks. The cold sensation evoked is indicated by filled circles at the end of the tick to the left of the trajectory. Scale is as indicated. Each site where a cell was recorded or stimulation was carried out, or both, is indicated by the same number in B and C. (C) P1 and P2 show the site number, projected field (PF) and RF for that site. The threshold (in microamperes) is indicated below the PF diagram. Reproduced from Ohara and Lenz (2003), figure 2, with permission.

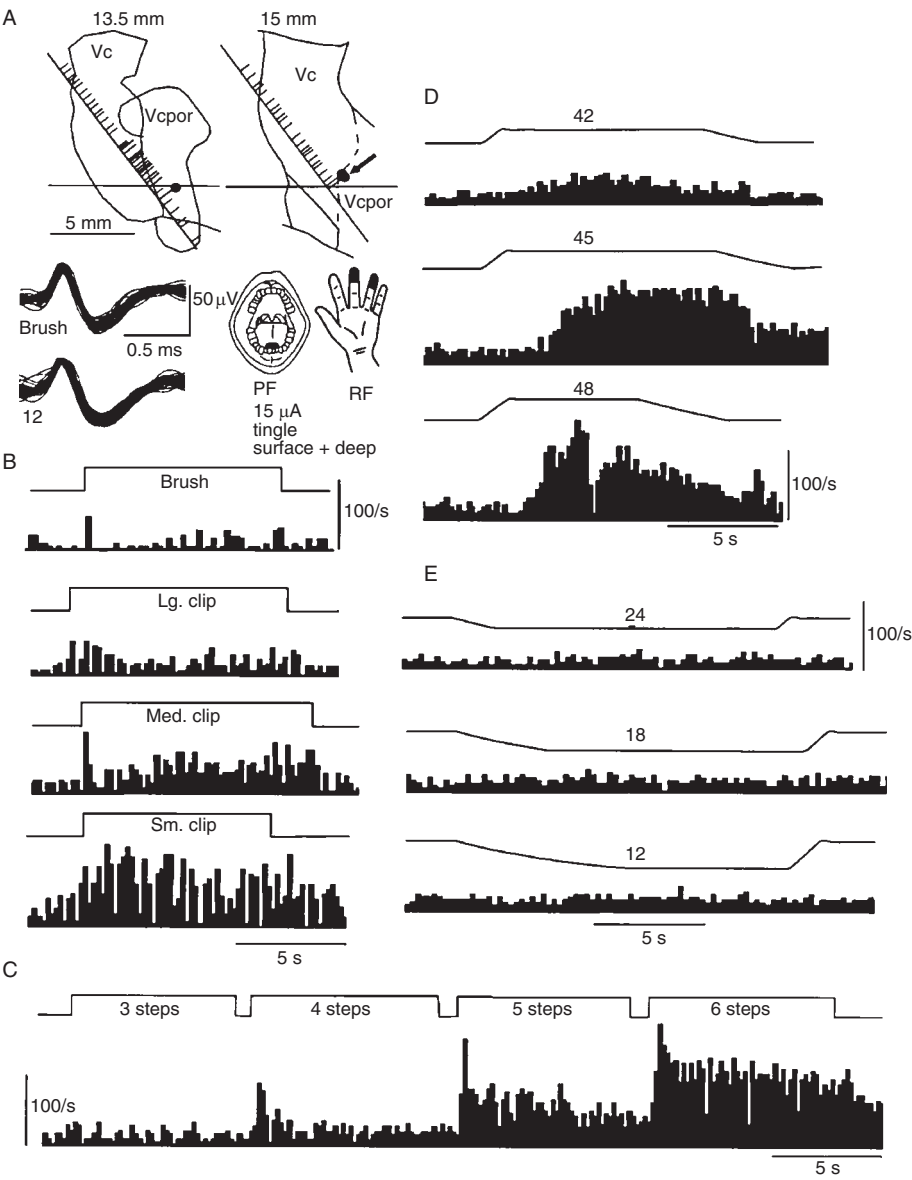


Fig. 4.3. Activity of a cell in Vc responding to painful mechanical and thermal stimuli. (A), location of the cell (arrow) relative to the positions of trajectories, nuclear boundaries and other recorded cells. The AC-PC line is indicated by the horizontal line and the trajectories are shown by the oblique lines (left, anterior; up, dorsal). Nuclear location was approximated from the position of the AC-PC line. Lateral location of the cell (in millimeters) is indicated above each map. Trajectories have been shifted along the AC-PC line until the most posterior cell with a cutaneous RF is aligned with the posterior border of Vc, because cells responding to innocuous sensory stimuli may

the Vc of awake patients (Lee *et al.*, 1999). The majority of cells in the WDR class responded to thermal stimuli, either cold (WDR-C, 2 cells) or heat stimuli (WDR-H, 7 cells) but not both. Twenty-five cells studied (MR or multireceptive cells) responded to both brushing and compressive stimuli although the responses were not graded into the painful range. Three cells in the MR class (MR-H) responded to heat stimuli and 5 cells (MR-C) responded to cold stimuli (Lenz and Dougherty, 1998), similar to a study in trained monkeys (Bushnell *et al.*, 1993). Some cells studied responded to brushing without a response to compressive or thermal stimuli (LT cells). Cells with responses to heat and painful mechanical stimuli were distributed throughout the region where cells responded to innocuous mechanical stimuli. These results demonstrate that cells in the region of the human thalamic principal somatic sensory nucleus respond to mechanical and thermal stimuli extending into the painful range.

The graded responses of WDR-H cells to both mechanical and thermal stimuli (Fig. 4.3) in the human data are also found in studies of monkeys (figures 3 and 5 in Bushnell *et al.*, 1993; figure 4 in Kenshalo, Jr. *et al.*, 1980) (Apkarian and Shi, 1994), strongly suggesting that these cells encode pain for these two modalities. However, except for two cells which might be classified as HT cells, all neurons in this population responded to non-painful stimuli and so were classified as WDR neurons. The function of such cells is less clear than that of cells that respond to noxious stimuli alone (Craig *et al.*, 1994). Microstimulation-evoked sensations provide one indicator of the modality signaled by the population of cells at a

Caption for Fig. 4.3. (cont.)

be located posterior to Vc (Apkarian and Shi, 1994). The locations of cells are indicated by ticks to the right of each trajectory. Cells with cutaneous RFs are indicated by long ticks, those without definable RFs by short ticks. Filled circles attached to the long ticks indicate that somatic sensory testing was carried out. The scale is as indicated. The shape of action potentials recorded at the beginning of the recording on this cell during application of the brush (upper) and at the end of the recording, during a 12 °C stimulus (lower). Action potential discrimination was triggered from up-going stroke of the action potential by using a voltage threshold of 30 μ V. The RF and PF for the natural, surface and deep, non-painful, tingling sensation evoked by threshold microstimulation (TMIS) at the recording site (threshold – 15 μ A) are also shown. (B), response to the brush, (BR), large clip (LC), medium clip (MC) and small clip. (C), the response of the neuron to progressive increase in pressure applied with the non-penetrating towel clip, indicated by the number of steps. D, responses to heat stimuli at 42, 45 and 48 °C. (E), responses to cold stimuli at 12, 18 and 24 °C. The upper trace in each panel is a footswitch signal indicating the onset and duration of the stimulus in (B) and (C) and the thermode signal in (D) and (E). The scales for the axes for all histograms (bin width 100 ms) are indicated in each panel. Reproduced from Lee *et al.* (1999), figure 2, with permission.

particular location (Ranck, 1975). However, the modality of sensations signaled by the neurons in this series did not correlate with the sensations produced by stimulation at the recording site. The results of neuronal recordings in humans are consistent with those in awake and anesthetized monkeys.

A study in awake cynomolgous monkeys reported 22 thermally responsive cells from a population of hundreds of VP neurons recorded (Bushnell *et al.*, 1993). The stimulus in this study was applied to a small (approximately 1 cm²) area on the maxilla or upper lip. Therefore this stimulus may have missed the thermal RFs of many cells and so may have underestimated the number of such cells. Eighteen percent (4/22) of these cells responded to noxious heat only. No such cells were found in the human study described above, perhaps because noxious and thermal search stimuli were not used (Lee *et al.*, 1999).

Neurons in VP with a WDR response pattern indicated by a response to noxious heating, and to innocuous cool, comprised 32% in that series (Fig. 4.1B) and 20% (3/15) in the largest human series (Lee *et al.*, 1999). Cells responding to innocuous mechanical stimuli with a phasic pattern comprised 23% of cells in that series. Among cells responding to light touch, 11% of which were inhibitory, some were striking (figure 7 in Bushnell *et al.*, 1993). In another monkey study of responses of cells in the ventral posterior nucleus (VPM) of awake monkeys to graded mechanical stimuli (Bushnell and Duncan, 1987), 10% of the cells (9/89) were classified as WDR based on their responses to mechanical stimuli. Cells with a WDR mechanical response pattern which also responded to heat stimuli graded into the noxious range comprised 27% of cells (6/22) in that study and 44% (7/16) of cells in the human series.

Congruent results have been reported in anesthetized monkeys. A study of this type in squirrel monkeys reported on cells (50/220) recorded in and around the VP nucleus (Apkarian and Shi, 1994), as confirmed anatomically. In that study, 40 cells in these nuclei responded to noxious mechanical stimuli; of these, 23 cells also responded to noxious heat and nine responded to noxious cold (Apkarian and Shi, 1994). Forty-four of the cells that did not respond to noxious cutaneous stimuli responded to stimulation of deep tissues, and four responded to both deep and cutaneous stimuli.

Noxious search stimuli, not possible in humans, can be used in studies of anesthetized monkeys (Chung *et al.*, 1986a; Apkarian and Shi, 1994; Kenshalo *et al.*, 2000) and thermal search stimuli have been employed in studies of anesthetized (Burton *et al.*, 1970) and unanesthetized monkeys (Bushnell *et al.*, 1993). The use of such search stimuli may account for the large number of WDR cells in these reports (Burton *et al.*, 1970; Chung *et al.*, 1986a; Bushnell *et al.*, 1993). Like most of these monkey studies, the largest human study employed a search stimulus that consisted of manual pinching (Lee *et al.*, 1999). The nature of this search stimulus

may explain the absence of cells in Vc responding exclusively to thermal stimuli (Poulos and Benjamin, 1968; Burton *et al.*, 1970; Chung *et al.*, 1986a).

Cells in the posterior inferior region have been identified with a significant selective response to noxious heat stimuli (Lenz *et al.*, 1993a) and cold stimuli (Craig *et al.*, 1994; Davis *et al.*, 1999), or to both (Lenz *et al.*, 1993a). These reports extend to humans the results of numerous monkey studies in which cells within VP (Casey, 1966; Kenshalo, Jr. *et al.*, 1980; Gautron and Guilbaud, 1982; Casey and Morrow, 1983; Chung *et al.*, 1986a; Bushnell and Duncan, 1987; Apkarian *et al.*, 1991; Bushnell *et al.*, 1993; Apkarian and Shi, 1994) and posterior and inferior to VP respond to noxious stimuli (Casey, 1966; Apkarian *et al.*, 1991; Apkarian and Shi, 1994; Craig *et al.*, 1994).

Location of cells responding to noxious stimuli in primate lateral thalamus

The location of the cells in the studies cited below is similar to that reported in monkeys with anatomic confirmation of recording sites (Apkarian and Shi, 1994). In a study of squirrel monkeys, cells responding to noxious thermal and mechanical stimuli were much less common in VP (18/203 – 9%) than in VPI (36/46 – 78%) and anterior Po (18/21 – 86%) (Apkarian and Shi, 1994). Wide dynamic range cells with facial RFs were clustered in ventral VPM in a study of awake cynomolgous monkeys (Bushnell and Duncan, 1987). Cells responding to noxious stimuli comprised 10% (1/10) of cells in VP and 8% (2/26) of cells in Po in another study of anesthetized monkeys (Casey, 1966). Two similar studies found cells responsive to noxious mechanical stimuli to be widely distributed in VP (Kenshalo, Jr. *et al.*, 1980; Casey and Morrow, 1983). These results are consistent with the human reports that cells differentially responsive to mechanical stimuli are located widely throughout VP. Cells responding to cold and innocuous mechanical stimuli were located dorsally in monkeys (Bushnell *et al.*, 1993) and in humans (Lenz and Dougherty, 1998).

A study of squirrel monkeys lightly anesthetized with “low dose pentothal” but judged to be awake based upon a high-frequency EEG activity and intermittent voluntary motor activity (Casey, 1966) found that 0/10 of cells in VP responded to noxious mechanical stimuli. Among other nuclei WDR cells were found in suprageniculate (2/8), limitans (2/6), posterior nucleus (2/26) and medial pulvinar (1/14). In another study of monkeys under light barbiturate anesthesia six neurons were found in VP which responded exclusively to stimuli thought to be noxious/painful as judged by the sensation evoked when the same stimulus was applied in man (Perl and Whitlock, 1961). These cells had small well-defined receptive fields to noxious pinching but could be activated by single stimuli applied to nerves on all four limbs.

The region below and behind Vc is defined relative to cells in the Vc core that respond to innocuous mechanical stimuli (Fig. 4.2). Neurons in this area may respond to thermal and noxious stimuli as described above (lateral thalamic nuclei: neuronal activity). This human region of Vc may correspond to the monkey VP, VPI, pulvinar and Po nuclei, since neurons in these nuclei also respond to innocuous cutaneous stimuli (Perl and Whitlock, 1961; Dykes *et al.*, 1981; Apkarian and Shi, 1994).

In a recent study 40 cells in these nuclei responded to noxious mechanical stimuli; of these, 23 cells also responded to noxious heat and 9 responded to noxious cold (Apkarian and Shi, 1994). These cells were located in VPI and Po more commonly than in VP, consistent with earlier studies (Perl and Whitlock, 1961; Casey, 1966). Studies in awake squirrel monkeys have found that up to 12% (9/76) of cells in VP responded to noxious mechanical stimuli (Casey and Morrow, 1983). These cells were widely distributed throughout VP. In another study, a smaller number of WDR and HT cells were found throughout VP in anesthetized rhesus monkeys (73 cells/thousands of cells) (Kenshalo, Jr. *et al.*, 1980).

Overall, monkey studies suggest that cells responsive to noxious stimuli are located in nuclei where cells can respond to innocuous stimuli – VP, VPI, pulvinar and Po (Perl and Whitlock, 1961; Casey, 1966; Casey and Morrow, 1983; Apkarian and Shi, 1994). Although the anatomic location of neurons recorded in human studies is uncertain, the largest human studies also demonstrate that cells responsive to painful mechanical stimuli are located in nuclei where cells respond to non-painful cutaneous stimuli. Clearly human Vc and monkey VP meet this criterion although cells responding to light mechanical stimuli have been found posterior to monkey VP (Perl and Whitlock, 1961). These monkey and human studies suggest that the thalamic principal sensory nucleus is involved in nociception.

It has been suggested that VMpo is physiologically as well as anatomically discrete with calbindin positive STT terminals (Craig *et al.*, 1994; Dostrovsky and Craig, 1996; Davis *et al.*, 1999; Blomqvist *et al.*, 2000). Neurons in this nucleus are reported to respond to noxious stimuli or thermal stimuli specifically. Figure 4.4 shows an example of a cell responding to cold stimuli. This proposal has been extended to humans based upon anatomical similarities of monkeys (Blomqvist *et al.*, 2000) and an electrophysiological study in humans (Davis *et al.*, 1999).

Multi-unit activity was recorded at a number of sites posterior and inferior to the medial aspect of human Vc and behind the central median nucleus. Sites were identified where microstimulation evoked cold sensations (average threshold 11 μ A). Cold stimuli were applied to these projected fields, and responses were dynamic so that unit activity diminished during the course of longer cold stimuli. These results may be consistent with recordings from spinal lamina I (Dostrovsky and Craig, 1996).

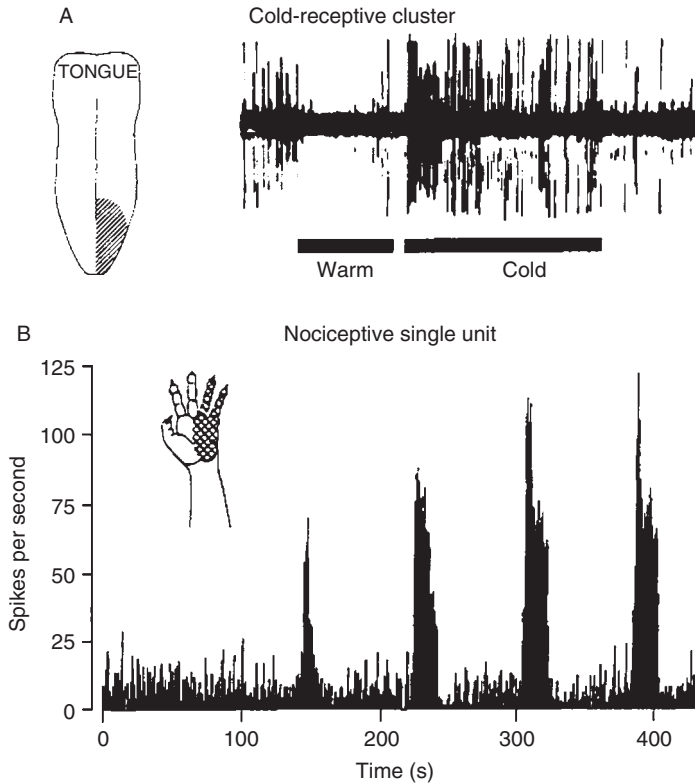


Fig. 4.4. Neuronal activity in putative nucleus VMpo to thermal stimuli. (A) A cluster of neurons which responded selectively to cold (ice cube) and were inhibited by warming. (B) A NS neuron responding in graded fashion to heat pulses into the noxious range. Receptive fields as indicated. Reproduced from Craig *et al.* (1994).

Anatomic studies of retrograde labeling of the spinal cord following injections into the ventral posterior thalamus or the region posterior, including VMpo (Craig, 2006) suggest that posterior injections, including into VMpo, preferentially label lamina I whereas those located in the ventral posterior nucleus preferentially label deeper laminae (Craig, 2006).

These descriptions of the properties of VMpo must be considered in the light of a recent anatomic study showing that many retrogradely labeled neurons following tracer injection into VPL/VPM in the primate thalamus were found in lamina I as well as in lamina V (Willis *et al.*, 2001). Another anatomic study demonstrated that trigeminothalamic lamina I injections led to labeling of terminations with calbindin negative labeling; this was widespread (Graziano and Jones, 2004). However, the most dense somatic calbindin labeling was found in the medial tip of VPM, and does not selectively delineate VMpo. This finding indicates that neurons in both laminae I and V contribute to the STT projections

to VPL/VPM. Therefore it is likely that both VMpo and VPL/VPM contribute to thermal and painful processing.

Lateral thalamic nuclei: patterned activity mediating pain and thermal sensations

Thalamic LTS (low-threshold spike) bursting is a fundamental property of thalamic neuronal membranes. This pattern of action potentials has been found in different animal preparations to be characteristic of bursts associated with the occurrence of calcium spikes (LTS spikes) (Deschenes *et al.*, 1984; Jahnsen and Llinas, 1984a; Domich *et al.*, 1986). It is usually associated with changes in state such as slow-wave sleep or drowsiness. Experimental studies have clarified the conductances underlying this bursting mode (reviewed by Steriade and Deschenes, 1984; Steriade and Llinas, 1988; Steriade *et al.*, 1990). The bursting mode occurs when the cell is hyperpolarized with respect to its normal resting membrane potential for approximately 100 ms, which leads to deinactivation of the active calcium conductance or calcium spike. During this calcium spike the cell fires a series of action potentials at high frequency termed a calcium spike-associated burst (Jahnsen and Llinas, 1984b; Roy *et al.*, 1984). Calcium spike-associated bursts are characterized by specific patterns of interspike intervals (Domich *et al.*, 1986).

Studies of the visual system have demonstrated that LTS bursting plays a role in the encoding of visual stimuli or the driving of saccadic eye movements which have an effect upon the encoding of visual stimuli (Lu *et al.*, 1992; Reinagel *et al.*, 1999; Martinez-Conde *et al.*, 2000, 2002). There are a few studies of the effect of this type of bursting upon transmission through the thalamus of signals encoding somatic stimuli (Lenz *et al.*, 1994c; Lee *et al.*, 2005).

Bursting of this type occurs at greater than baseline levels in response to many somatic stimuli. In a study of human Vc neuronal responses to somatic stimuli all neuronal categories have LTS bursts evoked by multiple somatic stimuli, based on standard LTS burst selection criteria. An example of these responses is found in Fig. 4.5. The responses were to cold and mechanical stimuli (MR-C neuron: see also figures 2, 4 and 6 in Lee *et al.*, 1999). This neuron fired in bursts of action potentials during the response to most stimuli. However there is a good deal of variability in bursting during spontaneous, prestimulus activity during the response to a cold modality of stimulation, e.g. 18 °C versus 24 °C. To account for this variability we combined all stimuli of each submodality and analyzed across neuronal categories.

Thalamic cells which respond to cold stimuli have higher rates of stimulus-evoked LTS bursting regardless of the modality of stimulation. The ratio of preburst interspike interval (ISI)/inverse of the primary event rate can be used

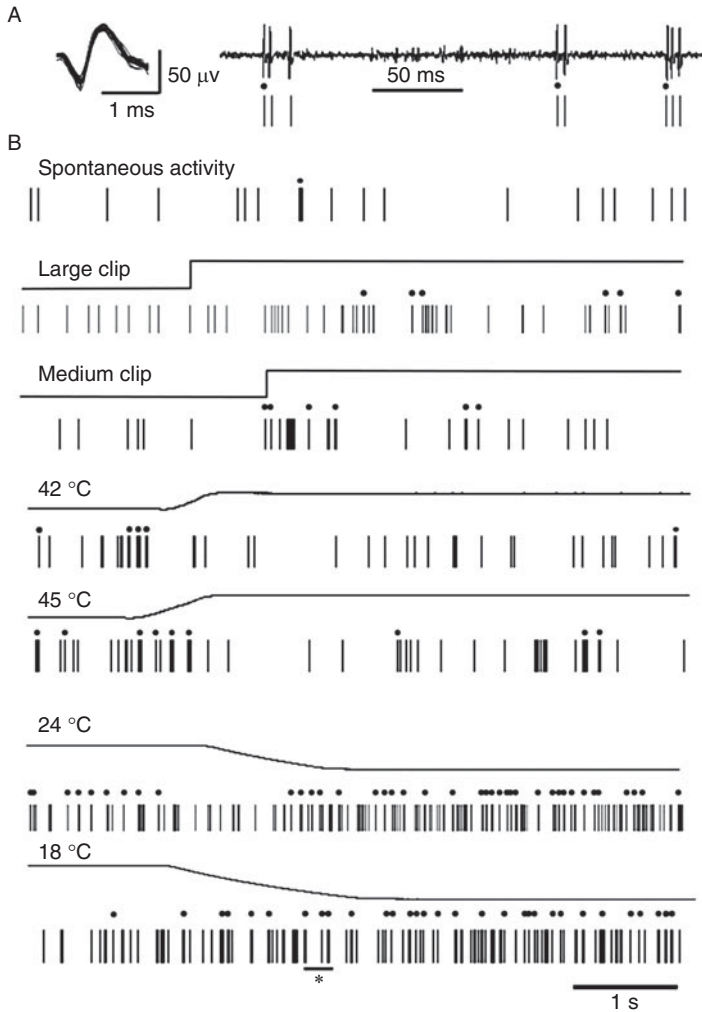


Fig. 4.5. Spike trains recorded from a neuron classified as multireceptive cold, MR-C (see section on lateral thalamic neuronal recordings). (A) Single neuron recording, at large scale, corresponding to the spike train segment above the calibration pulse in Panel B – 18 °C. (B) The discriminated spike train during the response to different stimuli as labeled. The filled circles above the tracing in (A), and the spike train in (B) indicate the first spike in a burst meeting criteria for a low-threshold spike (LTS) burst. The scale in (B) is so small that bursts like the second burst (dot) in Panel A can appear as a single spike in the corresponding segment of Panel B – 18 °C. Bursts like the first and third bar in Panel A can appear not as multiple single spikes but as thick, vertical lines in the corresponding segment in Panel B – 18 °C. Stimuli are indicated above the spike train as output of the thermode from the Peltier device for temperature stimuli and square wave signal from the foot pedal for mechanical stimuli. Adapted from Lenz *et al.* (1994a), figure 2.

to judge whether the preburst ISI is longer than ISIs between bursts, which indicates preburst inhibition. Analysis of this ratio demonstrates that the preburst ISIs were the result of significant preburst inhibition and not to slow firing between bursts, which is measured by the primary event rates. The preburst ISIs were not significantly shorter than 100 ms, consistent with maximal LTS amplitude, but were significantly longer than the 50 ms minimum preburst ISI required by the burst selection criteria.

The parameters of preburst inhibition were independent of the neuronal category and the stimuli, which suggests inhibitory mechanisms are similar across neuronal types. Therefore, these results do not reflect an artifact of the burst selection criteria. Altogether, these results are strong evidence for the presence of stimulus-evoked inhibition leading to LTS bursts during both spontaneous activity and the excitatory response of thalamic neurons to somatic sensory stimuli in awake humans.

The bursting activity of thalamic neurons responding to cold stimuli is reminiscent of the response of cold receptors to cold stimuli (Iggo, 1969; Kenshalo and Duclaux, 1977). Cool responsive neurons in the ventral posterior nucleus also respond with bursting activity at high frequency (ISIs of 2–4 ms) during the cooling phase following a heat stimulus (Martin, III and Manning, 1971). However, transmission of thalamic bursting from the periphery is in doubt because STT neurons responding to cold do not show bursting (Kumazawa *et al.*, 1975; Ferrington *et al.*, 1987), unlike the primary afferents and the thalamic neurons (Poulos, 1975; Iggo and Ramsey, 1976). The activity of these STT neurons may reflect their responses to multiple primary afferents firing out of phase. Therefore, it seems unlikely that thalamic bursting is the result of transmission of bursting activity from the periphery. The present evidence for stimulus-evoked LTS bursting in Vc argues for a mechanism based on thalamic circuitry rather than transmission of bursting activity to the thalamus via afferent pathways.

The origin of the inhibitory events which trigger LTS bursts may arise from several connections within thalamic circuitry (Fig. 4.6). In primate species, afferent axons terminate on postsynaptic sites containing excitatory amino acid (EAA) receptors based on both anatomic and electrophysiological criteria (Steriade *et al.*, 1997; Sherman and Guillery, 2001). Axons in the monkey dorsal column pathway form triadic structures in the ventral posterior nucleus by terminating on the dendrites of GABAergic local circuit interneurons (inset labels, L-c d1 and L-c d2) and a dendrite of the same thalamic projection neuron (Th-cx) (Ralston, III and Ralston, 1994). One population of these dendrites forms inhibitory synapses on the same projection neuron (L-c d1), while another population synapses on the dendrite of another inhibitory interneuron which may synapse on another inhibitory dendrite. Therefore, the afferent-evoked EPSP in

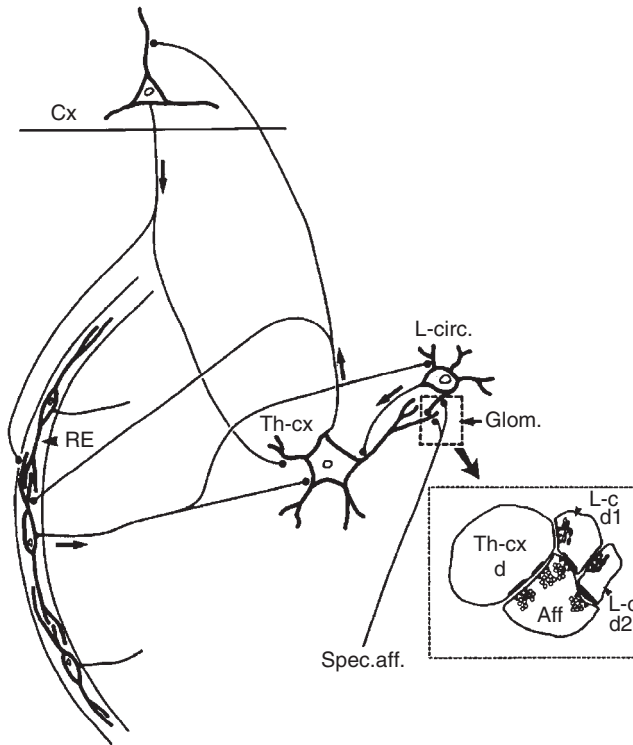


Fig. 4.6. Diagram of inhibitory circuitry of thalamic nuclei of the lateral group related to excitatory afferent inputs to, and efferent connections from, thalamus to cortex. See text for abbreviations. Adapted from Ralston and Ralston (1994) and from Steriade and Llinas (1988), figure 1, with permission.

the projection neuron is immediately followed by an IPSP produced by input from a GABAergic interneuron (Ralston, III and Ralston, 1994). This arrangement shortens the afferent-evoked EPSP and so provides short latency inhibitory feedback to excitatory somatic sensory input. Conversely, STT terminals commonly end in simple axo-dendritic terminations (Ralston, III and Ralston, 1994), which are clustered together on the dendrite.

Thalamic projection neurons also receive inhibitory GABAergic non-triadic synapses, arising from thalamic nucleus reticularis (Fig. 4.6, RE) and intrinsic inhibitory interneurons. Cortico-thalamic axons commonly send a branch to neurons of the thalamic reticular nucleus that project back to thalamic projection neurons, either directly or indirectly (Deschenes *et al.*, 1994; Bourassa *et al.*, 1995; Darian-Smith *et al.*, 1999). Axons of thalamocortical projection neurons then terminate on unidentified neurons in cortical laminae III–IV (Fig. 4.6, Cx). Cortical output from layer VI forms an excitatory projection to thalamic projection

neurons, or to interneurons in the nucleus reticularis or to local circuit interneurons (Steriade *et al.*, 1997; Sherman and Guillery, 2001). Either type of interneuron may send processes to projection neurons or local circuit interneurons or both. Therefore, there are many possible explanations of inhibitory events and the associated LTS bursting evoked by somatic sensory pathways afferent to the thalamus.

In comparison to other neuron types, those responding to cold have higher rates of stimulus-evoked LTS bursts, regardless of the stimuli analyzed. Therefore, it seems unlikely that burst firing is related directly to the afferent fiber transmitting cold. It is more likely that the increased bursting is the result of the properties and inhibitory connections of neurons responding to cold. These stimulus-evoked inhibitory events may result from afferent connections to the inhibitory circuitry described above (Jones, 1985; Steriade *et al.*, 1997; Sherman and Guillery, 2001).

Although neurons responding to cold have more stimulus-evoked LTS bursts, our inhibitory indices (preburst ISIs and the preburst ISI/inverse of the primary event rate) are not significantly different among neuronal categories, regardless of the stimuli analyzed. Therefore, increased bursting in neurons responding to cold may be the result of differences in the numbers of afferent-activated inhibitory events, the sizes of which are similar across neuronal categories in Vc.

It is not clear how stimulus-evoked LTS bursting relates to the assumption of linearity of thalamic pain and temperature transmission that is explicit in primate thalamic stimulus-response functions (Kenshalo, Jr. *et al.*, 1980; Bushnell *et al.*, 1993; Lee *et al.*, 1999). The same assumption is implicit in the graded mechanical stimulus-response function that defines WDR neurons in the dorsal horn (Willis *et al.*, 1974; Kumazawa and Perl, 1978; Maixner *et al.*, 1986), thalamus (Bushnell and Duncan, 1987; Morrow and Casey, 1992; Lenz *et al.*, 1994b) and cortex (Kenshalo, Jr. and Isensee, 1983; Price *et al.*, 2003). Patterned firing, as in the case of stimulus-evoked LTS bursting, may be related to non-linear, binary processes in the primate thalamus and cortex (Coghill *et al.*, 1999; Bornhovd *et al.*, 2002; Lenz *et al.*, 2004) which contribute to attentional or cognitive aspects of pain (Becker *et al.*, 1993; Zaslansky *et al.*, 1996; Bornhovd *et al.*, 2002).

Patterned spontaneous (LTS) bursting in lateral thalamus

The neuronal processes leading to evoked LTS bursting are different from those generating spontaneous bursts. Spontaneous firing patterns displayed bursts (primary event rate) for all different neuronal types. The burst rates and firing rate between bursts were not significantly different in different cell types. The ratio of burst/primary event rates during a spontaneous period were significantly higher for cells responding to the cold modality than for cells separated by

response type, i.e. WDR or NS. This suggests that among cells responding to cold, the firing rate between bursts is lower relative to the burst rate. Therefore the silent period or inhibition preceding any burst may be due in part to the lower firing rate or hyperpolarized resting membrane potential of these cells.

The lower primary event rate does not indicate that the bursting is due to a low primary event rate, because the ratios of preburst ISI/inverse of primary event rates were significantly greater than 1 for all neuron types. This indicates a significant spontaneous preburst inhibition for all types of neurons. Preburst ISIs during a spontaneous period were not significantly less than 100 ms for any neuron type, indicating the presence of preburst inhibition long enough to deinactivate LTS calcium spikes. Therefore, burst rates are similar because thalamic inhibitory circuitry responsible for spontaneous firing is relatively constant between functionally diverse neurons within a nucleus.

Spontaneous firing and bursting rates were examined between nuclei in patients with essential tremor (ET) (Ohara *et al.*, 2007). Essential tremor was studied because it can be characterized as a mono-symptomatic illness without the complex clinical pattern and anatomical/physiological abnormalities of Parkinson's disease (PD) and other neurological diseases treated with thalamic surgery (Deuschl *et al.*, 1998; Ohara *et al.*, 2007). In patients with essential tremor, firing rates were higher in Vim than in Vc, perhaps as a basic feature of thalamic activity in patients with ET, as compared to those in patients with pain or PD (Molnar *et al.*, 2005). This effect seems unlikely to explain the study of inter-nuclear firing since, in that study, firing rates were examined in Vim with the arm at rest which are significantly lower than during posture (Hua and Lenz, 2005). Whatever the explanation of the difference in firing rates between these nuclei, higher firing rates in Vim may be the result of a depolarized membrane potential.

Neurons in Vc also had higher LTS bursting rates than Vim and Vo, even after correction for primary event rates. This is consistent with studies in awake monkeys in which higher burst rates were found in monkey ventral posterior lateral nucleus of thalamus, corresponding to human Vc (Hirai and Jones, 1989).

There were also differences in preburst inhibition between Vc, Vim and Vo. Specifically, spike trains in Vc had longer preburst ISIs but smaller ratios of preburst ISI/inverse of the primary event rate. This indicates that, in Vc, the preburst inhibition is longer but the intensity of that inhibition is less than that among neurons in other nuclei. This is in contrast to the differences in the spontaneous firing between neurons in Vc which respond differently to painful and non-painful stimuli (Lee *et al.*, 2005). Within a nucleus, the ratio of burst rate/primary event rate was higher among neurons responding to cold stimuli, while the ratio of preburst ISI/inverse of the primary event rate was significantly greater than 1, although neither was significantly different between neuron types.

Therefore, during spontaneous activity LTS bursting rate and inhibitory circuitry differ between different human ventral thalamic nuclei. However, within one of these nuclei (Vc) functionally defined classes of neurons show different LTS bursting rates but inhibitory circuitry is relatively constant. The constancy of inhibitory circuitry and differences in burst rates between different functional classes in a nucleus may be an organizing principle of thalamic circuitry relevant to somatic transmission.

Stimulation of lateral thalamus

*Lateral thalamic nuclei: quality of sensations evoked
by stimulation within different subnuclei*

The interpretation of sensations evoked by microstimulation of the central nervous system rests upon an understanding of the sensations evoked by stimulation of the nervous system caudal to the thalamus. Sensations are evoked by intraneural microstimulation which may activate single nerve fibers originating in different mechanoreceptors (Vallbo, 1981; Ochoa and Torebjörk, 1983; Torebjörk *et al.*, 1984; Vallbo *et al.*, 1984; cf. Wall and McMahon, 1985). Intraneural microstimulation studies suggest that activation of slowly adapting type I fibers evokes a “pressure” sensation, while activation of Pacinian fibers evokes “vibration” (McComas *et al.*, 1970; Vallbo, 1981; Ochoa and Torebjörk, 1983; Torebjörk *et al.*, 1984; Vallbo *et al.*, 1984), and rapidly adapting fiber stimulation evokes “flutter,” “touch,” “tapping,” “vibration” and “tickle” sensations, which may be the perceptual substrate of frequency discrimination (Salinas *et al.*, 2000; Romo and Salinas, 2003).

These mechanoreceptive fibers project largely through the dorsal columns, consistent with the paresthesias or vibration evoked by stimulation of the dorsal columns and medial lemniscus (Emmers and Tasker, 1975; Tasker *et al.*, 1982; Willis and Coggeshall, 1991; Lenz *et al.*, 1993b; North *et al.*, 1993). These results are also consistent with mechanical, movement and tingle sensations evoked by stimulation of Vc (Ohara *et al.*, 2004e). Lesions of the dorsal column produce poor two-point discrimination, position sense, detection of repetitive stimuli and graphesthesia, consistent with loss of mechanoreceptive input (Nathan *et al.*, 1986; Willis and Coggeshall, 1991; Vierck, 1998; cf. Wall, 1970; Wall and Noordenbos, 1977). These results suggest that the mechanical/tingle sensations are the result of activation of thalamic structures receiving input from the dorsal columns.

Stimulation of A δ , C and high-threshold muscle afferent fibers evokes fast sharp, slow dull and dull crampy pain, respectively (Torebjörk *et al.*, 1984). Stimulation of cool fibers evokes a cool sensation (Iggo, 1985). These fibers mediate thermal or pain sensations and terminate on STT and spinal trigemino-

thalamic neurons (Jones, 1985; Willis, 1985). Stimulation of the STT in the cervical spinal cord and cervicomedullary junction evoked warmth, cool or burning in patients with nociceptive pain as opposed to patients with neuropathic pain (see below) (Tasker, 1976, 1977; see also Hitchcock, 1972, 1973). Similar sensations are commonly evoked by stimulation of the STT in the mid-brain (White and Sweet, 1969; Mayer *et al.*, 1975; Tasker *et al.*, 1982; Bosch, 1991; Ohara and Lenz, 2003), while STT lesions produce analgesia and thermal anesthesia (White and Sweet, 1969; Tasker *et al.*, 1982; Bosch, 1991; Tasker, 1992).

These results suggest that thermal/pain sensations reported in this study are the result of activation of thalamic structures receiving input from A δ , C and muscle afferents which is transmitted through the STT. The nature of STT transmission of these signals has been informed by an important study in patients undergoing cordotomy for nociceptive pain in cancer (Price and Mayer, 1975). The conduction velocity of fibers mediating pain was estimated by measuring the refractory period during paired pulse stimulation in the STT at the cervicomedullary junction (Price and Dubner, 1977). Successively longer interpulse intervals were applied until the sensation of pain increased stepwise. This abrupt increase in pain rating results at the current at which the fibers responded to both pulses for the first time (Mayer *et al.*, 1975). The conduction velocity corresponding to this interpulse interval was compared with estimates of the conduction velocities for fibers originating in lamina I versus the deeper laminae. The conduction velocity for axons subserving the sensory discriminative aspect of pain was found to correspond to that measured for axons originating in the deep laminae of the spinal cord in monkeys (Price and Dubner, 1977).

These results suggest that mechanical/tingle sensations are mediated through the dorsal columns, while thermal/pain sensations are mediated through the STT (Jones *et al.*, 1982; Jones, 1985; Rausell and Jones, 1991a; Rausell *et al.*, 1992). Nevertheless non-painful brushing can activate STT neurons and cold stimuli can activate neurons in the DC pathway (Willis *et al.*, 1974; Ferrington *et al.*, 1988). Noxious visceral stimuli can activate neurons in the postsynaptic DC pathway and lesions of this pathway can relieve visceral pain (see below) (Hirshberg *et al.*, 1996; Willis *et al.*, 1999; Nauta *et al.*, 2000). Therefore, the interpretation of the present psychophysical results in terms of inputs from the medial lemniscus and the STT to Vc should be treated as a useful simplification.

The largest study of pain and temperature responses evoked by stimulation in the lateral thalamus by threshold microstimulation examined these responses at 959 stimulation sites in the region of Vc (124 thalami, 116 patients) (Ohara and Lenz, 2003). The location of pain and temperature responses is defined relative to the posterior and inferior borders of the principal somatic sensory nucleus (Vc), as illustrated in Fig. 4.7 (Ohara and Lenz, 2003). Cellular location was classified

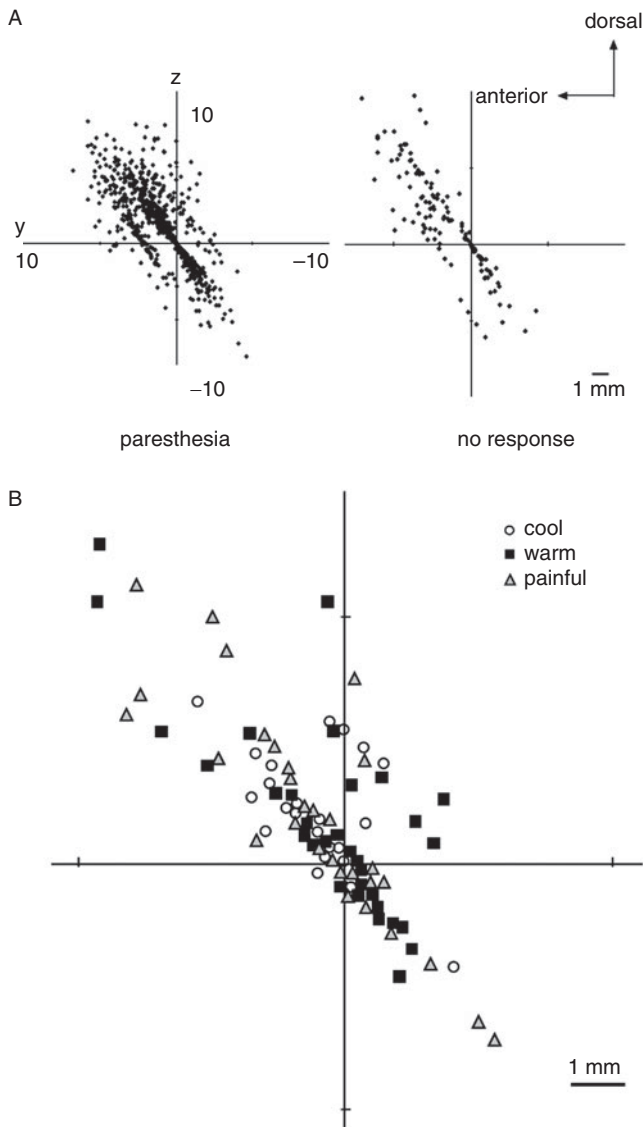


Fig. 4.7. Locations of sites where microstimulation evoked paresthesias. (A) Left, sites where stimulation evoked no response (NR). (A) Right, sites where stimulation evoked thermal and pain sensations. (B) Site location is shown relative to the posterior and inferior borders of the core of Vc. Note that thermal and pain sensations were evoked both in the core and posterior regions of Vc (see Fig. 4.2). Paresthetic sites are most dense where NR sites are least dense over the core and the posterior regions. Scale as indicated.

into core vs. posterior inferior, and medial vs. lateral plane based on whether the core neuronal RFs of any sagittal plane were intra-oral or facial vs. upper extremity RFs. Warm sensations were evoked more frequently in the posterior region (5.7%) than in the core (2.3%). In the posterior inferior region of the lateral (upper extremity) plane the proportion of sites where warm sensations were evoked was significantly higher than in any other region. The proportion of pain sites was significantly higher in the posterior inferior region than in the core of the medial plane. No other significant medial lateral differences for any sensation were found in the core or posterior region or overall.

There are other recent reports of the sites where microstimulation evokes thermal and pain sensations. One report suggests that thermal and painful sensations were evoked by microstimulation at sites located medially near the border between the core and the posterior inferior region and that they were evoked more frequently at sites in the posterior inferior region than at sites in the core region (Lenz *et al.*, 1993b). Another similar study reported that most sites where stimulation evoked thermal and painful sensations, in 49 movement-disorder patients, were concentrated in the region 1–3 mm inferior and posterior to the inferior and posterior border of the Vc (Dostrovsky *et al.*, 2000). However, the largest thalamic microstimulation study found more sites in the medial aspect of the core region where stimulation evoked thermal sensations (Ohara and Lenz, 2003; see also figure 3 in Lenz *et al.*, 1993b and figure 2 in Dostrovsky *et al.*, 2000). The difference in the method to define regions in Vc, in the selection of patients or number of patients, might account for this difference.

The largest study of thalamic microstimulation (Ohara and Lenz, 2003) is at odds with earlier studies which report that a larger proportion of thermal/pain sites are evoked in the posterior and inferior regions (Lenz *et al.*, 1993b; Davis *et al.*, 1996). These latter studies took the anterior commissure–posterior commissure line (AC–PC) as the floor of Vc, contrary to atlas and physiological maps (see Fig. 4.2) (Schaltenbrand and Bailey, 1959; Lenz *et al.*, 1988). The largest study of microstimulation is the only one to require that posterior and inferior regions be cellular zones and the core be a cellular zone with cells having receptive fields to innocuous stimuli. Studies of the surrounding nuclei suggest that cells inferior and posterior to Vc can have RFs to innocuous stimuli (Casey, 1966; Apkarian and Shi, 1994). If these differences in defined borders are critical then these latter sites where pain or temperature was evoked must be very close to the borders of the core.

In the largest microstimulation study, thermal and painful sites are distributed in a relatively diffuse fashion in the region of Vc in intra-oral, face and upper extremity planes. There was no significantly different location of these sites by medial vs. lateral location. These sites were also found on the plane

where RF/PFs related to taste or pharynx. Nuclei mediating taste and pharyngeal somatic sensation are located in proximity to VMpo (Blomqvist *et al.*, 2000). The taste relay in the thalamus is located in monkey VPMpc (ventral posterior medial parvocellular nucleus) (Olszewski, 1952; Pritchard *et al.*, 1989) corresponding to human V.c.pc.i (ventro-caudalis parvocellularis internus) (Hassler, 1959a; Hirai and Jones, 1989; Lenz *et al.*, 1997). In monkey, it was shown that units in the medial half of VPM have RFs in the pharynx. Those nuclei in the human thalamus, ventral medial basal – VMb (or V.c.pc.i) and the medial aspect of VPM, are located just anterior or anterior-superior to VMpo (Blomqvist *et al.*, 2000). Therefore sites where thermal and painful sensations were evoked found in the taste/pharynx plane are most likely to be located as far medial as VMpo, although the distribution was not confined within the area corresponding to VMpo.

However, the largest study of microstimulation results suggests that thermal and pain sensations are processed diffusely throughout the region of Vc, including Vc core, plus Vcpc and Vcpor, respectively, corresponding to monkey VPI and pulvinar oralis, as well as VMpo (Hirai and Jones, 1989; Lenz *et al.*, 1993b). These nuclei are thought to be involved in pain processing based on: the presence of STT terminations after cordotomy (Walker, 1943; Bowsher, 1957; Mehler, 1962, 1966b), by the presence of neurons responding to painful stimuli (Lee *et al.*, 1999; Lenz *et al.*, 1993b, 1994b), and by the presence of sites at which microstimulation evokes pain and thermal sensations (Davis *et al.*, 1996, 1999; Lenz *et al.*, 1993a, 1998a, 1998b).

The degree to which VMpo may be specific for thermal and pain processing is unknown. A recent microstimulation study in humans reported that many thermal and pain sensations were evoked at locations that were clearly lateral to the location of VMpo, perhaps due to stimulation of fibers of passage. At microstimulation sites in presumed human VMpo cold sensations were evoked in small projected fields on the face, arm and leg (Davis *et al.*, 1999). At these stimulation sites the intensity of the cold sensation evoked varied with the intensity of microstimulation. Overall, these results support the view that VMpo is a component of pain and thermal pathways (Figs 4.6 and 4.7). They also suggest that these pathways involve Vc core, Vcpor, Vcpc and regions posterior and inferior to Vc along its medial-lateral extent (Figs 4.2, 4.4 and 4.7).

*The sensations evoked by patterned stimulation
in the region of human Vc*

The relationship between LTS bursting and modality of somatic stimulation suggests that different patterns of stimulation of sites in the region of Vc might lead to different evoked sensations. Patterned stimulation at sites in the region of Vc (Fig. 4.8) evokes pain sensations consistent with one of two

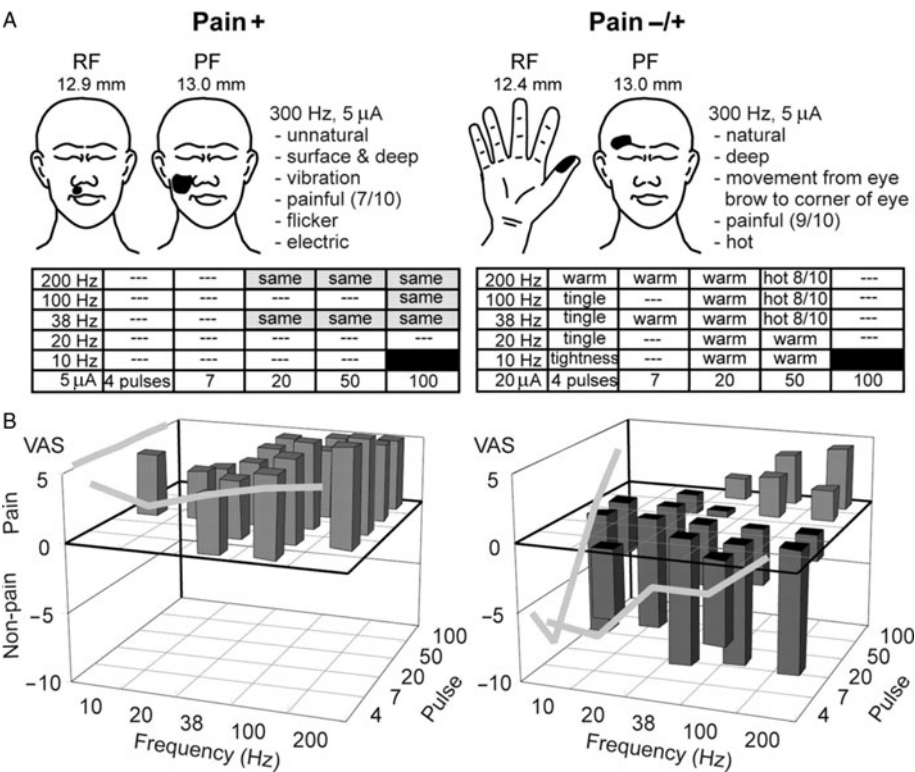


Fig. 4.8. Pain + and pain -/+ stimulation sites. Sensations evoked by threshold microstimulation were characterized by the projected field (PF), by descriptors from a validated questionnaire and by a visual analog scale of intensity (Lenz *et al.*, 1993b; Lenz and Byl, 1999). (A) Left, site where stimulation at 300 Hz and 5 μ A produced pain in the PF (shown in the illustration) and of the quality described. Pain identical to that evoked by 300 Hz was evoked at most sites with trains of >20 pulses and frequencies of $\geq$ 20 Hz (shaded rectangle). (A) Right, site where tightness was evoked in the first column at 10 Hz and then a tingle at 20, 38 and 100 Hz. Except for a few sites where no sensation was evoked, warmth was evoked at all steps in the ascending staircase from 4 pulses and 200 Hz to 50 pulses and 20 Hz. At subsequent steps along the staircase only painful heat was evoked. (B) Average VAS ratings across all pain + and pain -/+ sites. Ratings were taken in response to pulse and frequency pairs ascending the staircase. The lines along the outside surfaces of the 3-dimensional displays indicate the average VAS ratings across all sites by frequency and number of pulses. Reproduced from Lenz *et al.* (2004), figure 2, with permission.

pathways: one binary (pain +) and the other analog (pain -/+). Specifically, current was applied at five frequencies (10, 20, 38, 100 and 200 Hz) in bursts with variable numbers of pulses (4, 7, 20, 50 and 100 pulses) in an ascending staircase protocol, commonly used in studies of pain (Gracely *et al.*, 1988;

Yarnitsky and Sprecher, 1994; Greenspan *et al.*, 2004). Therefore the staircase ascended from 4 pulses/10 Hz, to 4 pulses/20 Hz, and so on to 100 pulses/200 Hz. Stimulation at pain + sites evoked a constant high level of pain over large, often cutaneous, PFs. These sites were characterized by descriptors which did not change along the staircase, and by more intense stimulation-evoked pain than that evoked at the pain -/+ sites. These results suggest that pain + sites participate in a “binary,” exteroceptive, labeled line which signals the presence of a painful external stimulus.

The thalamic stimulation thresholds for non-painful and painful sensations are not significantly different (Lenz *et al.*, 1993b; Ohara and Lenz, 2003) suggesting that pain -/+ sites did not result from activation of the system transmitting non-painful sensations (largely medial lemniscal) before that transmitting painful sensations (largely STT) (Willis, 1985). In addition, the equivalence of current, pulse and frequency thresholds for pain at pain -/+ and pain + sites predicts that the neural elements, i.e. WDR and NS cells, should be activated together if they were found at the same site. At such sites analog pain + responses would be predicted to occur because of the combination of binary plus analog neural properties. However, such sites were not observed. For all these reasons, it is plausible that our observations may be the result of selective activation of two functionally distinct pathways.

The plot of VAS score versus neuronal mean firing rate for the response to painful stimuli demonstrated that HT neurons have a steeper slope than WDR neurons (figure 4 in Lenz *et al.*, 2004). The responses of multiple individual WDR neurons versus VAS is less steep than that for NS neurons. This difference in slope arises because there was a significantly steeper initial rise in VAS scores for the neurons that only responded to painful stimuli (NS neurons), than for WDR neurons. The steep initial rise of VAS with the firing rate of NS versus WDR neurons (Fig. 4.8B) is consistent with the shorter dynamic range of thalamic NS cells (Apkarian and Shi, 1994), and with the binary response to stimulation at pain + sites (Fig. 4.2B).

We suggest that the first pathway is characterized as a binary pain response signaling the presence/absence of painful stimuli, consistent with an alerting/ alarm function (Becker *et al.*, 1993; Zaslansky *et al.*, 1995). The second pathway may be an analog route in which activity is graded with intensity of the painful stimulus, consistent with STT neurons which encode the properties of external stimuli (Willis, 1985; Price *et al.*, 2003). Itch was rarely evoked and never in isolation. Emotion descriptors (e.g. nauseating, cruel, suffocating) were uncommonly endorsed at either pain + and pain -/+ sites (cf. Lenz *et al.*, 1995). Therefore, both painful responses to stimulation were described in terms usually applied to external stimuli (exteroception) rather than to internal or emotional

phenomena (interoception). Exteroreceptive sensations can be associated with a strong affective dimension.

Lateral thalamic nuclei: inputs from the viscera

There is also evidence that the primate lateral thalamic nuclei mediate noxious visceral sensation. Cells in the monkey thoracic spinal cord projecting to VPL respond to coronary artery occlusion (Blair *et al.*, 1984) or intracardiac injection of bradykinin (Blair *et al.*, 1982; Meller and Gebhart, 1992; Meller *et al.*, 1992). Neurons in the posterior lateral nucleus of the thalamus in cats are also activated by intracardiac bradykinin (Horie and Yokota, 1990) or stimulation of cardiac sympathetic nerves (Taguchi *et al.*, 1987). Neurons in the VP thalamus also respond to input from other visceral afferents of the gastrointestinal and genitourinary system in the monkey (Fig. 4.9) (Bruggemann *et al.*, 1992; Chandler *et al.*, 1992) and the rat (Berkley *et al.*, 1993).

Studies of visceral inputs from multiple hollow organs in the squirrel monkey VP have demonstrated that 85% of cells in VP responded to visceral inputs (Bruggemann *et al.*, 1992). Most of these also responded as visceral nociceptive-specific (65%) or visceral wide dynamic range (34%) neurons, and to somatic stimuli with a WDR or NS pattern (Bruggemann *et al.*, 1994). The majority of neurons in VP responsive to visceral inputs also responded to innocuous cutaneous input from the body below the waist. These visceral inputs may be transmitted through the monkey midline dorsal column system (Foreman *et al.*, 1981; Al Chaer *et al.*, 1998). Finally, interruption of this pathway has been demonstrated to relieve visceral pain in patients with cancer of abdominal or pelvic origin (Nauta *et al.*, 1997, 2000). These results are also congruent with the results of stimulation of the lateral nuclear group in patients with a prior experience of visceral or somatic pain with a strong affective component.

Visceral sensations have been evoked at sites in Vcpc, the human equivalent of VPI, in a patient with a previous history of angina, treated by coronary artery angioplasty procedures (Lenz *et al.*, 1994a). At one such site microstimulation (Fig. 4.10) evoked an unnatural, painful (visual analog scale: 5/10), mechanical sensation in the flank and an unnatural non-painful electrical sensation involving the left arm and leg. At sites 51 and 53 (see Fig. 4.10B, 4.10C) microstimulation evoked a sensation described by the patient as “heart pain” which was “like what I took nitroglycerin for ...” except that “... it starts and stops suddenly.” It was not accompanied by dyspnea, diaphoresis or after-effects. The projected field involved the precordium and left side of the chest from the sternum in the midline to the anterior axillary line. Microstimulation at site 51 also evoked a sensation of non-painful, surface tingling in the left leg, which coincided with the stimulation-associated angina.

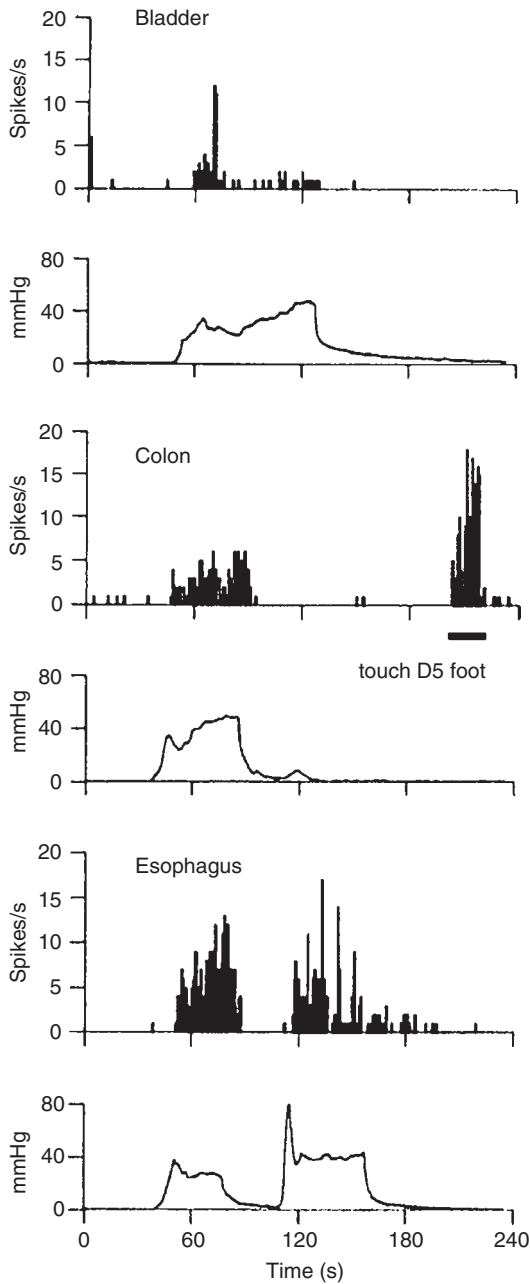


Fig. 4.9. Peristimulus time histograms for the responses to low-threshold cutaneous stimulation (see touch at the right of the colon panel) and to visceral distension presumably into the noxious range for a number of hollow organs. Pressure tracings are shown below each histogram.

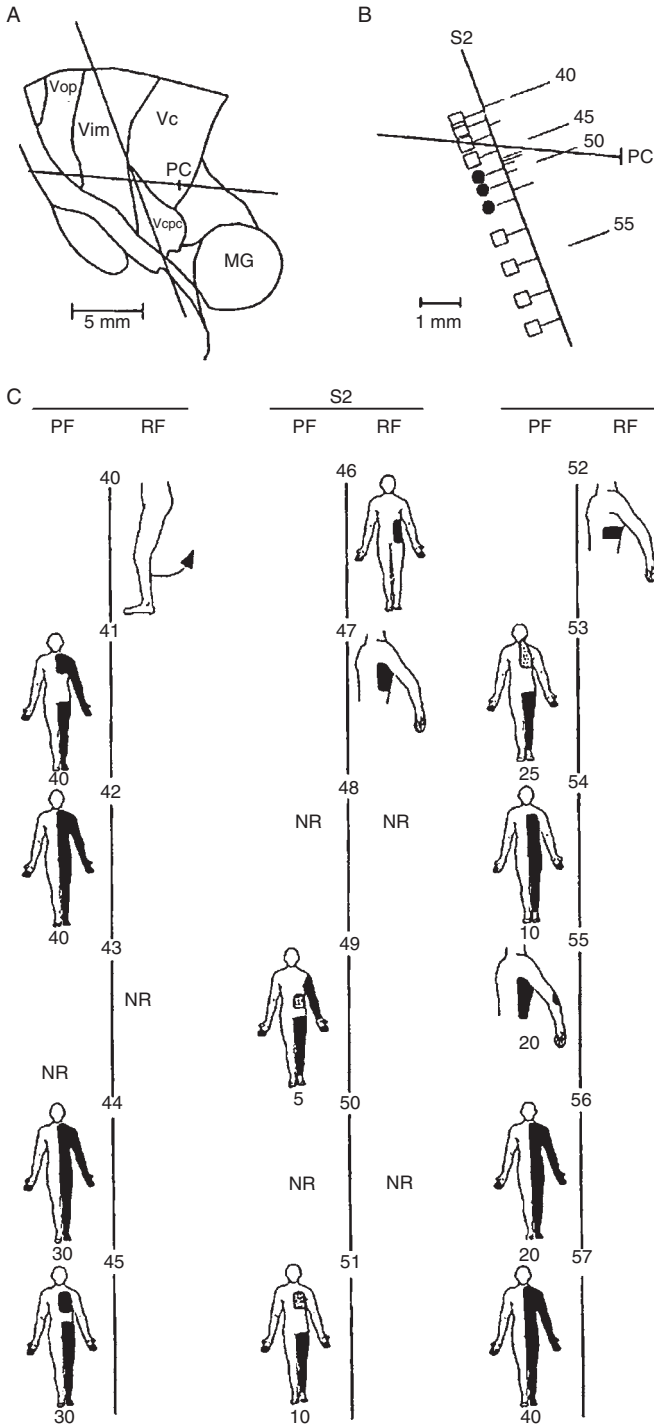


Fig. 4.10. (cont.)

Pain with a strongly unpleasant or affective component can be evoked by stimulation of the lateral thalamus in the Vc, Vcpc and Vcpor, all of which receive input from the STT (Lenz *et al.*, 1994a; Davis *et al.*, 1995a). These sensations have the character of “memories” of a previously experienced pain, unlike the pain sensations evoked by thalamic sensation which are not related to previous experience (see above) or a diffuse unpleasant sensation of the type evoked by stimulation of the medial thalamus (see below). In the first case, stimulation in Vcpc (Fig. 4.10) evoked chest pain with an affective dimension “almost identical” to her prior angina (Lenz *et al.*, 1994a).

Characteristics of the patient’s stimulation-associated angina and usual angina were measured by using a questionnaire. The same descriptors for stimulation-associated angina were chosen intraoperatively during stimulation at both sites 51 and 53 (Fig. 4.10) including: natural, deep, painful (visual analog scale: 10/10), squeezing, frightful, fatiguing and identical to her angina. The questionnaire was administered three times over several months post-operatively to describe the patient’s usual angina. The following descriptors were chosen: natural (3/3 administrations), deep (3/3), painful (3/3), squeezing (3/3), frightful (2/3), suffocating (2/3) and fatiguing (2/3). Her usual angina involved the left side of the chest, arm and neck and was associated with a surface (3/3), non-painful (3/3) and tingling (3/3) in the left arm and hand. This coincidence of descriptors is unlikely to occur at random ($P < 10^{-6}$, combinatorial analysis).

Similar “emotional” responses, including crying in response to thalamic stimulation in the same region, have been reported in the case of atypical chest pain, dyspareunia and the pain of childbirth (Davis *et al.*, 1995a; Lenz *et al.*, 1995).

Caption for Fig. 4.10. Map of receptive and projected fields for a trajectory 16 mm lateral to the midline in a patient with a history of angina. (A) Position of the trajectory, indicated by the oblique line, relative to the AC-PC line and the nuclear boundaries as estimated from the position of the AC-PC line. (B) Locations of cells, stimulation sites and trajectory SII relative to the posture commissure (PC). Locations of cells are indicated to the left of the trajectory while stimulation sites are indicated to the right of the trajectory. Long ticks to the left are sites where a sensation was evoked as indicated by the symbol at the end of the tick: open square represents tingling while solid circle represents pain. Numbers in (B) correspond to those in (C) which are adjacent to a number indicating the microstimulation threshold and figurines showing the receptive and projected fields. In the projected field figurine black indicates the distribution of tingling sensations and stipple indicates the area of pain. Long ticks to the right indicate cells with receptive fields. The quality of the stimulation-evoked sensation is indicated by the symbol at the end of the tick to the left of the trajectory: an open square indicates tingling and a filled circle indicates pain. Reproduced from Lenz *et al.* (1994a), figure 2.

Clinical criteria including a battery of cardiac tests (enzymes, EKGs, stress test) ruled out angina of cardiac origin in both these patients. Explorations in 50 patients without a history of angina found that stimulation-associated angina was not evoked at any of 19 stimulation sites with PFs on the chest wall. Projected fields were located on the left chest wall at three sites and the right chest wall at 16. At one of these 19 sites an unnatural, sharp, mechanical, painful or vibratory sensation was described in response to stimulation but emotional descriptors were not endorsed.

Pre-operative pain was clearly of cardiac origin in the patient with angina (Lenz *et al.*, 1994a), but clearly not of cardiac origin in the patient with panic disorder. The association of stimulation-associated angina and the affective dimension was not unexpected (Lenz *et al.*, 1994a) since angina is often associated with a strong affective dimension, unlike other chest pains (Matthews, 1985; Braunwald, 1988; Procacci and Zoppi, 1989; Pasternak *et al.*, 1992). Stimulation-evoked sharp chest pain occurred without an affective dimension in a retrospective analysis of patients without prior experience of spontaneous chest pain with a strong affective dimension. Therefore, it is possible that the stimulation-associated chest pain included an affective dimension as a result of conditioning by the prior experience of spontaneous chest pain with a strong affective dimension.

The parasyllian cortex and the memory of pain

Pain with a strong affective dimension evoked by stimulation of the region of Vc may be related to activation of its parasyllian cortical projection zone (see above) (Locke *et al.*, 1961; Mehler, 1962; Van Buren and Borke, 1972). These vivid “memories” are similar to those evoked by stimulation around the lateral sulcus and amygdala in patients with epilepsy (Halgren *et al.*, 1978; Gloor *et al.*, 1982; Gloor, 1990; Moriarity *et al.*, 2001). Therefore, these thalamic stimulation results may be related to the activation of limbic structures (Lenz *et al.*, 1995) through insular connections to the amygdala and hippocampus (Mishkin, 1979; Friedman *et al.*, 1986). Painful stimuli sometimes lead to long-term changes in pain processing, as well as to signaling the presence of the stimulus. This appears to be the situation in the case of stimulation sites in posterior Vc, where stimulation can evoke complex pain sensations in the patients with angina or atypical chest pain. Sensations of this type have never been reported in response to STT stimulation.

Secondary somatosensory and insular cortical areas involved in pain processing also satisfy criteria for areas involved in memory through corticolimbic connections (Mishkin, 1979). In monkeys, a nociceptive submodality selective area has been found within SII (Dong *et al.*, 1994; Willis *et al.*, 2001). The SII cortex

projects to insular areas that project to amygdala (Friedman *et al.*, 1986). The SII and insular cortex have a bilateral primary noxious sensory input (Chatrian *et al.*, 1975), and cells in these areas responding to noxious stimuli have bilateral representation (Dong *et al.*, 1994) and project to the medial temporal lobe (Chatrian *et al.*, 1975; Dong *et al.*, 1989). Therefore cortical areas receiving input from Vcpc and Vcpor may be involved in memory for pain consistent with Mishkin's hypothesis of corticolimbic connections (Mishkin, 1979).

Lateral thalamic nuclei: effects of lesions

The previous studies of sensory loss following thalamic lesions have been carried out in patients with post-stroke central pain (CPSP). These studies have employed routine interpretation of structural imaging studies to identify lesions of the posterior thalamus leading to CPSP. Some studies have identified lesions which may be limited to Vc (Hirai and Jones, 1989; Leijon *et al.*, 1989; Vestergaard *et al.*, 1995; Bowsher *et al.*, 1998). In these studies patients with lesions limited to Vc were not reported as a separate group from those with lesions including Vc. One of these studies demonstrated a small, isolated lesion seeming to involve left Vc and right internal capsule leading to pain on the left body and right face. In none of these cases were results reported for the small number of patients with isolated unilateral lesions of the thalamus.

A number of historical studies have examined the effects of lesions of Vc for treatment of neuropathic pain. These studies have documented contralateral decreases in experimental mechanical (Albe-Fessard *et al.*, 1970) and thermal pain (Spiegel and Wycis, 1953; Mark *et al.*, 1961; Albe-Fessard *et al.*, 1970), proprioception (Mark *et al.*, 1961; Richardson, 1974) and touch (Albe-Fessard *et al.*, 1970; Richardson, 1974). The extent of these lesions and details of the extent and type of the resulting sensory loss is unclear in this series and previous studies of CPSP.

There are two reports of quantitative sensory testing in patients with CPSP with small lesions in the region of Vc, as characterized by atlas-based nuclear mapping of MRI scans of the lesion. One study is a case report which used this technique to locate a stroke involving a large part of Vc and sparing VMpo. This lesion led to a "marked" decrease in ipsilateral laser-evoked potentials (LEPs) and somatic sensory-evoked potentials (SSEPs) (Montes *et al.*, 2005). Quantitative sensory testing showed a contralateral decrease in detection of tactile stimuli, in graphesthesia, in two-point discrimination, detection and discrimination of hot and cold (pain and non-pain) sensations. The patient had clinical evidence of tactile and cold allodynia.

The second study has reported the results of clinical CPSP in four patients with lesions restricted to Vc ("Vc only" lesions, see Fig. 4.11), or to Vc and the

region posteriorly (“Vc plus”) (Kim *et al.*, 2007). This study demonstrated that tactile sensibility was decreased in all patients tested, including patient 8 with the “Vc only” lesion. Tactile sensibility was measured by von Frey hair and moving brush stimuli, which are mediated through the dorsal column – medial lemniscal pathway (Mountcastle, 1984). These results are consistent with studies of spinal cord lesions which demonstrate that the dorsal columns are essential for normal tactile sensibility (Noordenbos and Wall, 1976; Nathan *et al.*, 1986). Previous studies have demonstrated that neurons in Vc, the terminus of the dorsal column-medial lemniscus pathway, respond to innocuous tactile stimuli and that microstimulation in Vc evokes sensations like those evoked by tactile stimuli (Lenz *et al.*, 1988; Ohara *et al.*, 2004e). These lines of evidence demonstrate that tactile sensibility involves the dorsal column – medial lemniscus pathway to Vc.

One of these patients (patient 13) had central dysesthesia syndrome, and experienced dysesthesias in response to joint movement. This patient also had diminished tactile perception without tactile allodynia, which suggests that deep afferents may mediate movement-evoked dysesthesias. The lesion in this patient included dorsal Vim and anterodorsal Vc, which may receive muscle afferent input via the medial lemniscus (Jones *et al.*, 1982). The location of this part of Vc is unclear because it is not shown in the Schaltenbrand atlas or other atlases (Schaltenbrand and Bailey, 1959; Nowinski *et al.*, 1996). In anterodorsal Vc neurons respond to joint movement, and stimulation evokes deep and movement sensations (Lenz *et al.*, 1988; Ohara *et al.*, 2004e). These observations suggest that input arising from deep afferents may be interrupted by the “Vc plus” lesion in patient 13, so that sensitivity, or hypersensitivity, to movement is mediated through the STT, which is another source of deep afferent information to Vc thalamus (Foreman *et al.*, 1979; Leijon *et al.*, 1989; Dougherty *et al.*, 1992; Bowsher, 1996).

Caption for Fig. 4.11. (cont.)

with the dark stipple are the lesions, and those indicated by the light stipple and the star are the locations of thalamic nuclei (see inset at left on the lowest row). Lpo, nucleus lateropolaris; Voa, nucleus ventral oral anterior; Voi, nucleus ventral oral internal; Vop, nucleus ventral oral posterior; Vim, nucleus ventral intermediate; Pf, parafascicular nucleus; Ce, nucleus central medial; Li, nucleus limitans; Pu, pulvinar; M, medial dorsal nucleus; Vcpor, nucleus ventral caudal portae; Vcpc, nucleus ventral caudal parvocellular; Cmp, posterior commissure; Dc, lateral posterior nucleus; Dime, dorsal intermediate external; Doe, dorsal oral external; Vime, nucleus ventral intermediate external; Vce, nucleus ventral caudal external; Gm, medial geniculate nucleus; Dim, nucleus dorsal intermediate; Vci, nucleus ventral caudal internal. Reproduced from Lenz *et al.* (1994a), figure 2.

The results of the second study of isolated lesions of the region of Vc demonstrated that innocuous heat sensations were only found for the lesions which extended behind Vc (Fig. 4.11, lowest row, patients 13 and 18). Structures within and behind Vc contain both neurons that respond to non-painful heat (Lenz *et al.*, 1993a; Lee *et al.*, 1999) and sites where stimulation commonly evokes non-painful heat sensations (Lenz *et al.*, 1993b; Ohara and Lenz, 2003). In total, these studies suggest that the sensation of non-painful heat is mediated through structures that are located posterior to Vc.

Painful heat thresholds were normal in all patients tested. However, LEPs, that are mediated through a nociceptive heat pathway, were diminished in a patient with a lesion of Vc which was much larger than the present lesions (Montes *et al.*, 2005). These results suggest that the sensation of painful heat is impaired by larger lesions of Vc, or by lesions of anterior and ventral Vc, which were spared by lesions in the present results. This is consistent with the broad distribution both of neurons responding to painful heat in Vc, and of sites where stimulation evokes painful heat (Lenz *et al.*, 1993b; Ohara and Lenz, 2003).

The results of the second study demonstrate that small lesions of posterior Vc alter the sensation of cold pain, while “Vc plus” or larger “Vc only” lesions are required to impair innocuous cold sensibility. In these regions neurons respond to painful and non-painful cold, and microstimulation may evoke the sensation of cold or cold pain (Lenz *et al.*, 1993a; Davis *et al.*, 1999; Lee *et al.*, 1999; Ohara and Lenz, 2003). These results suggest that small lesions of posterior Vc are sufficient to alter cold pain sensibility, and larger lesions of Vc are required to impair cold sensibility. Alternately, the location of the lesion within Vc may be the main determinant of altered sensibility.

Dimensions of lesions required to impair perception

The discriminative aspect of somatic sensation can be measured in monkeys by the detection of an airpuff, or a small temperature step (T2) which occurs after a larger thermal step from adapting temperature into the range of cool or noxious heat (Fig. 4.1) (Bushnell *et al.*, 1983). This protocol has been used to apply graded stimuli to the peri-oral skin before and after injections of a local anesthetic into the medial aspect of the ventral posterior nucleus (VPM). Three recording electrodes were located 1 mm apart in the rostral to caudal direction, and the caudal two electrodes were combined with the injection ports 2 mm dorsal to the tip of the microelectrode (Fig. 4.12). Simultaneous injections into VPM silenced neurons 2 mm ventral to the site of the caudal injection site (Fig. 4.12, left) but not 1 mm rostral to the rostral recording site. Volumetric analysis of neuronal recordings and histological reconstructions suggest that in Fig. 4.12A lidocaine injected in this experiment silenced neuronal activity within

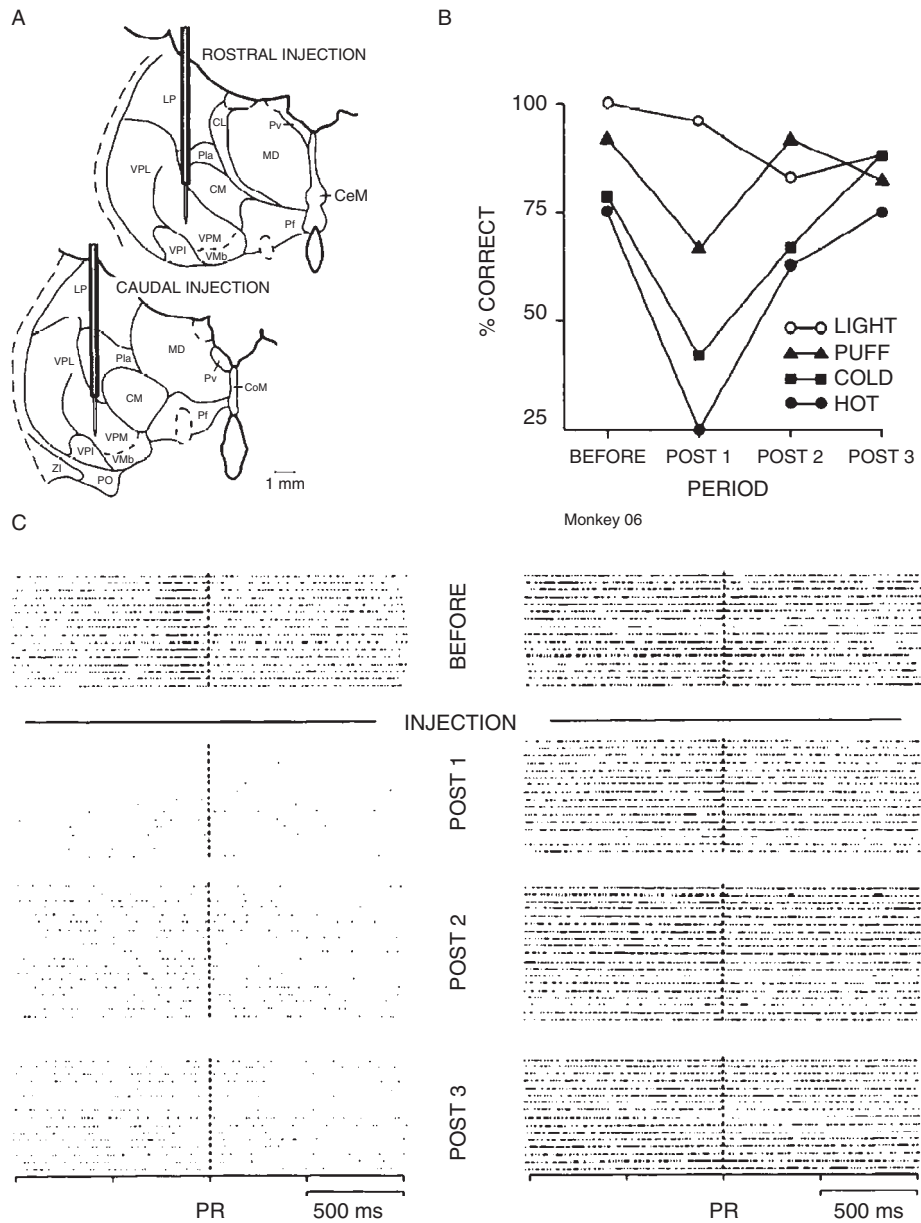


Fig. 4.12. (A) Approximate histologic locations of microelectrode and cannulae for injection of local anesthetic. (B) Percent correct detection of airpuff, cool, painful heat and visual stimuli before and after infusion of local anesthetic, which show significant decreases in all categories except visual stimuli. (C) Left, rasters of activity 2 mm below the caudal injection, at 0, 20 and 40 min after the injection labeled as Post 1, 2 and 3. (C) Right, rasters for electrode 1 mm above the rostral injection (see microelectrodes in panel A). Reproduced from Duncan *et al.* (1993).

a region of VPM from the medial dorsal border of VPM/CM to its ventral lateral border with VPI (Duncan *et al.*, 1993). The authors concluded that structures, including Pf and submedius, located 4–5 mm ventral and medial were not inactivated by these injections (Bushnell and Duncan, 1989; Hirai and Jones, 1989; Craig, 1990a).

Figure 4.12B demonstrates that these injections impaired detection of an air-puff and small (Fig. 4.1, T2) changes in the intensity of heat and cold in the painful range or of an airpuff. All experiments consisting of two or three separate, simultaneous injections into VPM decreased detection of all three modalities, which suggests that these are mediated by discrete anatomic elements within VP (Jones *et al.*, 1982; Rausell *et al.*, 1992; Patel *et al.*, 2006). In no experiment did single injections impair detection of any of the tactile, noxious heat or noxious cold stimuli tested (Duncan *et al.*, 1993).

The second human study of strokes in the region of Vc suggests that a “Vc only” lesion of $\geq 16\%$ of Vc, and perhaps as little as 12% (in “Vc plus” lesions), is sufficient to impair discrimination of tactile sensation. The sensation of cool or cold pain is impaired by a “Vc only” lesion with a volume of $\geq 16\%$. If the volume of the lesion in Vc is $< 16\%$ then extension of the lesion posterior to Vc with a volume $\geq 17\%$ is sufficient to impair the sensation of cool or cold pain. This volume-dependent impairment of sensations may be related to the monkey anatomical and human psychophysical subnuclear divisions (or elements) of modality specificity within Vc (Jones *et al.*, 1982; Rausell *et al.*, 1992; Patel *et al.*, 2006). These elements may also be the basis of separate, subnuclear thalamic networks for painful and non-painful modalities (Apkarian *et al.*, 2000).

Implications for the disinhibition hypothesis of central pain

The disinhibition hypothesis of central pain proposes that thalamic lesions leading to loss of cold sensibility and to CPSP include the region posterior to Vc, including VMpo. There are two reports of clinical and quantitative sensory findings following strokes in the region of Vc ($n = 5$ patients), as defined by atlas-based analyses of MRI scans (Montes *et al.*, 2005; Kim *et al.*, 2007). In these studies all lesions had involvement of the posterior aspect of Vc, and all patients tested had alterations of tactile and cold pain sensibility. Cold hypoesthesia was observed in all cases except the smaller of the “Vc only” lesions which suggests that sensory loss occurs only in lesions involving discrete elements within Vc (Duncan *et al.*, 1993). None of these lesions involved VMpo which was located posterior to “Vc only” lesions, and ventral to “Vc plus” lesions (Fig. 4.11) (Blomqvist *et al.*, 2000). We conclude that lesions of Vc are sufficient to impair cold and tactile sensibility, and that thalamic lesions leading to CPSP do not necessarily include VMpo.

The largest photon emission tomography (PET) study of CPSP-induced allodynia involved patients with a lateral medullary stroke (Wallenberg syndrome) (Peyron *et al.*, 1998). The allodynic test stimulus was a cold/mechanical stimulus described as “a cold non-noxious stimulus (ice in a flat plastic container) ... moved slowly” over the skin. When this stimulus was used on the affected side it produced activation of contralateral sensorimotor cortex, SII/inferior parietal lobule and insula, but not ACC, a pattern of structures very similar to those activated in a cold waterbath stimulation of the allodynic hand in patients with CPSP (Cesaro *et al.*, 1991; Hirato *et al.*, 1994; Kim *et al.*, 2007). Pain evoked by painful cold-water immersion (6 °C) evoked increased blood flow in sensorimotor cortex, SII/inferior parietal lobule, bilateral ACC and insula (Casey *et al.*, 1996). In total these studies suggest that central pain results from lesions to the posterior aspect of Vc with or without involvement of nuclei located posteriorly, including VMpo. The cold allodynia of this syndrome is more likely to be mediated through activation of the sensorimotor cortex than ACC.

Cortical pain-related activity

A long series of imaging studies has demonstrated activation of human cingulate (ACC), postcentral (SI) and parasyllvian (PS) cortical structures in response to painful stimuli (Craig and Zhang, 1996; Casey, 2000; Davis, 2000). It is not clear whether these structures receive nociceptive input, whether they are modulated by attention, or how they are related to each other and to pain perception. The answers to these questions can be approached by physiological and lesion studies in primates.

Primary somatosensory cortex

Painful stimuli may produce increased blood flow (PET results) and increased BOLD signals in contralateral human primary somatosensory cortex (SI) (Talbot *et al.*, 1991; Casey *et al.*, 1994; Coghill *et al.*, 1994; Davis *et al.*, 1995b; Craig *et al.*, 1996; Coghill *et al.*, 1997, 1999; Derbyshire *et al.*, 1997; Bushnell *et al.*, 1999; Gelnar *et al.*, 1999; Ploghaus *et al.*, 1999). Other studies have failed to find pain-related activity in SI using PET (Jones *et al.*, 1991; Derbyshire *et al.*, 1994; Rosen *et al.*, 1994; Hsieh *et al.*, 1995; Derbyshire *et al.*, 1998; Iadarola *et al.*, 1998), magneto-encephalographic (MEG) or evoked potential techniques (Carmon *et al.*, 1978; Becker *et al.*, 1993; Bench *et al.*, 1993; Craig *et al.*, 1994; Casey *et al.*, 1996; Buchner *et al.*, 2000). The lack of activation of SI may be related to cognitive factors (e.g. distraction), failure to resolve small somatotopically appropriate activations in SI, and mixed inhibitory/excitatory effects within cortex (Bushnell *et al.*, 1999). Magneto-encephalogram recordings have been used to identify a laser-evoked potential (LEP) dipole/generator, which is medial and posterior of

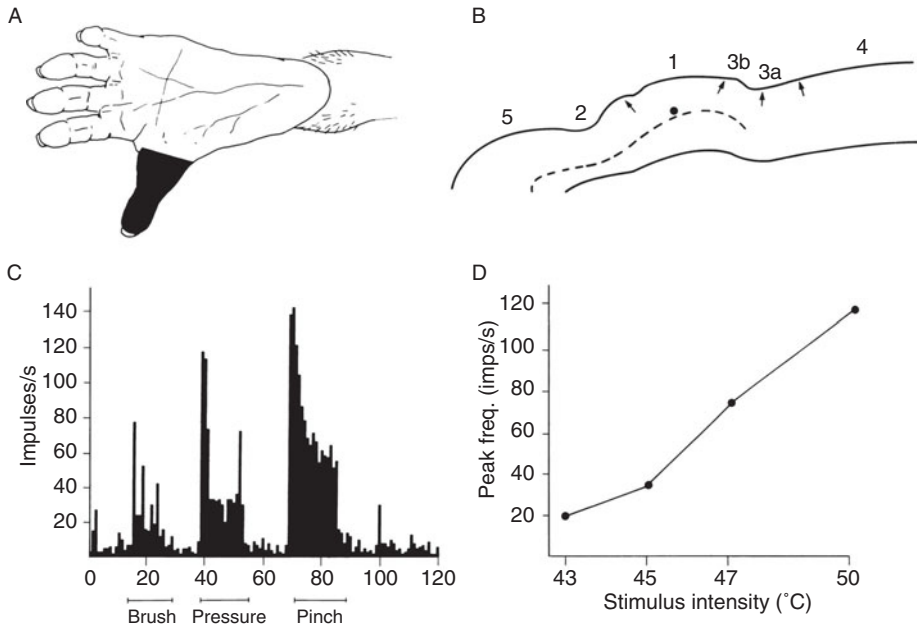


Fig. 4.13. Response properties of a WDR cortical neuron. The low-threshold receptive field was located in the glabrous skin of the thumb, as indicated by the shading in (A). As indicated in (B) this neuron was located in Brodmann area 1 (filled circle) as indicated by arrows which indicate the approximate boundaries of different cortical areas in (B). The histogram (bin width 1 s) in (C) indicates the response to brush (non-painful in humans), pressure (sometimes painful) and pinch (painful). The response to heat modulated into the painful range. Reproduced from Kenshalo *et al.* (2000), figure 1.

the eSEP (N20-P20) generator (Ploner *et al.*, 2000; Timmermann *et al.*, 2001); see discussion of LEPs below.

Studies of anesthetized monkeys (Kenshalo, Jr. and Isensee, 1983; Tommerdahl *et al.*, 1996) and human MEG studies (Tommerdahl *et al.*, 1998; Ploner *et al.*, 1999b; Kanda *et al.*, 2000) suggest that these LEPs may result from activation of area 3a (see location of cortical areas in Fig. 4.13B) (Tommerdahl *et al.*, 1998), of area 1 (Ploner *et al.*, 1999b; Kenshalo *et al.*, 2000), or at the border between areas 1 and 3b (Kenshalo, Jr. and Isensee, 1983). A recent anatomic study has identified projections from putative nociceptive, thalamic nucleus VMpo to SI: BA 3a and 1 (see Craig *et al.*, 1994, cf. Graziano and Jones, 2004).

Numerous studies have demonstrated that a population of single units in SI respond in differential or selective fashion to mechanical or thermal stimuli or both (Kenshalo, Jr. and Isensee, 1983; Kenshalo, Jr. *et al.*, 1988; Kenshalo *et al.*, 2000). Postcentral cortical neurons with selective responses to noxious toothpulp

stimuli have been reported in awake monkeys (Chatrian *et al.*, 1975; Biedenbach *et al.*, 1979; Chudler *et al.*, 1986).

The most extensive study of SI neuronal responses to noxious cutaneous stimuli (171 neurons, 17 animals) examined responses to heat and mechanical modalities in rhesus monkeys under anesthesia induced with ketamine and maintained with choralose. The SI neurons responding to noxious stimuli were in small clusters in cortical layers III to IV of Brodmann's area 1 of SI (Fig. 4.13B) (Kenshalo *et al.*, 2000). These neurons had typical WDR or NS response patterns. Wide dynamic range cells had large RFs and larger responses to equivalent stimuli than did NS cells (Kenshalo, Jr. and Isensee, 1983). There was also evidence that these SI cells were arranged in a manner approximately parallel to SI somatotopy for innocuous stimuli.

Primary somatosensory cortex neurons responsive to noxious stimuli seem to encode the intensity of these stimuli in awake monkeys (Kenshalo, Jr. *et al.*, 1988). This study measured the response to a small increase in temperature (T2) occurring during a larger step of temperature from adapting temperature into the painful range as shown in T1 (see Fig. 4.1). The latency of the monkey's response to the different sizes of temperature step was correlated with the neuronal response of WDR neurons to the same stimuli.

The SI has also been studied by analysis of the intrinsic optical signal in response to tactile and heat stimuli in anesthetized squirrel monkeys (Tommerdahl *et al.*, 2002). Noxious heating (52 °C) led to a change in optic signal in 3a which was larger than that in response to 37 °C, while the signal in 3b and 1 was smaller (Tommerdahl *et al.*, 1996). Repetitive heating (37 °C) produced an optical signal, characterized as decreased reflectance from areas 3 and 4, but an increase in reflectance from 3b and 1 (Tommerdahl *et al.*, 1998), while cutaneous flutter stimuli led to decreased reflectance from 3b and 1. These results were interpreted to represent an inhibitory interplay between 4–3a and 3b–1.

An important strategy to clarify human neuronal mechanisms of pain is the use of a painful cutaneous laser stimulus to activate cutaneous heat nociceptors selectively (Carmon *et al.*, 1976, 1978; Bromm and Treede, 1984), which evokes LEPs and changes in EEG power and synchrony. A series of recent studies have examined LEPs recorded from the cortical surface, during subdural grid implantations for the treatment of epilepsy. When LEPs and ongoing EEG signals are recorded from the scalp, they are limited by muscle and blink artifacts. They are also limited by low pass and spatial filtering at the scalp, skull and CSF (Cooper *et al.*, 1965; Pfurtscheller and Cooper, 1975; Gevins *et al.*, 1994), and by large inter-electrode distances (Gevins *et al.*, 1994). Studies with subdural recordings eliminate all of these limitations and decrease the inter-electrode distances by a factor of 3 to 4. There is only one other report of LEPs recorded during these difficult,

rare, subdural procedures – a case report (Kanda *et al.*, 2000; cf. Frot and Mauguiere, 1999; Frot *et al.*, 1999, 2001; Barba *et al.*, 2002).

Typical LEP and SEP potentials from each of the three cortical areas are shown in Fig. 4.14. The positions of subdural electrodes relative to the central sulcus (CS) and the sylvian fissure (SF) were determined by SEP N20-P20 polarity reversal and MRI data. The sulcal anatomy based on 3-D CT-MRI data was then used to make diagrams of the cortical surface. The locations of SEP N20-P20 polarity reversal is the heavy dotted line. The fit of this line with the radiological estimate of the central sulcus is remarkable. For each electrode site LEPs are shown for three different laser energy levels, as indicated below the left cartoon of the brain in Fig. 4.14A. The LEP N2 was recorded over SI, parasyylvian and MF regions at peak latencies of approximately 145 ms, and the P2 at approximately 230 ms. In contrast, vSEP was recorded first over SI with MF and parasyylvian vSEP peaks recorded later.

The N2 peak was distributed over both pre- and post-CS areas as indicated by the open circles on either side of the central sulcus. An N2 phase reversal was not found for any of the subjects studied ($n = 4$). The P2 peak revealed a similar distribution, but was associated with polarity reversal over the central sulcus as indicated by the filled circles behind the central sulcus and open circles in front. This was not a consistent finding and indicates an LEP P2 generator at the central sulcus in some subjects.

Parasyylvian cortex

Blood flow and BOLD signals from parasyylvian (PS) cortex indicate pain-related activation of the parieto-frontal operculum, including SII, PV (Disbrow *et al.*, 2000), BA7b and insula (Talbot *et al.*, 1991; Casey *et al.*, 1994; Craig *et al.*, 1996; Derbyshire *et al.*, 1997; Davis *et al.*, 1998; Coghill *et al.*, 1999; Gelnar *et al.*, 1999; Ploghaus *et al.*, 1999; Peyron *et al.*, 2000; Rainville *et al.*, 2000). Parasyylvian cortex activations have been described as both single foci and as two separate foci, usually parietal operculum and insula (Peyron *et al.*, 2000; Apkarian *et al.*, 2005). Elements within these areas have also been reported including mid/anterior insula, and a separate posterior region of insula (Casey *et al.*, 1994; Coghill *et al.*, 1999), and activation of one/both of these areas with parietal operculum (Casey *et al.*, 1994; Coghill *et al.*, 1994, 1999, 2001).

Single LEP generators have been identified in PS cortex based on source analysis of scalp recordings (Tarkka and Treede, 1993; Chen and Bromm, 1995; Kitamura *et al.*, 1995). Combined data from depth electrodes traversing the parietal operculum and insula, PET, fMRI and source analysis of scalp LEPs have been unable to resolve two separate LEP generators in PS cortex (Peyron *et al.*, 2002). Source analysis of subdural LEPs has demonstrated that nociceptive inputs

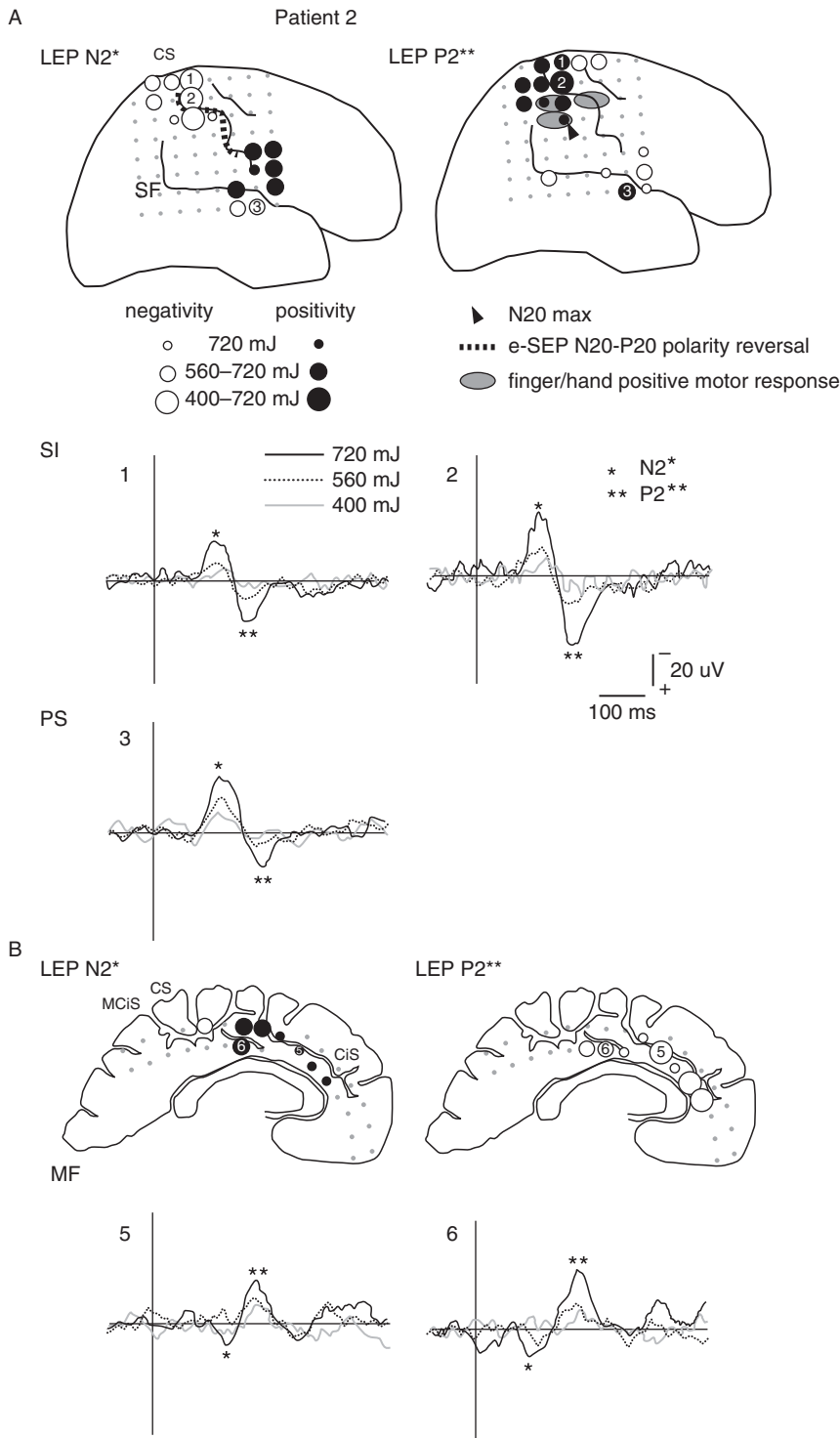


Fig. 4.14. (cont.)

produce subdural LEPs with a generator between the superior parietal operculum and the insula (Craig, 1995; Lenz *et al.*, 1998a; Vogel *et al.*, 2003). However, this source analysis did not employ deep/medial temporal electrodes which might have been able to identify deep PS generators, like the insula.

In the parasyllian region (PS), the N2 peak was recorded with polarity reversal across the sylvian fissure as indicated by the open circles below, and the filled circles at and above the sylvian fissure. The P2 also reverses at the anterior aspect of the parasyllian region as indicated by the filled circle below and the open circle above the sylvian fissure. These reversals were consistent across all subjects studied and indicate generators for the LEP N2 and P2 in the parasyllian area (Fig. 4.14, upper right panel, Fig. 4.15A upper).

Subdural electrode recordings commonly demonstrate that P2 LEPs can be recorded across most of the horizontal limb of the sylvian fissure (Lenz *et al.*, 1998a; Ohara *et al.*, 2004c) although source modeling of superficial electrodes demonstrate a generator on the deep surface of the posterior parietal operculum (Craig, 1995; Lenz *et al.*, 1998a; Vogel *et al.*, 2003).

Our studies of patients with lesions involving parietal operculum and insular cortex demonstrate increased pain thresholds (decreased sensitivity) and pain tolerance elevations, respectively (Greenspan *et al.*, 1999). This lesion study and numerous imaging studies (Davis, 2000; Peyron *et al.*, 2000; Rainville *et al.*, 2000) suggest that there are two distinct pain-related structures in parasyllian cortex.

Medial frontal (MF)

The participation of ACC in pain processing is suggested by pain-related functional activation of ACC (BA 24) (Jones *et al.*, 1991; Talbot *et al.*, 1991; Casey *et al.*, 1994, 1996; Coghill *et al.*, 1994; Davis *et al.*, 1995b, 1998; Craig *et al.*, 1996; Vogt *et al.*, 1996; Derbyshire *et al.*, 1997; Rainville *et al.*, 1997; Ploghaus *et al.*, 1999;

Caption for Fig. 4.14. Distribution of LEP N2* and P2** peaks over the convexity (A) and the medial surface (B) of the hemisphere in Patient 2. Significant LEP N2* and P2** peaks were recorded from electrodes over SI, parasyllian and medial frontal regions. Asterisks indicate that the positive or negative potential at any site is at the same latency as N2 (*) and P2 (**) over the ACC. Sample LEP waveforms (recorded vs. average reference) are shown for two electrodes in each region (marked 1–6 in the figurines). The energy for different potentials is indicated by the size of the open or filled circle at the location of the electrode in the corresponding figurine and the pattern of the tracing of the potential in the inset located in panel A lower left. Note that the amplitudes of N2* (*) and P2** (**) at individual electrodes as well as the number of electrodes with significant LEPs were graded with laser energy in all three regions. CS, central sulcus; CiS, cingulate sulcus; MCiS, marginal branch of the cingulate sulcus, which merges with the postcentral sulcus. Reproduced from Ohara *et al.* (2004b), figure 3.

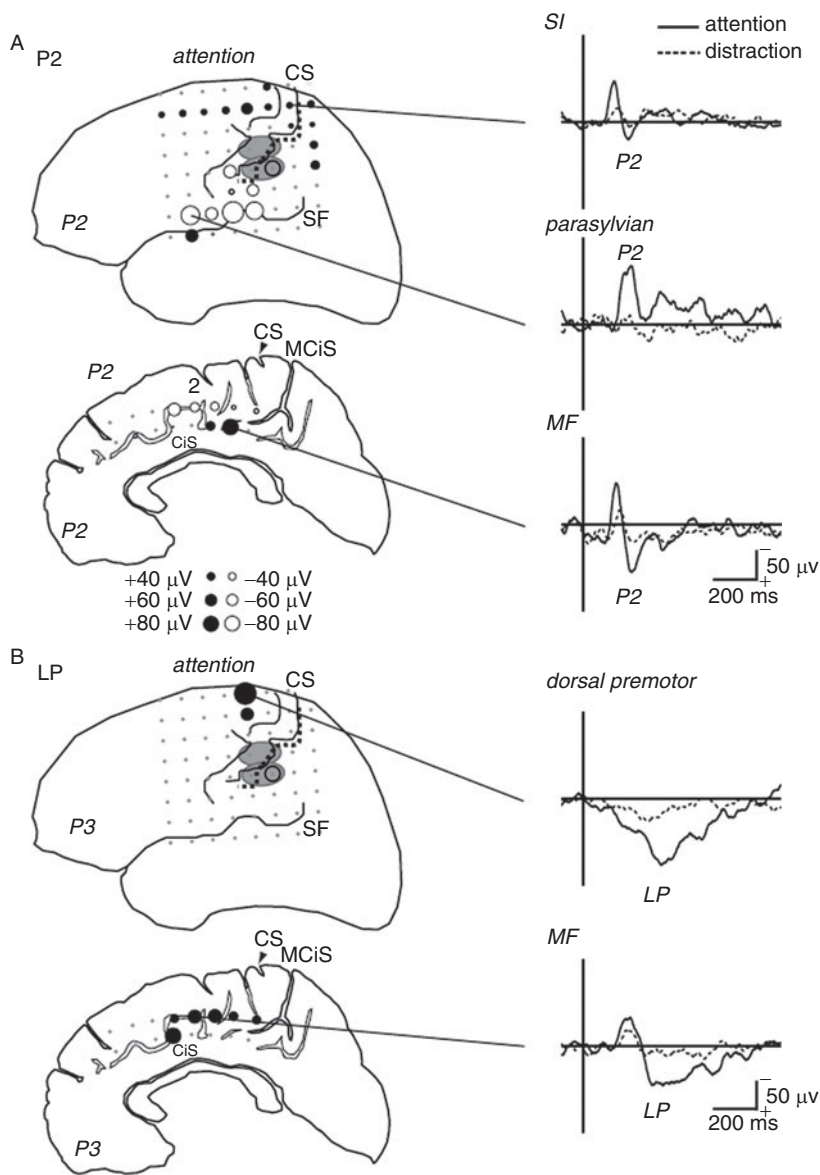


Fig. 4.15. Distribution of negative N2* and positive P2** and LP peaks of the laser-evoked subdural potential during attention condition and representative waveforms as labeled. P2** peaks were recorded from primary somatosensory (SI), parasyllvian (PS) and medial frontal (MF) cortical regions. The amplitude of the P2** peak was strongly enhanced during the attention task. The LP was recorded from the MF region and a part of the lateral premotor area only during the attention condition. Conventions as in Fig. 4.14. Adapted from Ohara *et al.* (2004d), figure 2, with permission.

Lorenz *et al.*, 2003). There is some electrophysiological evidence that neurons in the human ACC (11/125) display pain-related activity (Hutchison *et al.*, 1999) (see also Sikes and Vogt, 1992). Scalp LEPs having a vertex maximum (Carmon *et al.*, 1978; Bromm and Treede, 1984) may arise partly from generators in the ACC, in evidence from scalp source analysis (Tarkka and Treede, 1993; Chen and Bromm, 1995; Kitamura *et al.*, 1995). Our recordings from subdural medial frontal cortex (MF) localized nociceptive input to the human caudal ACC, just anterior to the paracentral lobule (Lenz *et al.*, 1998b; Rios *et al.*, 1999; Ohara *et al.*, 2004b, 2004c).

The different functions of ACC along the caudal-rostral axis are suggested by functional imaging studies demonstrating a pain-related blood flow increase or BOLD activation in caudal ACC (Hsieh *et al.*, 1995; Davis *et al.*, 1997; Derbyshire *et al.*, 1998). Mid-ACC is selectively activated by increased unpleasantness of pain produced by hypnosis (Rainville *et al.*, 1997). Perigenual ACC is activated by the pain of heat allodynia but not by heat producing the same pain (Lorenz *et al.*, 2002), by expectation of pain (Ploghaus *et al.*, 1999), by anxiety about pain (Ploghaus *et al.*, 2001) and by intravenous opiates (Wagner *et al.*, 2001). Attention-related tasks (e.g. verbal fluency or Stroop) activate mid-ACC (Davis *et al.*, 1997; Derbyshire *et al.*, 1998) based on group analysis, while analysis of individual responses revealed foci throughout MF cortex (Davis *et al.*, 1997; Derbyshire *et al.*, 1998).

Over the MF region, LEPs were found at and anterior to the paracentral lobule. A polarity reversal was consistently observed across the cingulate sulcus at the posterior part of the anterior cingulate gyrus (Fig. 4.14B lower, and Fig. 4.15A lower). The N2 phase reversals and the P2 phase reversal were consistent across subjects. In total, these findings indicate the presence of a generator in the cingulate sulcus at the posterior extent of the ACC. The rostral caudal extent of nociceptive input to the anterior cingulate cortex is indicated in Fig. 4.14B. The large anterior-posterior extent of electrodes at which LEPs could be recorded in this patient was not a consistent finding across subjects. A similar lack of consistency is found in single-subject PET studies of the response to painful and non-painful heat stimuli (Vogt *et al.*, 1996; see also Davis *et al.*, 1998).

The SEP peaks for a vibratory stimulus applied in the upper extremity were recorded broadly around the central sulcus at 45 ms, parasyllian sulcus at approximately 95 ms, and medial frontal cortex at approximately 48 ms (not shown). The vibratory SEP peaks over the SI region showed polarity reversal across the central sulcus. The distribution of this peak overlapped with median nerve SSEP N20 maximum and with the finger motor area as defined by cortical stimulation, but was located ventral to that of the LEP and P2 with minimal overlap. In the parasyllian region, the v-SEP peak showed polarity reversal across

the sylvian fissure. The distribution of v-SEPs in the MF region was similar to that of LEP peaks, but without polarity reversal. The e-SEP P25 component at 22 ms was recorded from a small post-CS area (Ohara *et al.*, 2004c). The distribution of P25 was located between v-SEP and LEP peaks.

Grading of cortical response with stimulus intensity

Graded neuronal response to stimulus intensity in the painful range is a necessary but not sufficient condition for the identification of neurons subserving the sensory-discriminative aspect of pain (Price and Dubner, 1977; Price *et al.*, 2003). Neurophysiological studies in primates reveal that many neurons in the primary somatosensory cortex (Kenshalo, Jr. and Isensee, 1983; Kenshalo, Jr. *et al.*, 1988; Kenshalo *et al.*, 2000), and parasyllian cortex encode noxious stimuli in an approximately linear fashion (Dong *et al.*, 1989; 1994).

An all-or-none response to graded stimulus intensity was observed in other cells in SI (Kenshalo, Jr. *et al.*, 1988; Kenshalo *et al.*, 2000), anterior cingulate cortex (ACC) (Koyama *et al.*, 1998; Hutchison *et al.*, 1999) and PS cortex (Dong *et al.*, 1989, 1994). Neurons in primate ACC often have complex responses, such as anticipation of pain (commonly) and grading of the response with intensity (uncommonly) (Koyama *et al.*, 1998; Hutchison *et al.*, 1999).

Increasing blood flow or MRI BOLD signal has been reported to correlate with increased pain intensity for the SI, SII and insula (Derbyshire *et al.*, 1997; Coghill *et al.*, 1999; Bornhovd *et al.*, 2002), as well as the parietal operculum (Derbyshire *et al.*, 1997; Coghill *et al.*, 1999).

Similarly, electro- (EEG) or magneto-encephalographic (MEG) responses to painful stimulation in human are graded with pain intensity (Kakigi *et al.*, 1989; Beydoun *et al.*, 1993; Timmermann *et al.*, 2001). The correlation of MEG responses with pain intensity has been reported to be more linear in SI than in SII (Timmermann *et al.*, 2001; Torquati *et al.*, 2002). These findings suggest that there are significant differences between the pain-related activity of cortical areas responding to painful stimuli (Coghill *et al.*, 1999).

Imaging results are interpreted in terms of neuronal activation (Davis, 2000; Rainville *et al.*, 2000), while LEP studies can be interpreted in light of the evidence that the early N2 LEP reflects stimulus-related (exogenous) factors, while the P2 also reflects endogenous factors, such as attention. The scalp N2 and P2 waves are highly correlated with exogenous factors such as laser stimulus intensity and pain intensity (Carmon *et al.*, 1978; Bromm and Scharein, 1982), and they are suppressed by analgesics (Beydoun *et al.*, 1997; Bromm *et al.*, 1992). The scalp LEP P2 amplitude is also modulated by an endogenous factor, i.e. attention evoked by novel stimuli (Becker *et al.*, 1993; Kanda *et al.*, 1996; Miltner *et al.*, 1989; Siedenberg and Treede, 1996; see also Legrain *et al.*, 2002).

A study of LEPs through subdural electrodes implanted for surgical treatment of medically intractable epilepsy examined the effect of laser stimulus intensity (three energy levels – weak, medium and strong) on LEPs recorded from the human primary somatosensory (SI), parasyllian (PS) and medial frontal (MF) cortical surfaces (Fig. 4.14) (Ohara *et al.*, 2004b). Significant differences in LEP N2 amplitudes were observed across three energy levels by regions overall. Post-hoc testing revealed that N2 amplitudes were significantly different for all three pairs of energy levels (weak–medium, medium–strong, weak–strong) over SI alone.

Amplitudes in PS and MS were significantly different for weak–strong alone. LEP P2 amplitudes were significantly different between three laser energy levels by regions overall. Post-hoc testing showed that P2 peaks over SI were significantly different between weak–strong energy levels, while none of the three pairs was significantly different for PS or MF. No N2 or P2 peaks were recorded in response to weak stimuli, perhaps due to the unique anatomy of this region. The N2 and P2 amplitudes of the largest potential regions showed significant correlation with laser energy, excepting N2 over the PS region. The energy threshold to evoke N2 peaks, as estimated with multiple regression analysis, was lower in SI than in MF (Ohara *et al.*, 2004b). These results suggest that N2 LEPs over all areas and P2 LEPs over SI encode the intensity of the peripheral stimuli, but this encoding is more accurate and extends over a wider stimulus range over SI.

Attention and cortical pain-related activity

Any stimulus occurring during distraction or a “neutral” cognitive state may evoke attention which is related to the stimulus, known as “externally generated” or exogenous attention. In contrast, “internally generated” or endogenous attention may be provoked by directed attention toward a stimulus. Endogenous attention can also be produced by novelty in an oddball paradigm composed of infrequent stimuli (oddballs, e.g. strong tones) which occur randomly in a train of frequent stimuli (e.g. weak tones) (Picton, 1992). That train would be counterbalanced by another in which frequency of the stimuli is reversed (i.e. infrequent weak tones and frequent strong tones). The waveform evoked by frequent strong stimuli is then subtracted from that of the infrequent strong stimuli to produce the auditory P300 for strong tones (Kiss *et al.*, 1989; Smith *et al.*, 1990; Halgren *et al.*, 1995b). Often the paradigm requires the subject to detect the occurrence of a target stimulus, usually the infrequent stimulus, and to signal detection of that stimulus by a button push (Picton, 1992).

Stimuli of many modalities in an oddball paradigm lead to the emergence of a widespread late positive P300 scalp peak (Picton, 1992). Thus, the P300 is an attention-specific potential evoked by infrequent events which alert the subject

Table 4.1. *Attention-related potentials.*

	Description	Evoked by:	Location: attention-related structure	Location: anatomy
N2	Exogenous – stimulus related	Laser stimuli	Site – if increased by directed attention	SI, PS, MF
P2	Endogenous – alerting response like P300	Laser stimuli	Site – if increased by directed attention	SI, PS, MF
P300	Endogenous response to infrequent events	Infrequent stimuli in an oddball paradigm	Source – if N2 not recorded there*	Medial temporal, parietal, MF
LP	Endogenous response to attended stimulus	Attention directed to stimulus vs. distraction	Source – if N2 and P2 not recorded there**	MF, dorsal BA6

Note:
* P2 in isolation may be similar to P300.
* and **, presence of N2 and/or P2 may indicate that the adjacent areas serve as a site and a source.
SI, primary somatosensory cortex; PS, parasyllvian cortex; MF, medial frontal cortex.

and produce a state of expectancy (Becker *et al.*, 1993; Zaslansky *et al.*, 1995, 1996) (Table 4.1).

Painful stimuli have an intrinsic alerting quality (Posner, 1978; Bushnell *et al.*, 1985) which has led to the suggestion that the P2 may signal the alertness or expectancy evoked by the laser/pain stimuli, like the P300, rather than the activation of nociceptors per se (Becker *et al.*, 1993; Zaslansky *et al.*, 1995, 1996). The latency of the scalp P2 may be the same as in Zaslansky *et al.* (1996) or earlier than the P300 (Becker *et al.*, 1993; Kanda *et al.*, 1996; Legrain *et al.*, 2002). In turn, the P300 for infrequent laser stimuli may have a “later component” related to detection of the target stimulus (i.e. button push; cf. Zaslansky *et al.*, 1996), which may have a smaller amplitude (Zaslansky *et al.*, 1996; Dowman, 2001), and a parietal vs. central location. Finally, short interstimulus intervals attenuate positive potentials later than the LEP P2, consistent with the “psychological refractory period” for cognitive processing (Telford, 1931; Woods and Courchesne, 1986; Tomberg *et al.*, 1989). These findings suggest that the P2 is separate from later positive components related to novelty and stimulus detection.

Two conditions of any stimulus quality can be incorporated into an oddball paradigm as frequent and infrequent stimuli, such as two locations of the stimulus. In a recent study, infrequent laser stimuli were delivered to one hand randomly in a train of frequent stimuli delivered to the opposite hand (Legrain *et al.*, 2002; see also Becker *et al.*, 1993). Among stimulus qualities other

than that of the oddball stimulus, the amplitude of the P300 for laser/painful stimuli is independent of stimulus amplitude (Becker *et al.*, 1993; Zaslansky *et al.*, 1995; Bornhovd *et al.*, 2002) and stimulus location (Towell and Boyd, 1993; Kanda *et al.*, 1996; Legrain *et al.*, 2002), as in the case of the P300 for other sensory modalities (Papanicolaou *et al.*, 1985).

Across paradigms involving different sensory modalities, the subdural P300 has maxima over the medial temporal lobe and ACC in the absence of significant sensory EPs at these maxima (for infrequent and frequent stimuli) (Kiss *et al.*, 1989; Smith *et al.*, 1990; Halgren *et al.*, 1995a, 1995b; Lenz *et al.*, 2000). These subdural results are consistent both with functional imaging studies (Picton, 1992; Waberski *et al.*, 2001; Sevostianov *et al.*, 2002), and with BESA analysis of the somatosensory and auditory scalp P300 potentials (Tarkka *et al.*, 1995, 1996; Tarkka and Stokic, 1998). The role of medial temporal lobe in novelty is also suggested by the abolition of the P300 by lesions of the hippocampus (Knight and Grabowecky, 2000). Therefore, converging lines of evidence suggest that the medial temporal lobe is a source for the attention evoked by novelty.

The stimulus independence of positive potentials following the P2 is consistent with functional imaging studies demonstrating the existence of brain regions where the application of a painful stimulus activates a region while further increases in stimulus intensity do not produce increased activation (Coghill *et al.*, 1999; Bornhovd *et al.*, 2002). These potentials may be involved in cognitive processes, like attention or alertness or memory, which may be triggered by a stimulus but otherwise may be independent of the stimulus (Coghill *et al.*, 1999; Bornhovd *et al.*, 2002). These results point to the significance of cortical areas not usually related to pain in cognitive aspects of pain.

In addition to changes in LEP amplitude, attention to a laser stimulus leads to event-related desynchronization (ERD), defined as a depression of EEG power which is not phase locked to the stimulus. Event-related spectral modulation of scalp EEG has been applied to the cortical processing of painful stimuli (Mouraux *et al.*, 2003) and of subdural EEG in response to laser stimuli (Ohara *et al.*, 2004a).

Laser-evoked ERD occurs in the same three cortical regions that receive nociceptive input (ACC, PS, SI), as assessed by the presence of subdural LEPs (Fig. 4.14). Subdural ERD was uniformly observed over primary somatosensory and parasyllian (PS) cortex, and occasionally over medial frontal cortex during attention to the stimulus. Event-related desynchronization was more widespread and intense during attention to laser stimuli (counting stimuli) than during distraction from the stimuli (reading for comprehension), particularly over PS. In addition, there was an apparently random variation in the pain rating of as much as five-fold, with the same task (attention or distraction) and with constant laser energy levels (Ohara *et al.*, 2004a). In each case the higher perceived intensity was associated with greater and more widespread ERD than that with

lower perceived intensity. This effect appeared to be greatest near SI and medial frontal regions.

The topographical differences between the effects of attention/distraction and perceived intensity on ERD distribution and magnitude suggest that attention/distraction exerts a greater influence over pain processing in parasyllian cortex, presumably involving SII and/or insula than over SI. The perceived intensity of pain exerts its greatest influence on pain processing in SI, and possibly in medial frontal regions, including ACC.

The attention-related activation of PS cortex is consistent with previous imaging (Davis *et al.*, 1997; Bushnell *et al.*, 1999) and LEP source analysis studies (Schlereth *et al.*, 2003), which show attentional modulation of blood flow and LEPs in those cortical regions (see Chapter 5). However, some of the imaging studies showed increased blood flow activation during the distracting tasks in a rostral part of ACC and orbito-frontal cortex. Furthermore, we observed only limited posterior superior PS ERD changes during attention even in a subject whose subdural grids covered those regions, perhaps because of the relatively simple distraction task, as opposed to the tasks used in other studies, such as the Stroop task, maze task and verbal attention task (Lezak, 1995).

*Classification of cortical areas by activity related
to attention to painful stimuli*

An anatomical classification of structures can be made related to directed attention and novelty in which “sources” are specific to attention and are not involved in other functions, such as motor behavior or sensory processing (Posner, 2000) (Table 4.1). We identified sources both by the emergence of potentials during attentional states, such as directed attention (e.g. LP) or attention to novel stimuli (e.g. P300), and by the absence of potentials evoked by the sensory stimuli in either the attention/distraction conditions or in the frequent/infrequent conditions. “Sites” are structures where attention acts during task performance to alter computations involved in the task, like the gain of LEPs, which is increased during the stimulus counting task.

“Sources” and “sites” may be identified in recordings of subdural LEPs during attention to the laser, i.e. counting laser stimuli, versus distraction, i.e. reading for comprehension. In this paradigm, the results demonstrate that attention to the painful laser stimulus can evoke a significant change in LEPs in ACC, SI and parasyllian cortex (Fig. 4.15); LEPs in all three areas were characterized by dramatic, attention-related increases in the N2 and P2 components of the LEP. Over the anterior aspect of the medial frontal lobe and dorsal premotor cortex (Brodmann area 6; Brodmann, 1907) a long latency positive component emerged with an approximate peak latency of 350 ms (termed LP).

Neglect or inattention is a clinical phenomenon in which the subject generally ignores one side of the body, usually the left. Inattention is most commonly seen following lesions of the right parietal cortex (Heilman *et al.*, 1993). LEPs can be recorded over this area in at least a proportion of patients (see Fig. 4.15, and figure 3 in Ohara *et al.*, 2004b). This raises the possibility that lesions of this area could be associated with neglect of painful stimuli.

Inattention to painful stimuli was a chance finding during recordings from an Old World monkey with compression of the rostral inferior parietal lobule (area 7b) and parietal operculum (area 7b, SII, insular and auditory areas) with marginal compression of the superior parietal lobule (area 5), postcentral gyrus (areas 1, 2) and superior temporal gyrus (area T1) (Dong *et al.*, 1996). The mechanism of this phenomenon may be related to the neuronal recordings from monkey Brodmann area 7 (Dong *et al.*, 1994). These recordings demonstrated that the neurons were responsive to noxious heat. They also responded differentially to the position of threatening objects or non-threatening objects in extrapersonal space (Fig. 4.16).

A related phenomenon has been described in which patients with insular lesions showed loss of avoidance and defensive reactions to noxious cutaneous stimulation, to visual threat of injury, and sometimes to verbal threat of bodily harm (Berthier *et al.*, 1988). However, any interspecies comparisons must be tempered by the fact that the symptom of contralateral neglect is less remarkable in monkeys than in humans because lateralization of spatial function to one hemisphere is less profound in monkeys (reviewed by Mountcastle *et al.*, 1975).

Directed attention in the attention/distraction paradigm was associated with emergence of an LP over parts of the ACC and dorsal area BA6. Therefore, these structures may be “sources” for directed attention, consistent with their role as a part of the executive attentional system involved in target selection or response (Corbetta *et al.*, 1991; Bench *et al.*, 1993; Devinsky *et al.*, 1995; Picard and Strick, 1996). These results are also congruent with the finding that cingulotomy impairs intention and spontaneous response production (Cohen *et al.*, 1999). Increased LEPs at SI, PS and ACC during directed attention may identify these cortical structures as “sites” (Posner, 2000).

Stimulation studies of cortex

Penfield has often been quoted for his observation that pain is rarely evoked by cortical stimulation in awake humans (1.4% of stimulation sites; Penfield and Jasper, 1954a). However, a careful review reveals numerous reports of the sensation of pain related to cortical stimulation (Kenshalo, Jr. and Willis, 1991) and the discharges of focal epilepsy, as recognized by Penfield (Penfield and

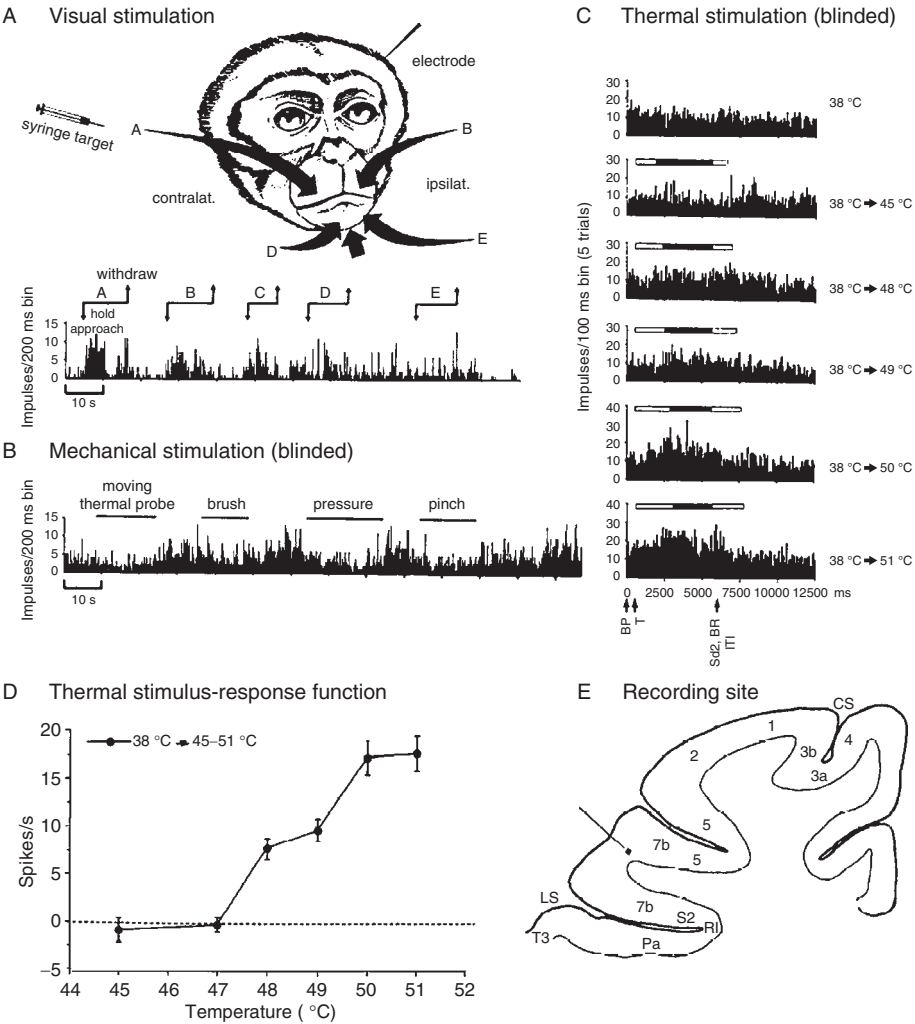


Fig. 4.16. Response properties of a neuron with wide dynamic range response to graded noxious heat stimuli. (A) Responses of this cell to approach of a threatening stimulus toward different parts of the face, as indicated in the figurine. (B) With the animal blinded innocuous stimuli applied to the contralateral maxillary region consistently led to a decrease in the firing rate of the neurons, which was greater than that with application of the stimulus to the ipsilateral maxillary region (not shown). (C) Histograms showing the response to heat stimuli as indicated by the label to the right of each histogram. (D) Stimulus response function for the firing rate to heat stimuli during the plateau of the heat stimulus indicated by the filled part of the bar above the histogram in (C). (E) Location of recorded site (black square) identified by the oblique line to the left of the dot shown on an approximately coronal section showing midline, central sulcus (CS), intraparietal sulcus (IPS) and lateral sulcus (LS). Reproduced from Dong *et al.* (1994), figure 7, with permission.

Jasper, 1954b). Many of the relevant cortical areas are in sulci and so not accessible to direct stimulation from the surface of the brain. In SI areas 3a and 3b are located in the central sulcus, while in parasyllian cortex insula, parietal and frontal operculae are deep in the sylvian fissure (Kenshalo, Jr. and Willis, 1991). Anterior cingulate gyrus contains cortical structures which are deep in the interhemispheric fissure or deep in the cingulate gyrus off the interhemispheric fissure.

A recent study has overcome some of these difficulties by stimulation through depth electrodes implanted in the parietal operculum and insula for investigation of epilepsy (Ostrowsky *et al.*, 2002). The sensation of pain was evoked by stimulation in posterior superior insula in approximately one-third of patients studied, predominantly in the right hemisphere. Non-painful somatic sensations were also evoked in the same area in about one-third of patients, although these sites did not overlap by site or by patient. This may correspond to the cortical nociceptive area identified in source analysis of subdural recordings in humans and monkeys which may be somatotopically arranged with leg posterior, arm/neck anterior (Vogel *et al.*, 2003; Baumgartner *et al.*, 2006).

Lesioning and synchrony studies of cortex

Acute pain is a complex experience that is associated with increased blood flow or BOLD in multiple structures in the brain (reviewed by Davis, 2000; Rainville *et al.*, 2000), which have often been characterized as a “network” or “neuro-matrix” (Melzack, 1990; Gelnar *et al.*, 1999; Peyron *et al.*, 1999; Casey, 2000; Strigo *et al.*, 2003) rather than as a collection of centers, each subserving a different dimension of pain (Melzack and Casey, 1968). A network consists of a collection of neural elements, their connections, and connectional weights, often equated with neurons or brain structures, axons and synapses, respectively (Churchland and Sejnowski, 1992). The functional connectivity of such a network may be conceived of as the network properties that enable its neural elements jointly to process inputs or outputs, or both. The psychophysical consequences of CNS lesions are an important predictor of the nature of the underlying network (Bullinaria and Chater, 1995; Bullinaria, 2002).

If lesions of different structures produce different, non-overlapping effects upon some neurologic function, then these lesion effects are referred to as “double dissociation” (Bullinaria, 2002). “Double dissociation” is characteristic of hierarchical networks in which component structures, such as individual cortical areas, are modules or local networks, each serving a different function. Hierarchical networks are assumed to account for neurologic functions such as language, in which two different modules (inferior frontal and superior temporal areas) may subserve speech production and reception (Bullinaria,

2002). Therefore, psychophysical deficits after specific lesions can be used to identify the networks related to neurologic function.

Lesions of anterior cingulate cortex (ACC)

There are a number of reported cases of quantitative sensory testing in radiologically confirmed, surgical lesions of the frontal lobe, for treatment of psychiatric disease. Pain-related function has been reported pre- and post-operatively in two patients with psychiatric disease treated by anterior cingulotomy just posterior to the genu of the corpus callosum. The results are congruent between the two patients, the first with “schizo-affective disorder” (Davis *et al.*, 1994), and the second with obsessive-compulsive disorder (Greenspan *et al.*, 2008). Both studies showed increased ratings of the intensity and unpleasantness of heat pain, and the intensity of cold pain. The first study showed increased ratings of the unpleasantness of cold pain (Davis *et al.*, 1994), while the other did not. The pre- and post-operative psychophysical test session revealed that cool, warm, cold-pain and heat-pain thresholds were within the normal range, and without a laterality difference. The post-operative thresholds were not significantly different from the pre-operative thresholds.

One psychophysical study has examined the effects of anterior capsulotomy upon the perception of acute pain in a patient without any MRI abnormality. Anterior capsulotomy is a procedure for psychiatric disease which produces a more extensive lesion than cingulotomy by interrupting afferent and efferent fibers to the mid-ACC and other frontal lobe structures (Talbot *et al.*, 1995). In contrast to the studies of cingulotomy this study found decreased ratings for painful stimuli, yet decreased tolerance post-capsulotomy. Anterior capsulotomy partially disconnects and disinhibits, but does not destroy, the mid-ACC, perhaps leading to psychophysical changes opposite to those of cingulotomy (Talbot *et al.*, 1995).

Both cingulotomy and frontal leukotomy, a more extensive lesion than capsulotomy, have been observed to make chronic or cancer pain less unpleasant but not less intense (Foltz and White, 1962). More recent studies of the effect of cingulotomy upon chronic pain (reviewed by Abdelaziz and Cosgrove, 2002) report a decrease in chronic pain, but not a selective decrease in the unpleasantness of pain. The difference between the effect of cingulotomy on chronic and acute pain may be considered consistent with imaging studies in which allodynic stimuli in patients with chronic pain activate MCC less consistently than do acute pain stimuli in controls (Apkarian *et al.*, 2005).

Lesions of the parasyllian cortex

The human parasyllian cortex has been identified in the parietal opercular region with evoked potentials, MEG and PET signals (see above). The spatial

resolutions of these techniques do not allow for the same precision of localization as in monkey studies with histologic reconstruction, so it may not be possible to determine whether separate loci of activity are associated with painful versus innocuous stimulation. Functional MRI studies in human subjects do allow for greater anatomical precision in localizing stimulus-related brain activation. Recent reports have shown that coincident regions in the parietal operculum are activated with both tactile and noxious stimuli (Davis, 2000; Apkarian *et al.*, 2005) (see Chapter 6). Therefore, one might expect damage to this region to produce effects upon both tactile and pain perception.

Hypoalgesia has been reported in patients with cerebral lesions involving the parietal operculum, posterior insula and/or underlying white matter. Davison and Schick (1935) described two patients exhibiting unilateral hypoalgesia, hypothermesthesia and hypesthesia. Autopsy revealed an infarct of the insula and parietal operculum, but sparing the thalamus, internal capsule, and most of the postcentral gyrus (SI). Biemond (1956) described two hypoalgesic patients with ischemic infarction of parasyllian structures; only the most lateral and inferior portions of the parietal lobe were affected, thus sparing most of SI. Obrador *et al.* (1957) described a patient with a small infarct just beneath the insula, which affected part of the claustrum and adjacent white matter, but appeared to spare the parietal cortex and thalamus. This person experienced spontaneous pains and hyperpathia primarily in the face and distal upper limb, but also demonstrated hypoalgesia and hypothermesthesia in the lower abdomen and lower limb, contralateral to the lesion. Schmähmann and Leifer (1992) studied six people who developed hemibody pain following parietal lobe lesions. All showed clinically observable reductions in pinprick and thermal sensation, and the common region of all lesions was the contralateral, posterior parietal operculum.

Another series studied patients with intrinsic parasyllian tumors defined by MRI and quantitative measures of sensation as measured with a thermode (Greenspan *et al.*, 1999). This report demonstrates that lesions of parietal operculum, but not insula alone, are sufficient for significant contralateral elevations of pain thresholds. For the cases in which the posterior parietal operculum is involved, encroachment of the postcentral gyrus (e.g. SI cortex) cannot be ruled out entirely. This is most evident for subject M. C., who had the largest lesion that involved the parietal operculum. However, functional imaging and evoked potential studies indicate that the hand representation of SI cortex is located superior to any of the lesions that approach the postcentral gyrus in this group of patients.

In one case (B. B.) with a small circumscribed lesion in the parietal operculum there was a significant laterality difference in mechanical pain thresholds but not heat or cold pain tolerance. This suggests that there may be modality segregation in this area. In the thalamic zone projecting to this area stimulation at most sites evokes only one modality of sensation (see above).

Four of the subjects in this study were evaluated for cold pain tolerance in a waterbath test, and two of these subjects (M.C. and C.M.) showed a greater cold pain tolerance contralateral to their lesions, and they were the ones whose lesions had large involvement of the insula (Greenspan *et al.*, 1999). Another study of pain tolerance described six patients with insular cortex lesions, documented with computer tomography images (Berthier *et al.*, 1988). Three of these patients were tested for average pain detection and tolerance thresholds for a repetitive electrocutaneous stimulus. Pain endurance was defined as the difference between these detection and pain thresholds, and both endurance and tolerance were significantly higher among patients than controls. Pain tolerance is a complex measure which involves the motivational, cognitive and affective components of pain (Blitz and Dinnerstein, 1968; Chen *et al.*, 1989). Both of these studies support the idea that the insula's role in nociceptive processing is related to autonomic, affective, motivational or other non-sensory components of pain.

Lesions of SI

There is strong historical evidence of loss of sensations of pain and temperature following postcentral lesions (reviewed by White and Sweet, 1969; Kenshalo, Jr. and Willis, 1991). The significance of SI in pain sensation is found in well-documented lesions resulting from bullet wounds of cortical and subcortical structures in soldiers wounded in World War II (Fig. 4.18). These lesions were identified at the gross anatomical level at surgery and correlated with clinical findings in studies proximate to the time of the injury. An example of this type demonstrated that patients with lesions including the postcentral gyrus developed long-term defects in painful and non-painful mechanical and thermal sensations as shown in Fig. 4.18, left panel (Russell, 1945). More posterior lesions resulted in loss of "discriminative sensations" such as two-point discrimination and position sense (right panel). Similar patterns of sensory loss were reported years after war injuries to parietal cortex including loss of proprioception, vibration, pinprick, painful and non-painful temperature sensations (Marshall, 1951). Historical resections of postcentral cortex for treatment of chronic pain have also led to variable reductions of tactile, pain and temperature sensations (White and Sweet, 1969; Kenshalo, Jr. and Willis, 1991).

A recent psychophysical study of a patient with a stroke including the SI and SII somatosensory areas reported loss of the sensory but not the unpleasantness dimension of pain (Ploner *et al.*, 1999a). Quantitative sensory testing was carried out 5 and 12 days after the stroke. In this study ratings of graded intensities of cutaneous laser stimuli and reaction times for detection of pain were used to determine pain thresholds. Pain thresholds were dramatically elevated contralateral to the stroke and reaction times were consistent with C-fiber conduction. These results suggest

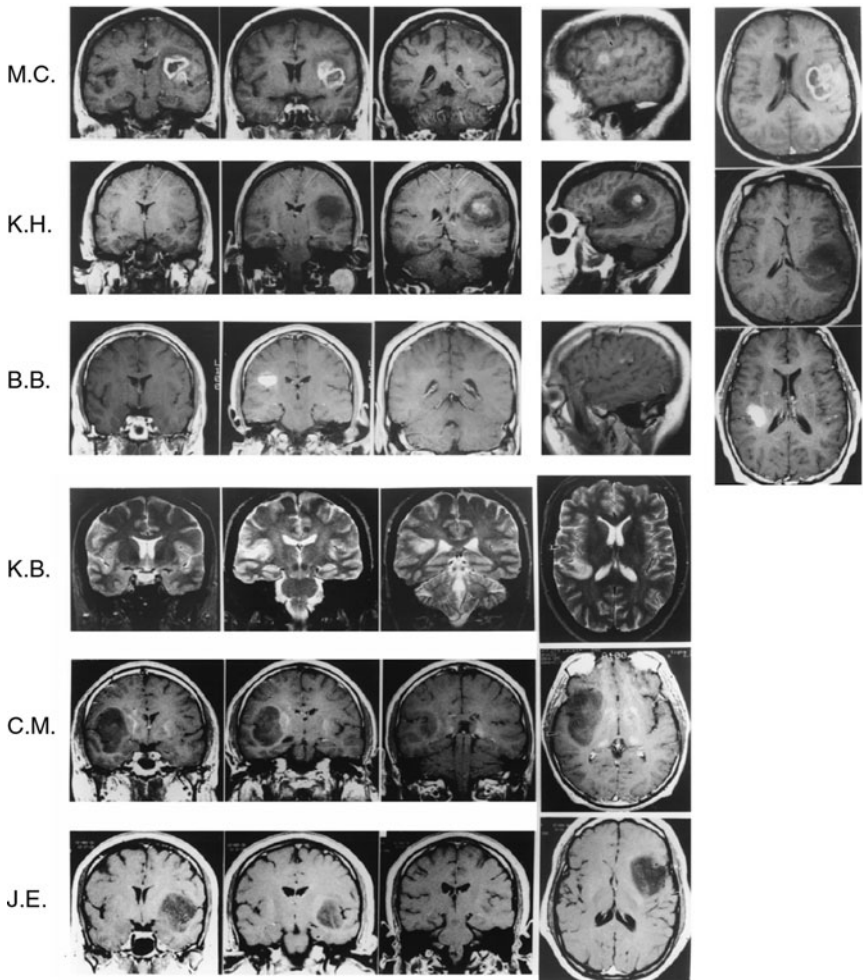


Fig. 4.17. Top three rows, gadolinium-enhanced, T1-weighted MR images of three subjects who demonstrated significant laterality differences in pain threshold. The three coronal images were chosen to be at the level of (1) the anterior insula, (2) the posterior insula and (3) the retroinsula. The sagittal and horizontal images were chosen to best reveal the pathology. Arrowheads on sagittal images indicate the central sulcus. Note that for subject M.C., the central sulcus is displaced anteriorly at its more lateral extent (arrow on sagittal image). Bottom three rows, T2-weighted (K.B.) and T1-weighted (C.M. and J.E.) MR images of three subjects who demonstrated no pain threshold abnormality. Arrowheads on the axial images denote the central sulcus. Sagittal images were not available for K.B. or C.M. Reproduced from Greenspan *et al.* (1999).

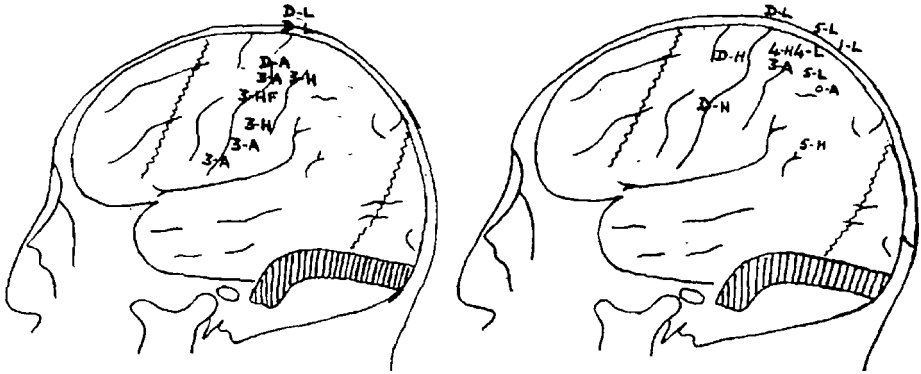


Fig. 4.18. Traumatic wounds during war. Left, the approximate locations of lesions causing deficits of all somatic sensations including pain and temperature. Right, lesions leading to loss of “discriminative function” such as orientation of a stimulus or two-point discrimination. D, depressed fracture without a dural tear; F, face; A, arm; L, leg. Numbers indicate the depth of the lesions in centimeters. Reproduced from Russell (1945), figures 5 and 6, with permission.

that the sensory discriminative aspect of pain is mediated through A δ fibers and the lateral STT pathway, the Vc nuclear complex and SI + SII.

At high laser pulse energies, the patient voluntarily described a sensation which was definitely unpleasant but poorly described, poorly localized and intensity dependent, suggesting that the pain pathway terminating at SI and SII does not mediate the motivational-affective aspect of pain. Multiple measures of tactile sensation were also elevated including two-point discrimination, von Frey thresholds, sharp–dull discrimination, joint movement, graphesthesia and stereognosia.

The clearest evidence for the effect of SI lesions on sensation is found in a study of two monkeys before and after anatomic lesions of SI (Kenshalo, Jr. and Willis, 1991). Pain detection was measured using the paradigm requiring detection of small temperature steps (T2) occurring on a larger temperature step (T1) into the noxious range (Fig. 4.1). Detection of temperature changes in the noxious range is analogous to detection of pain. Decreased detection of the small steps was observed after the resection and was dependent upon the size of both the T1 and T2 steps. The magnitude of the decreased detection trended toward but did not reach pre-operative levels over a 3-month period. In order to control for cognitive effects such as attention or grading performance the protocol included a visual control. The protocol consisted of a discrimination of light intensity which changed with steps analogous to the T1 and T2 steps. The lesions had no effect on the performance of the visual task. Taken together, clinical

studies and experimental studies in monkeys are strong evidence for the role of SI cortex in pain detection and discrimination.

Analysis of synchrony between cortical pain-related areas

The psychophysical effects of lesions involving parietal operculum, insula and MCC suggest that they are separate modules in a hierarchical pain network. Recent evidence of synchrony between local cortical field potentials suggest the presence of functional connectivity between MCC and parietal opercular and insular cortex (Ohara *et al.*, 2006). Together these studies suggest the presence of a hierarchical pain network, which may facilitate modeling studies of the pain network, as in the case of the visual system (Churchland and Sejnowski, 1992).

The synchronization of neural activity between modules or local networks may be dynamically formed during functional connectivity between modules (Lachaux *et al.*, 1999; Singer, 1999; Tallon-Baudry *et al.*, 2001). Oscillatory synchronization between separate parts of the brain may be measured by the phase locking value (PLV) (Classen *et al.*, 1998; Andres *et al.*, 1999; Rodriguez *et al.*, 1999; Mima *et al.*, 2001; Ohara *et al.*, 2001), and may be the substrate of functional connectivity or “binding” between structures in a network (Singer, 1993; Singer and Gray, 1995). Recent studies demonstrate task-specific ECoG synchrony between SI, PS and ACC.

Most theoretical approaches have described forebrain pain-related function in terms of relatively fixed models in which different structures may independently subserve different dimensions of pain (Melzack and Casey, 1968; Price and Dubner, 1977), or may be arranged in serial order, or a parallel order, or both (Wade *et al.*, 1996; Price, 2000). However, numerous imaging data and our data demonstrate that the structures activated by painful stimuli are not fixed but change significantly depending on the behavioral paradigm (Davis, 2000; Peyron *et al.*, 2000; Rainville *et al.*, 2000).

A recent study of synchrony of local field potentials recorded directly from the MF, PS and SI cortex shows significantly higher synchrony between attention compared with distraction. Prior to the laser stimulus, in the attention trial of the attention/distraction (counting stimuli/reading) paradigm, synchrony increased during attention vs. distraction between SI-PS electrode pairs during anticipation of the painful laser stimulus in the prestimulus period (Fig. 4.19, prestimulus PLV in beta range). After the stimulus, the task changes and the subject starts to count (Fig. 4.20, δ PLV in alpha range). During counting, after the laser stimulus, cortical synchrony was significantly more common during attention than during distraction for pairs of electrodes in SI and MF (Fig. 4.20). These results show that synchrony, and perhaps functional connectivity, is not fixed but changes rapidly during different tasks within one paradigm. This synchrony

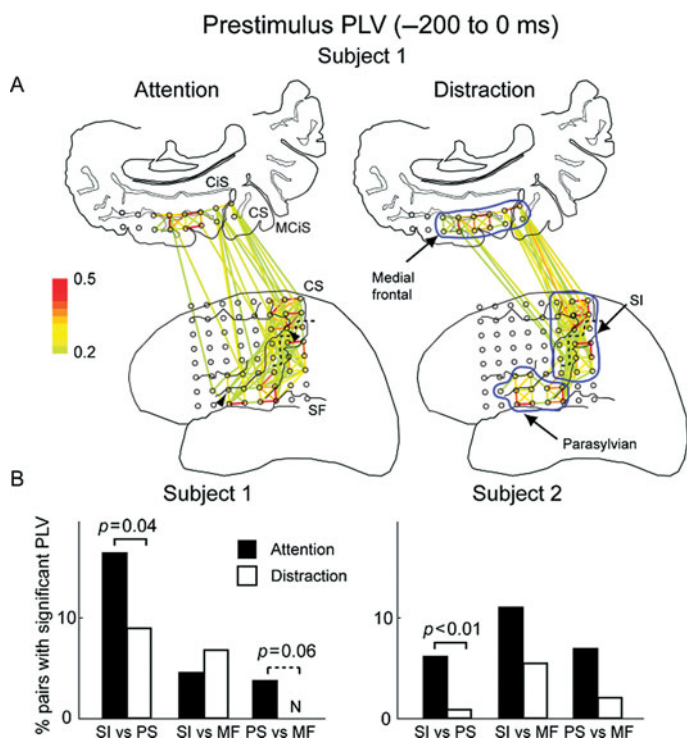


Fig. 4.19. Phase locked value (PLV) during the prestimulus period in beta range (16–24 Hz) in (A) subject 1 and (B) subject 2. A PLV value above significant level (T, threshold) was demonstrated by the color of the line connecting a pair of electrodes. Scale was shown in color bars. Three regions analyzed (SI, PS and MF) are circumscribed by blue lines. Note the clear difference between two conditions in degree of synchronization. Bar graphs indicate the proportion of electrode pairs between two regions where significantly increased baseline PLVs were recorded. Significant differences between the two conditions were consistently found between SI and PS regions. CS, central sulcus; SF, sylvian fissure; CiS, cingulate sulcus; MCiS, marginal branch of cingulated sulcus; PS, PS region; MF, MF region; N, no electrode pairs showing significant PLVs. Dashed lines in the diagram indicate SEP N20–P20 phase reversal, suggesting the location of the central sulcus. Reproduced after figure 2, Ohara *et al.* (2006).

analysis is consistent with evidence of pain-related sequelae of cortical lesions (see above).

To summarize, the analysis of lesions of pain-related structures led to different and separate losses of function. Lesions of the cingulate gyrus are associated with increased or unchanged ratings of painful stimuli but the emotional component of chronic pain is often reduced. Lesions of the insula are associated

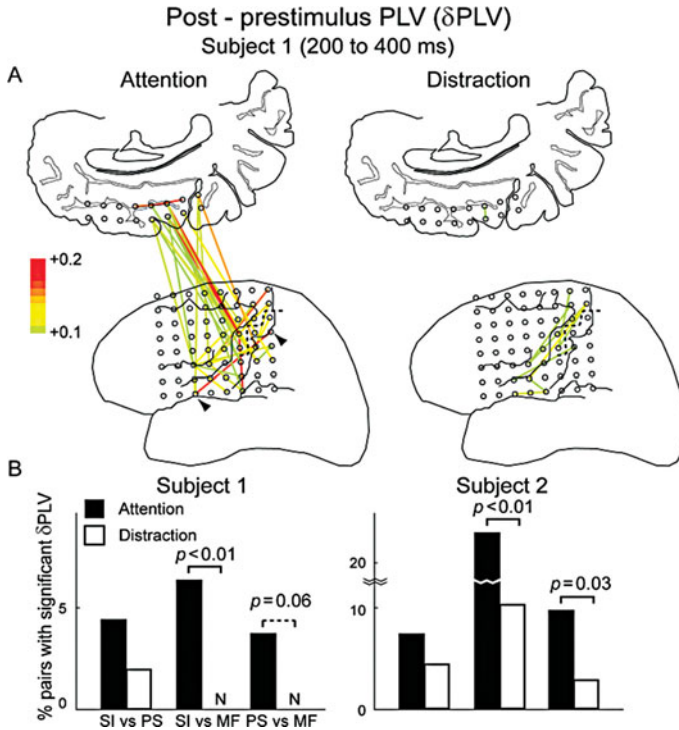


Fig. 4.20. Phase locked value (PLV) change from the baseline value (prestimulus period) (δ PLV) following laser stimulation in α -range (6–14 Hz) in (A) subject 1 and (B) subject 2. Significant δ PLV from the baseline value was demonstrated by the color of the line connecting a pair of electrodes. Scale was shown in color bars. Conventions as in Fig. 4.19. The arrows in the diagram of cortical anatomy in subject 1 indicate the locations of electrodes in SI and PS regions demonstrated in Fig. 4.19. Note the clear difference between two conditions in both subjects. Bar graphs on the right side of the figure indicate the proportion of electrode pairs between two regions where significant δ PLV (increase) was found. Significant or nearly significant difference between conditions was found between SI and MF regions and between PS and MF regions.

with increased tolerance of pain, and lesions of SI and SII are associated with loss of discrimination of painful stimuli. These non-overlapping effects of different lesions are known as “double dissociation” of pain perception, consistent with each of these structures functioning as a local network or module within a hierarchical network related to pain (Owen *et al.*, 1996; Bullinaria, 2002). These analyses help to characterize the type of network but do not define connections or connectional weights within the network. The analysis of synchrony suggests that SI is functionally connected with PS during anticipation of the stimulus, while SI and PS are functionally connected with ACC during the response to the stimulus.

The presence of task-related synchrony between cortical areas (functional connectivity) is most easily interpreted when it occurs between structures well known to be related to the task or function in question. An example is the successful application of this technique to subdural recordings of EEG to demonstrate synchrony between the supplementary motor area and motor cortex (Ohara *et al.*, 2000, 2001), which are well known to be activated during active movements (Schell and Strick, 1984; Hyland *et al.*, 1989; Gevins *et al.*, 1994; Tanji, 1994). By analogy, we focused on SI, MF and PS which have been related to nociception by a large number of primate anatomical, physiological, lesion and imaging studies. Finally, a number of imaging studies have been carried out showing correlation of blood flow between different cortical and subcortical structures (Faymonville *et al.*, 2003; Lorenz *et al.*, 2003).

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Functional brain imaging of acute pain in healthy humans

Introduction

Before the introduction of computerized tomographic (CT) brain imaging, studying human brain mechanisms of pain was largely limited to clinical reports and the post-mortem analysis of brain lesions. Although this approach provided important information and established the background for current investigations, these studies were usually limited by clinical descriptions of each patient's condition. Somatosensory psychophysics seldom included studies of pain and even then it was not possible to relate these observations to brain function or physiology. Because the living brain was invisible (except in the neurosurgery operating suite), research on pain mechanisms focused almost exclusively on the peripheral nervous system.

Brain CT scans introduced the opportunity to apply quantitative sensory testing to the study of living patients with visible, localized brain lesions and to begin to test hypotheses about functional localization and brain mechanisms of pain. The introduction of functional imaging by positron emission tomography (PET) and magnetic resonance imaging (MRI; fMRI) launched a new investigational paradigm into the study of pain mechanisms. Now it is possible to go well beyond the lesion analysis method and to relate human experience, in this case using somatosensory psychophysics, directly to a surrogate measure of activity in groups of neurons at the level of visible, localized brain structure. Since the early 1990s, the number and technical sophistication of functional brain imaging studies, including those related to pain, has increased at a rate that makes it almost impossible to incorporate the results into a conceptual framework. In this chapter, we will present and discuss some of these studies with the goal of providing a background for an improved understanding of human pain.

Physiological and technical background

Physiological basis of functional imaging

The hemodynamic response

The imaging techniques used most commonly for imaging brain functions during pain depend on the coupling between the supply of glucose, oxygenated blood and the local activity of neuronal populations. In 1890, Roy and Sherrington published the first demonstration, in anesthetized animals, that local cortical blood volume increased during electrical stimulation of a sensory nerve (Roy and Sherrington, 1890). The investigators measured changes in brain volume in anesthetized dogs or rabbits through a skull trephine opening. Most, but not all, volume changes were related to changes in systemic arterial pressure or venous return from the brain but the systemic intravenous injection of acid or of brain extract from a dog phlebotomized 4 hours earlier produced marked increases in cerebral volume without an accompanying change in arterial or venous pressures. This suggested that brain metabolic activity could increase brain blood volume independent of autonomic responses to somatic stimulation. The authors concluded that, in addition to the passive changes in cerebral blood volume due to systemic vascular changes, there is an active metabolic agent, produced by neuronal activity, that creates an acid that increases cerebral blood volume by active dilation of cerebral vessels. In a brief review of the history of the hemodynamic response, Raichle cites several earlier and subsequent clinical and experimental studies supporting the observation that neuronal activity is associated with a local increase in cerebral blood flow (Raichle, 1998). There has been an accelerated interest in this phenomenon since the development of functional brain imaging because an understanding of the mechanisms mediating this neurovascular response is necessary for interpreting the results of functional brain imaging studies.

Temporal and spatial features of the hemodynamic response

In vivo optical imaging provides the most detailed information about the time course and extent of the local vascular events following a stimulus that excites the bioelectrical responses of neurons. Optical imaging relies on the wave-length specific absorption of light by oxygenated hemoglobin (HbO) and deoxyhemoglobin (HbD) during neuronal activity as blood flows into the active site. Typically, changes in the intensity of light reflected from the cortical surface (reflectance) are quantified to reveal the temporo-spatial distribution of HbO and HbD during the vascular response. Optical imaging experiments have been conducted in rodents, cats and monkeys, so there are differences among

experiments in the timing and intensity of these events. However, the main features are similar enough to provide a good approximation of the physiology of hemodynamic response in primates, including humans.

Within 100 ms or less of the arrival of presynaptic electrical activity, there is an “initial dip” in HbO and an increase in HbD so that total hemoglobin (HbT) remains unchanged. The spatial extent of this early phase is limited to approximately 5.6 mm^2 in rat somatosensory (barrel) cortex (Chen-Bee *et al.*, 2007). After approximately 600 ms, there is a marked increase in regional cerebral blood flow (rCBF), local cerebral blood volume (CBV), HbO and a decrease in HbD. This phase of the vascular response is an “overshoot” because it provides HbO and glucose in excess of that required for oxidative metabolism of the tissue supplied (Fox *et al.*, 1988). The duration of the overshoot period depends on the duration of the excitatory stimulus and extends over an area that is approximately four times larger than the initial dip phase in rat cortex (Chen-Bee *et al.*, 2007). The period of increased rCBF and HbO may be sustained for the duration of the locally increased neuronal activity, although not at the same intensity as the initial response; this will be discussed in more detail in a subsequent section.

Following a brief excitatory stimulus (e.g. 1 s), the hyperoxygenation period ends with an undershoot of variable duration but of less intensity; this period has been studied less than the preceding vascular events but probably reflects a return to a mixture of HbD and HbO that is sufficient to maintain the prestimulus levels of cellular activity. An example of the three predominant phases of the hemodynamic response is shown in Fig. 5.1 (Chen-Bee *et al.*, 2007). These investigators used red illumination (at 635 nm) to image the sequence of vascular events in the rat somatosensory “barrel cortex” for up to 28.5 s following a 1 s stimulation of a whisker; this technique detects changes in multiple components of the “intrinsic signal” (including HbT, HbO and HbD) and is thought to approximate the blood oxygen level dependent (BOLD) signal used in fMRI. Only the overshoot phase is detected in most human fMRI studies but the early initial dip has been detected with functional MR spectroscopy in humans (Ernst and Hennig, 2007).

Mechanisms of the hemodynamic response

The physiological mechanisms underlying the hemodynamic response are still being investigated. For example, the role of local energy demand and its distribution among cellular activities, such as neurotransmitter recycling and action potential generation, is a subject of continuing discussion (Attwell and Laughlin, 2001; Attwell and Iadecola, 2002; Shulman *et al.*, 2004). There is general agreement, however, that the well-known link between astrocytic glia and cerebral blood vessels forms one anatomical basis for the response. Previous *in vivo* experiments using calcium (Ca^{2+}) sensitive dyes demonstrated that

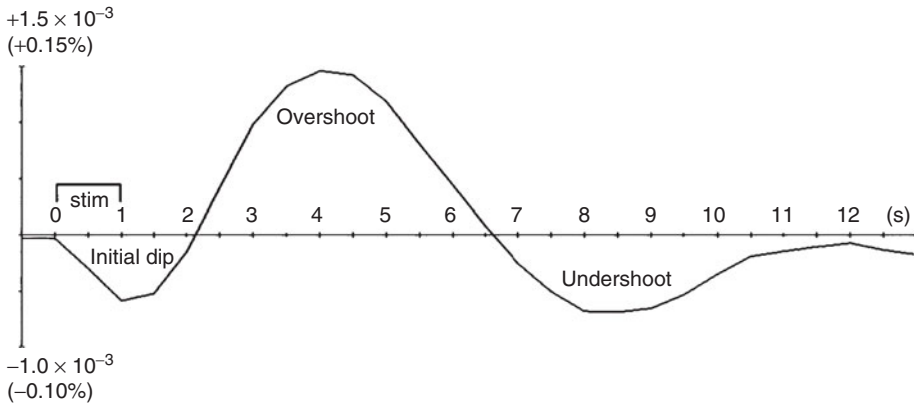


Fig. 5.1. Time course of the hemodynamic response, measured as changes in the reflectance of light at 635 nm from rat somatosensory cortex following a 1 s whisker stimulation. The line plot of the fractional change was obtained from a single pixel within the imaged cortex at a temporal resolution of 500 ms. Note the initial dip followed by an overshoot and then an undershoot. Adapted from Chen-Bee *et al.* (2007).

the presynaptic release of glutamate from neurons would stimulate Ca^{2+} uptake in astrocytes (Porter and McCarthy, 1996). During the initial dip phase, the neurotransmitter (e.g. glutamate) released by presynaptic terminals immediately activates astrocytic receptors, permitting calcium (Ca^{2+}) uptake, as shown by Ca^{2+} imaging (Fig. 5.2) (Winship *et al.*, 2007). The initiation of Ca^{2+} -activated intracellular biochemical cascades leads to the production and release of vasoactive agents through the metabolism of arachidonic acid (see Fig. 5.3), thus controlling precapillary smooth muscle (Haydon and Carmignoto, 2006). Some of these arachidonic acid metabolites are vasoconstrictive, so the net vasodilatory effect may depend on the background state of vascular tone and the interactions with other vasoactive agents.

Other vasoactive substances released during neural-astrocytic activations include potassium, nitric oxide, adenosine and possibly several neurotransmitters including acetylcholine, serotonin, dopamine, noradrenaline and gamma-aminobutyric acid (GABA). In addition to the astrocytic mediation of rCBF, there is evidence for the participation of endothelial cells and local interneurons that have contacts with capillary and precapillary pericytes, forming a “neurovascular unit” that mediates the local control of rCBF by acting at both local precapillary and arteriolar sites (Iadecola, 2004; Girouard and Iadecola, 2006). Thus, the hemodynamic response associated with neural activity depends on the concerted action of several cell types that are in close anatomical association with the cerebral vasculature and that together produce several vasoactive compounds.

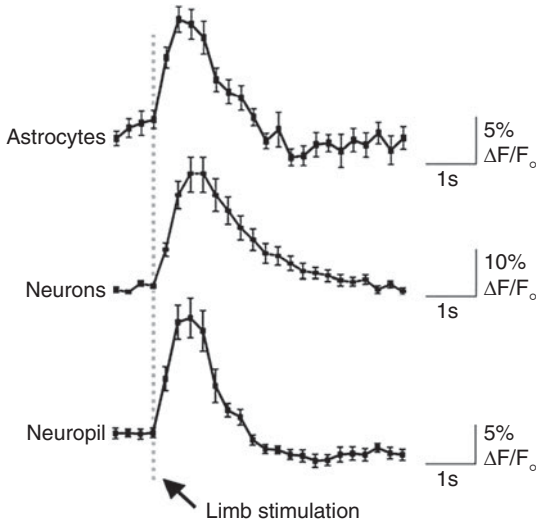


Fig. 5.2. Change in Ca^{2+} fluorescence relative to baseline ($\Delta F/F_0$) of 20 astrocyte responses and matched neuronal and neuropil responses during brief movement stimulation of the contralateral hindlimb. A somatotopic organization of these responses could be demonstrated by comparing responses to ipsilateral hind- and forelimbs. Error bars show the standard error of the mean. Adapted from Winship *et al.* (2007).

Neurovascular coupling

Experiments combining optical imaging and electrophysiological recordings in cats and rodents confirm the link between neuronal activity and specific components of the hemodynamic response. Thompson and colleagues recorded changes in tissue oxygen in the cat visual cortex and showed that simultaneously recorded neuronal spike activity is tightly coupled with the early deoxygenation during the “initial dip” of the vascular response (Thompson *et al.*, 2003) (see Fig. 5.4). In studying the effect of transcranial magnetic stimulation on the excitability of neurons in cat visual cortex, Allen and colleagues confirmed the coupling of neural activity with early decreases in tissue oxygenation and, using time-lagged correlation analysis, obtained evidence that neural activity precedes these early oxygenation changes (Allen *et al.*, 2007). During this initial phase, the energy required for neural activity is thought to be provided through astrocytic glycolysis and the shuttling of lactate to neurons for more sustained oxidative phosphorylation and the production of adenosine triphosphate (ATP) (for review, see Raichle and Mintun, 2006).

The later overshoot period of the hemodynamic response persists throughout the duration of increased neuronal activity. During this continuing increase of cellular activity, glucose consumption increases much more than oxygen

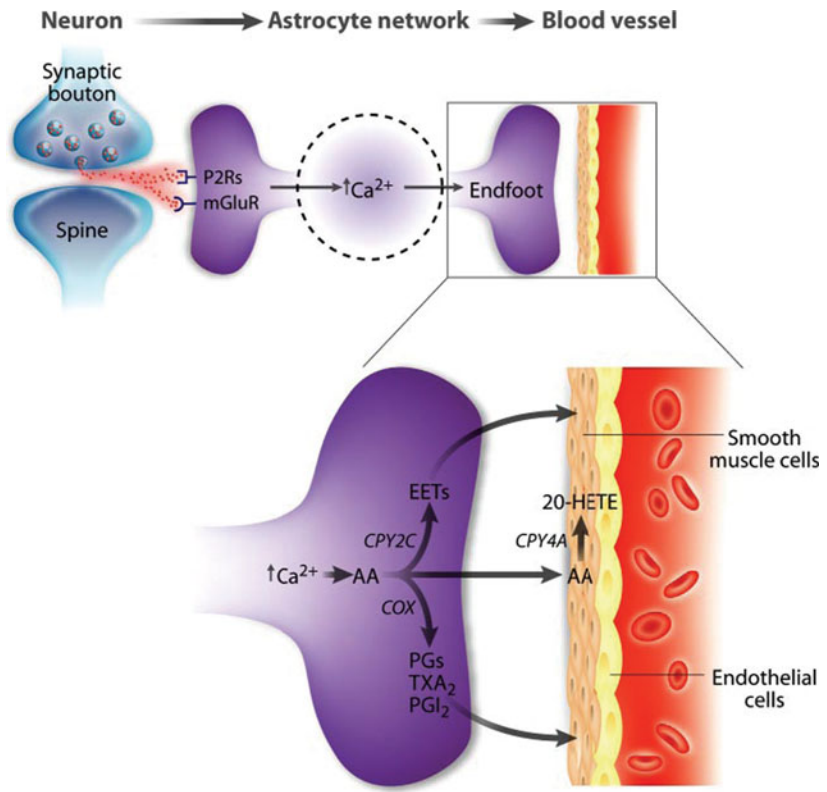


Fig. 5.3. Summary diagram of proposed neurovascular coupling mechanisms through the activation of astrocytes. The presynaptic release of glutamate activates astrocytic metabotropic glutamate (mGluR) and purinergic (ATP; P2Rs) receptors, leading, via phospholipase C, to increased astrocytic Ca^{2+} , which propagates to the astrocytic endfoot abutting the precapillary arteriole. There, Ca^{2+} facilitates the metabolism of arachidonic acid (AA) to prostaglandins (PGs, PGI_2), and thromboxaneA2 (TXA_2) via the cyclooxygenase (COX) pathway, and epoxyeicosatrienoic acids (EETs) via the cytochrome P 450 enzyme CPY2C pathway. Direct release of AA to smooth muscle cells promotes the formation of 20-HETE (20-hydro epoxyeicosatrienoic acid) via another cytochrome P 450 pathway (CPY4A). Some of these products are vasodilatory (e.g. EETs, PGs) and others vasoconstrictive (TXA_2 , 20-HETE); their predominant combined action may depend on the vasoactive tone prevailing at the time of release from the astrocyte (for review and details, see Haydon and Carmignoto, 2006). Adapted from Haydon and Carmignoto (2006).

consumption, resulting in an excess of oxygen availability consistent with maintaining oxidative glycolysis (Fox *et al.*, 1988). The mechanisms mediating the transient oversupply of HbO are not understood fully (see Raichle and Mintun, 2006).

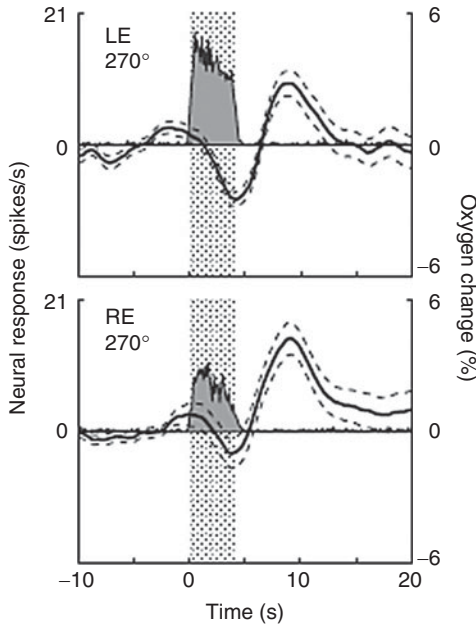


Fig. 5.4. Mean (SE) neuronal responses (left ordinate; gray shading) and % O_2 change (right ordinate; solid line) recorded simultaneously from a neuron in cat visual cortex in response to a grating stimulus (72 trials; 270° orientation; stippled area) delivered to the dominant left (LE) or non-dominant right (RE) eye. Adapted from Thompson *et al.* (2003).

The period of increased rCBF, HbO and glucose is the source of the blood oxygen level dependent (BOLD) signal that is used in fMRI; this relationship is discussed in more detail in the discussion of fMRI specifically (page 339). Logothetis and colleagues used the BOLD signal to demonstrate the temporal and response intensity relationship between the hemodynamic response as detected in fMRI and two forms of neuronal activity in the visual cortex of the anesthetized monkey: action potentials generated by populations of neurons (multiple unit activity or MUA) and local field potentials (LFP), which have a spectral power profile matching the occipital electroencephalogram of the monkey visual cortex (Juergens *et al.*, 1999; Logothetis *et al.*, 2001). The electrophysiological recordings were made with the monkey in an fMRI scanner during the generation of a BOLD response to a visual stimulus of varying intensity and duration, enabling an estimation of the correlation between evoked MUA, LFP and BOLD measurements. The result reveals strong correlations of BOLD amplitude and duration with both MUA and LFP responses, the latter showing the strongest correlation (Logothetis *et al.*, 2001). The hemodynamic response, as reflected by the BOLD signal in fMRI, is sustained throughout the duration of the stimulus.

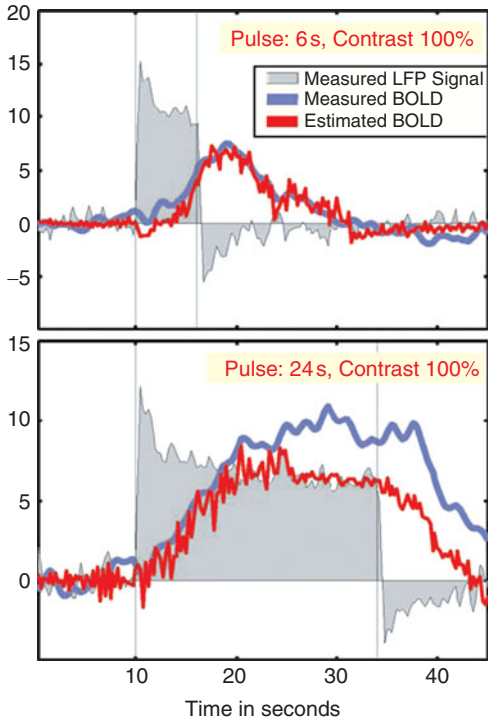


Fig. 5.5. Temporal and intensity relationship of neuronal (LFP) activity with the BOLD response in monkey visual cortex. The amplitude of the measured BOLD response (blue line) evoked by prolonged (24 s) visual stimulation exceeds the BOLD response estimated by a model that assumes a time-invariant linear response correlated with LFP activity. Adapted from Logothetis (2003).

However, toward the end of longer-duration stimuli (~24 s), the measured BOLD response exceeds the level predicted by a time-invariant linear relationship of BOLD to the recorded LFP (Fig. 5.5).

Optical imaging experiments have since confirmed a non-linear relationship between neural activity and the hemodynamic response although the degree of non-linearity and the conditions under which it occurs remain uncertain. Devor *et al.* (2003) used a wide range of stimulus intensities to evoke MUA, LFP and hemodynamic (HbO, HbT) responses in the rat somatosensory (barrel) cortex; they showed that the hemodynamic response continued to increase after the neuronal response (both MUA and LFP) saturated during the highest stimulus intensity. The hemodynamic response was related to neural activity by a power function with an exponent >1 in all cases.

In similar optical imaging studies, Sheth *et al.* (2004) monitored HbO, HbD and HbT in rat somatosensory cortex while varying the intensity of evoked potential

responses to varying intensities and frequencies of 2 s trains of electrical hindpaw stimulation. These investigators found linear relationships, above a threshold level, between normalized calculated oxygen consumption (CMRO_2) and the normalized summed field potential amplitudes; a similar relationship was found, without threshold, between changes in rCBF and changes in CMRO_2 . A linear model also described adequately the relationship between hemodynamic and neuronal responses but not over the full range of response intensities; the best fit was obtained with a power function with an exponent greater than 1. The observation that CMRO_2 was a better linear predictor of the intensity of neural activity and rCBF responses suggests that the metabolic demand associated with increasing the activity of *both neurons and glia* is an important determinant of the hemodynamic response. Overall, the results of optical imaging in rodents and fMRI experiments in monkeys indicate that the hemodynamic response is a linear predictor of a population measure of neuronal activity but only within a limited physiological range; hemodynamic responses may underestimate this activity at the lower end of the range (a threshold or measurement sensitivity effect) and overestimate it at the upper end.

Neuronal activity and the hemodynamic response

What aspects of neuronal activity are related to the hemodynamic response? The answer to this question is still incomplete and may not apply to all brain areas because of variations in the density of the vascular supply and of neuronal and glial populations. (For a recent review of this specific issue, see Logothetis, 2008.) After the development of the 2-deoxyglucose method of assessing the local glucose utilization in the brain (Kennedy *et al.*, 1975), it was possible to demonstrate that most energy metabolism occurred within the neuropil and not at the neuronal cell bodies (Kennedy *et al.*, 1975; Schwartz *et al.*, 1979; Mata *et al.*, 1980). However, the weight of current evidence indicates that electrophysiological recordings of LFPs and MUAs or single cell spike activity each show strong correlations with the hemodynamic response as detected by BOLD signal recordings in fMRI. Tolias and colleagues, in fMRI recordings from functionally distinct areas of the monkey visual cortex, showed that the BOLD signal intensity suggested a stronger neurophysiological response to moving stimuli than would be predicted by spike activity recordings; they suggested that this discrepancy might reflect the sensitivity of the vascular response to metabolic demands associated with local synaptic activity (Tolias *et al.*, 2001).

Mukamel and colleagues obtained evidence that spike activity also contributes strongly to the hemodynamic response (Mukamel *et al.*, 2005). By sampling the amplitude of the BOLD signal (reflecting the HbO phase of the hemodynamic response) every 3 seconds, it was possible to reveal a strong intersubject

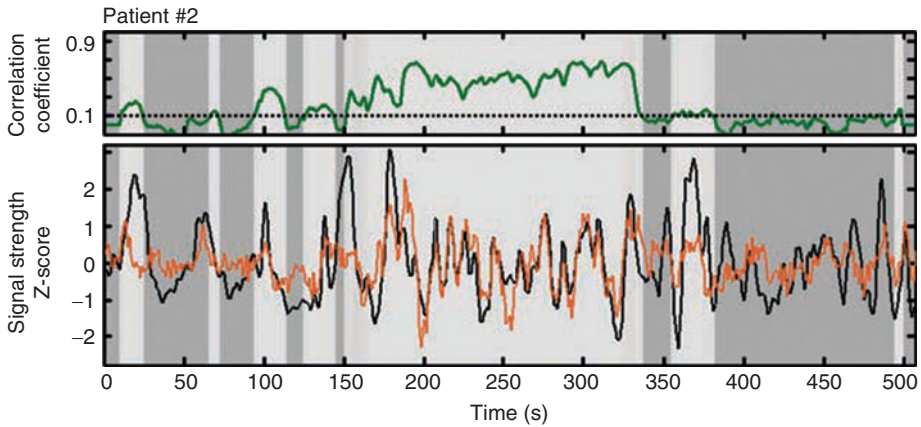


Fig. 5.6. Correlation of the BOLD signal predicted from a patient's neural spike data (Z-score; black traces) with the BOLD signal recorded from six healthy subjects (orange trace) while each group watched identical movie clips. When the BOLD signal correlation between healthy subjects was greater than 0.1 (dashed line, upper graph; light gray areas), there was a high correlation between the predicted and recorded BOLD signal (green trace, upper graph). Adapted from Mukamel *et al.* (2005).

correlation of BOLD activity in visual, auditory, limbic and even somatosensory brain areas while participants watched and listened to identical 30-minute segments of a movie (Hasson *et al.*, 2004). This information provided the rationale for modeling predicted BOLD responses from the spike activity of neurons recorded from the auditory cortex (Heschel's gyrus) of two presurgical epilepsy patients while they watched a 9-minute movie segment. The spike predictor model developed from the patients was applied to the analysis of fMRI data obtained, in separate sessions, from six healthy subjects who watched and listened to the same movie segments. Within Heschel's gyrus, there was a strong spatial and temporal correlation of the spike-predicted BOLD with the actual BOLD activity recorded during fMRI (Fig. 5.6) (Mukamel *et al.*, 2005). In a related analysis, the spectral power of the LFP also provided a reliable BOLD predictor but primarily within the higher frequency range (40–130 Hz). These results support the interpretation that both LFP and spike activity are strongly associated with the generation of the hemodynamic response.

There is an important exception to the relationship between spike and hemodynamic activity. Inhibitory interneurons in the thalamus and cortex are critical components of local circuits in cortical and subcortical structures, receive excitatory synaptic input and perform a wide variety of modulatory functions (Jones, 1993, 2002; Gupta *et al.*, 2000; McBain and Fisahn, 2001). It is reasonable to expect that these cells and the excitatory synaptic inputs that drive them would

contribute to the generation of the hemodynamic response. Indeed, an increase in rCBF during increased inhibitory synaptic activity is expected because of the local increase in glucose metabolism during long-term inhibitory synaptic activity (Ackerman *et al.*, 1984). In this regard, it is significant that Mathiesen and colleagues showed that, although monosynaptic activation of the excitatory climbing fiber pathway generated cerebellar Purkinje cell spikes and increased rCBF, stimulation of the disynaptic inhibitory parallel fiber pathway suppressed spike activity while rCBF increases persisted (Mathiesen *et al.*, 1998). These results are supported by the observation that blocking GABA_A-mediated inhibition increased Purkinje cell discharges while rCBF was unchanged (Thomsen *et al.*, 2004). Although these observations were confined to cerebellar cortex, they support the conclusion that both excitatory and inhibitory synaptic activity may contribute to generating the hemodynamic response in other brain structures and that functional imaging studies should be interpreted accordingly (Heeger *et al.*, 2000; Lauritzen, 2005).

General principles of functional imaging

Detecting the hemodynamic signal: fMRI

In brain imaging activation studies, the metric of interest is the amplitude of the hemodynamic response and its correlation with neuronal activity. In fMRI activation, the BOLD signal is the indicator of the HbO-rich phase of the hemodynamic response. (A detailed discussion of the physics and basic physiology of acquiring the BOLD signal is found in Buxton, 2002, and in Logothetis and Wandell, 2004.) The BOLD signal is produced by applying periodically an external electromagnetic radiofrequency pulse to a brain in which a fraction of the nuclei of hydrogen atoms have been oriented within a magnetic field of constant intensity (typically 1.5–4 Tesla). The brief (milliseconds) radiofrequency pulse, when applied at the resonant spin frequency of the hydrogen nuclei, temporarily forces their axial displacement. In passively recovering to their originally oriented state, the hydrogen nuclei emit energy in the form of magnetic signals that are detected by the radiofrequency coil within the scanner. Dynamic and static electromagnetic heterogeneities within brain tissue interfere, to varying degrees depending on tissue constituents, with the rate of recovery of the displaced nuclei and hence with the strength and duration of the signals they emit. In the resting state, before an increase in neuronal activity, venous and capillary blood contain a mixture of deoxyhemoglobin and oxyhemoglobin depending on the level of oxygen consumption at the time. Deoxyhemoglobin, which is paramagnetic, reduces the strength of the magnetic signal generated in response to the radiofrequency pulse but HbO, which

is diamagnetic, does not; consequently, the signal is enhanced during the overshoot, HbO-rich phase, of the hemodynamic response (Ogawa *et al.*, 1990, 1992). This enhanced signal is detected in fMRI as the BOLD response and, as discussed above, reflects, within an important but limited range, the intensity of neuronal activity (LFP, MUA and spike activity). The spatial resolution of fMRI is determined in part by slice thickness (typically 5 mm) and by setting the acquisition matrix of the scanner. In most fMRI studies, this in-plane resolution is 2×2 mm, but in-plane resolutions of 0.5 mm can be obtained under well-controlled experimental conditions. Very high resolution fMRI shows that the BOLD signal arises from small venules in cortical sulci (Hoogenraad *et al.*, 1999). The voxel size of the BOLD signal itself is typically 30 mm^3 (Buxton, 2002). Much of the BOLD signal is retained in veins that are near, but variably removed from, the site of neural activation; the signal from some of these veins, especially the larger ones, may present a problem in localizing activation sites accurately.

The temporal resolution of fMRI is determined in part by the repetition time (TR) of the radiofrequency pulse; this is specified in the experimental protocol and may range from several seconds to a few hundred milliseconds depending on the experiment. A major limiting factor in fMRI temporal resolution, however, is the onset and duration of the hemodynamic response. The hemodynamic response and the BOLD signal it produces begins 2–4 s after the onset of neural activity, reaches a plateau (the overshoot) after another 5–6 s, and has a duration that depends on the duration of the stimulus. For very brief stimuli (e.g. 1 s), the vascular response can be modeled as a gamma function, which is then used as the hemodynamic response function (HRF; $h(t)$). Despite the within- and inter-subject variability of the hemodynamic response, a linear model predicts the form of the hemodynamic response and the BOLD signal quite well when stimuli of longer durations and variable intensities are used in fMRI studies (Figs 5.7 and 5.8) (Friston *et al.*, 1994; Boynton *et al.*, 1996). Accordingly, in event-related experimental designs, the canonical HRF ($h(t)$) is convolved with the stimulus $x(t)$ to estimate the fMRI signal $y(t)$ ($y(t) = x(t) * h(t) + E$, where E = an error or noise function). Given a recorded fMRI signal $y(t)$ and a function $x(t)$ representing a series of noxious stimuli, for example, deconvolution can be used to compute the average event-related hemodynamic response function $h(t)$ within a particular voxel ($h(t) = y(t) *^{-1} x(t)$). Noise in the observed signal ($y(t)$) is included as noise in the estimated event-related response function $h(t)$ (Pike and Hoge, 2000). Experience with fMRI has shown that it is reasonable in most event-related experiments to assume that overlapping responses combine additively and that the contribution of individual events does not vary over time; exceptions to these assumptions, however, should be considered in the design of particular experiments.

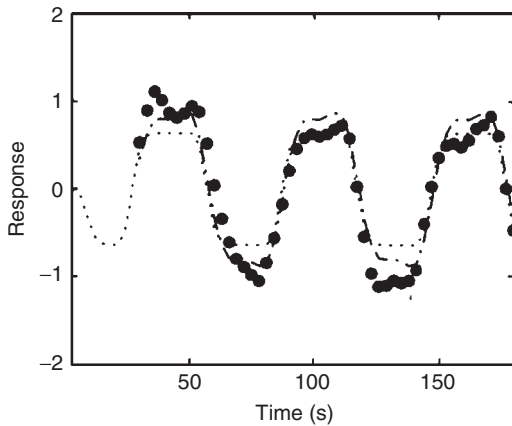


Fig. 5.7. Actual fMRI BOLD response to a visual stimulus (heavy dots) and the response predicted by Poisson (dotted line) and least squares deconvolution (broken line) estimates of the response. The model is based on convolving the stimulus with an estimate of the hemodynamic response function and determining correlations between them. Ordinate in arbitrary units. Adapted from Friston *et al.* (1994).

Positron emission tomography activation studies

In PET activation, the hemodynamic response is detected by estimating rCBF over approximately 60 s. Typically, a radioactive tag (e.g. H_2^{15}O) is injected intravenously and rCBF is computed from the coincidental counts of gamma rays emitted by the annihilation of positrons and electrons within the surrounding tissue. The accumulated radiation emitted within a time window in a volume of perfused tissue is an indicator of the total blood perfusion. The location of that volume (a voxel) within the brain is computed from the intersection of the radial lines formed by the set of opposing (180°) detectors that have registered the gamma emissions from that site. Typically, a 3D voxel is a cube approximately 2.5 mm on each side; however, the spatial resolution of PET is limited by the smoothing introduced by image reconstruction filters and by the ability of the radiation detectors to differentiate the radiation emitted from two separate point sources.

For PET, the detectable distance is the width of the distribution of radioactivity at one-half of the maximum counting rate, called the “full width at half maximum” (FWHM). For many scanners used for PET activation studies, the FWHM is between 10 to 15 mm. However, the spatial accuracy in the localization of an activation focus is improved (to less than half the FWHM) when subtraction images are made. The temporal resolution of PET is determined by the time required to determine the rCBF. The ^{15}O has a half-life of 122 s, which is sufficient for CBF measurements because, at the CBF levels being measured in human

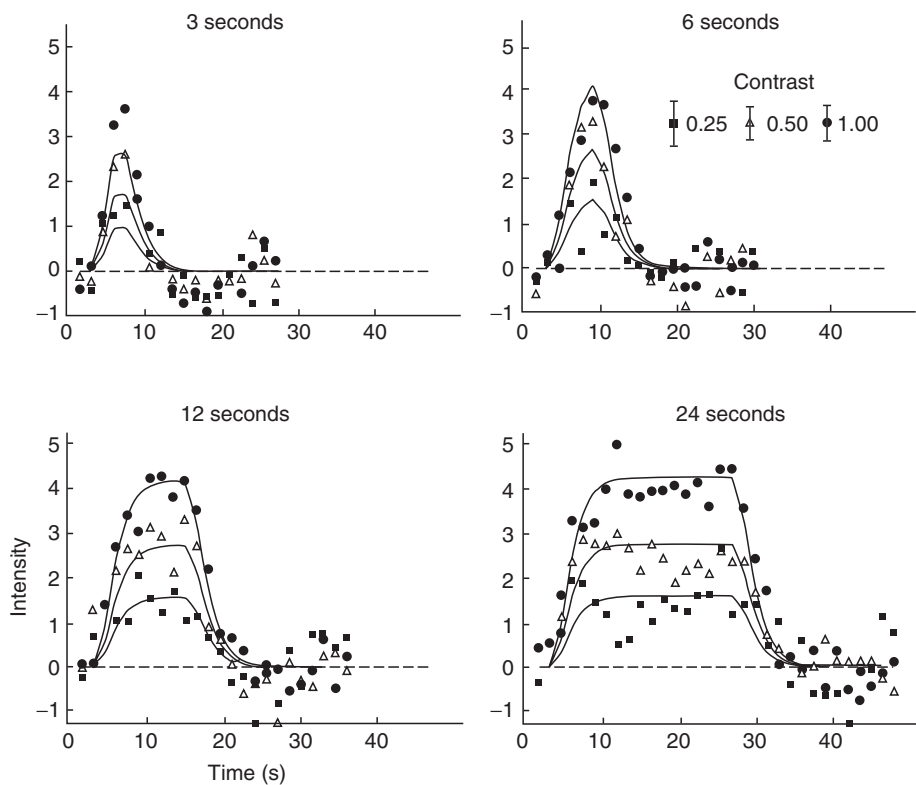


Fig. 5.8. Linear model of fMRI response (lines), using a gamma function model of the hemodynamic response to estimate response duration and a hyperbolic ratio formula to estimate neural response intensity; these models were fitted to actual BOLD responses (symbols) to visual stimuli of different strengths (contrast) and durations. Ordinate in arbitrary units. Adapted from Boynton *et al.* (1996).

studies, a bolus injection (e.g. 60 mCi) of this compound is nearly completely diffused into brain tissue on the first arterial pass (Ter-Pogossian *et al.*, 1969). The count of emissions from a given volume of brain tissue is therefore a good estimate of the perfusion of that brain region during the counting period (approximately 60 s for a typical scan). This measure of local perfusion can be compared with the perfusion of the same tissue volume in the resting state following stereotactic alignment of functional and anatomic images (Minoshima *et al.*, 1992, 1993). An important advantageous feature of PET (and SPECT; see below) compared with fMRI is that it is possible to obtain an estimate of rCBF (as regional perfusion), and therefore of neuronal activity, in the baseline or resting condition. A measure of baseline activity can be obtained with fMRI by detecting spontaneous (not task-related) regional fluctuations in the BOLD signal using correlation methods (Fox *et al.*, 2005; Fox and Raichle, 2007) but these

spontaneous fluctuations may occur on a depressed or elevated background of total activity. Functional MRI detects, through the BOLD signal, stimulus-induced changes in local activity compared with the preceding prestimulus period (or as correlated with another BOLD event); but the ability to obtain an estimate of resting or baseline activity for longer, temporally distributed periods is limited by the difficulty in obtaining reliable measurements of small baseline BOLD signal fluctuations. Positron emission tomography and SPECT, however, provide an opportunity to determine the magnitude of a hemodynamic response compared with a baseline measurement that may more accurately reflect the activity prevailing over long time periods throughout the study. This feature is an important consideration in pain imaging studies of patients with persisting abnormalities of rCBF or neuronal activity.

Single photon emission computerized tomography activation studies

In single photon emission computerized tomography (SPECT) trapping agents (technetium-99m-d,l-hexamethylpropyleneamine oxime, ^{99m}Tc -HMPAO, and technetium-99m-L,L-ethyl cysteinate dimer, ^{99m}Tc -ECD) are used as radioactive tracers for the estimation of regional perfusion or rCBF. These agents distribute into the brain through cerebral capillaries during the first pass and accumulate in proportion to regional blood flow and generally with very slow washout. Once in the brain, the tracer is relatively stable over time so that SPECT imaging can be performed subsequently in a resting state. Thus, a subject may receive stimulation outside of the SPECT scanner, and a tracer injection can be performed to obtain an estimate of neuronal activity at the time of injection. The stability of SPECT tracers is also an advantage in functional brain imaging studies of animals following noxious stimulation or during chronically painful conditions because the animal can be anesthetized and the brain examined hours after tracer is injected during the condition of interest (Morrow *et al.*, 1998).

There are several drawbacks to SPECT tracers for use in functional imaging. First, because of a longer radionuclide half-life, only one scan, or two with dose differentiation, can be obtained in a single day. Thus, task-baseline paired scanning may require separate days. Second, there are limitations inherent in SPECT imaging such as lower sensitivity and spatial resolution as compared with PET and much lower compared with fMRI. Third, the accumulation of ^{99m}Tc -HMPAO and ^{99m}Tc -ECD within the brain does not have a strictly linear relation to regional cerebral blood flow. There is attenuation of radiotracer accumulation in a high flow area due to limited first pass extraction and increased back diffusion, which consequently may underestimate the magnitude of brain activation. Finally, regional clearance of radiotracer from the brain is

not necessarily uniform so the timing of imaging after radiotracer accumulation must be consistent from scan to scan and subject to subject. For ^{99m}Tc -HMPAO and ^{99m}Tc -ECD, image acquisition typically starts several minutes to half an hour after radiotracer administration and typically lasts for 15 to 30 minutes. Positron emission tomography and SPECT image sets can be analyzed in a similar manner once paired image sets (stimulus and control/baseline) are obtained. However, PET ^{15}O -water studies generally have a greater number of repetitions within a subject, resulting in more robust statistical power.

Metabolic and receptor binding studies

Positron emission tomography is the method most frequently used for studies of local changes in neuronal glucose metabolism and receptor binding. Fluorodeoxyglucose (FDG) PET is based on the intracellular trapping of deoxyglucose, a ligand that easily passes the blood-brain barrier and is sufficiently stable to permit determinations of changes in regional glucose utilization (rGLU) within or between subjects. Fluorodeoxyglucose PET is used most often in the analysis or detection of pathological conditions, such as Alzheimer's disease, in which neuronal and synaptic degeneration occurs; it has not been used in studies of acute pain although it could be used to detect metabolic changes that develop during chronically painful conditions. Similarly, the central benzodiazepine receptor antagonist ^{11}C flumazenil has not been used in pain-imaging studies although it is of potential interest for use in chronic pain because it binds to the γ amino butyric acid α (GABA_A) complex and could detect damage to inhibitory mechanisms that modulate nociceptive processes.

The selective μ opioid receptor ligand carfentanyl (^{11}C carfentanyl) and the less selective ^{11}C diprenorphine and ^{18}F cyclofoxy opioid receptor ligands are of particular interest in pain-imaging studies because of the presence of opioid receptors in the primate brain (for review, see Lever, 2007). The greatest concentrations of μ opioid receptors (carfentanyl) are found in the basal ganglia and thalamus (Frost *et al.*, 1985; Sadzot and Frost, 1990). Diprenorphine binds to μ and κ receptors primarily in the striatum, cingulate cortex and frontal cortex; the μ and κ receptor antagonist cyclofoxy has maximum binding in the caudate, amygdala, thalamus and brainstem (Heiss and Herholz, 2006). Carfentanyl has been used effectively in acute pain studies (see below) to detect the release of endogenous opioid during pain and during the placebo effect. The basic strategy is to identify regions in which the μ opioid receptor binding potential (BP') for carfentanyl has been reduced, consistent with receptor occupation by an endogenous μ opioid. The BP' is estimated by determining the ratio of radioactive counts (integrated over time) detected in the target tissue (e.g. thalamus) to those obtained from a comparison site without opioid receptors (e.g. visual cortex),

which may be assumed to estimate plasma concentration; the slope of a Logan plot of these values is the BP' in the target tissue (Logan *et al.*, 1990). This value is used for further statistical modeling and parametric brain mapping (see below).

Analysis of functional imaging

A complete discussion of the analysis of functional imaging is beyond the scope of this chapter; there are several sources that cover this topic in detail (Friston *et al.*, 1991, 1996a, 1999b; Price and Friston, 1997; Buxton, 2002; Nichols and Holmes, 2002; Friston *et al.*, 2005). We present some of the major features of analysis, as it pertains to functional imaging studies in general, in the following paragraphs.

An important step in the analysis of functional images is determining the presence and location of activation in response to a stimulus or physiological condition. A sample of the signal (BOLD, counts of gamma emissions, etc.) is obtained within each voxel or a population of voxels in the brain; the size of this population may vary depending on the experimental design and the hypothesis under examination. In the human brain, the analysis may include the entire gray matter, which typically comprises 50,000 to 100,000 voxels, or it may be limited to a smaller voxel population within a structure of specific interest (volumes of interest or VOI). The VOI must be based on some *a priori* hypothesis or the results from a separate data set. The VOI may be selected by manually applying spatial coordinates for a specific volume shape and size within a brain structure or by using a method that estimates the probability that a coordinate set is located within a specific brain structure (Hammers *et al.*, 2003; Nielsen and Hansen, 2004).

The analysis strategy is to identify, within each voxel and each condition (e.g. stimulus or control), a signal that is different from the signals in all other voxels in the comparison population; a statistically significant difference of signal strength between conditions defines an activation (or deactivation) in one of the compared conditions. Essentially, this strategy is a subtraction paradigm for identifying condition-specific activations. It is important to recognize the limitations of this method and to account for them in interpreting the results of imaging studies (Friston *et al.*, 1996b, 1999a, 2005). For statistical modeling, it is necessary to establish a threshold to avoid a Type 1 error (while considering the likelihood of Type 2 errors). There are several analysis software programs available that allow the user to set the statistical threshold and obtain statistical parametric maps (SPMs) of activation in the brain based on specific assumptions about the stochastic properties of the activation process.

The statistical analysis is based on the general linear model (GLM), which assumes that most statistical analyses can be described as a linear combination of variables. The known variables, such as movement, stimulus characteristics

and others that may affect the estimation of signal strength in each voxel, are introduced into the analysis as determinant factors. Given the large number of voxels present, even within smaller VOI, the analysis must adjust the statistical threshold (e.g. $P < 0.05$) to correct for the error accumulated by comparing the signal within a single voxel with that of all other voxels within the whole brain (an omnibus or voxel-by-voxel analysis) or within VOI. The analysis may be modified by combining voxels within volumes determined by the image resolution ("resels"), which reduces the number of independent statistical comparisons within a VOI (Worsley *et al.*, 1992). The adjustment of statistical threshold is based on a consideration of the statistical properties of random fields and the application of this theory to the particular conditions of brain imaging (Adler and Hasofer, 1976).

The analysis must take into consideration the correlation among voxels, the stationarity of the process under investigation and other variables that may affect the statistical properties of activation detection and location. Selecting a relatively small VOI may offer greater statistical power but this must be based on a reasonable a priori hypothesis derived from prior knowledge or experimental results. The SPMs obtained from most analytical programs provide Z or t scores for the statistical significance of activations within one or more voxels. Adjustments of the level of significance can be made for the number of contiguous activated voxels (Forman *et al.*, 1995). Non-parametric analyses, which do not assume a normal distribution of voxel activity, are also available for statistical modeling (Nichols and Holmes, 2002). Other statistical tests can be applied to brain activation studies. Whatever the analysis method, it is critical to determine whether the analysis of multi-subject data is based on the variance among scans (fixed-effect analysis) or among subjects (random effects analysis) because this determines whether statements about the activations apply only to the specific group studied, as in the former instance, or to the general population of which the study group is a sample.

Conjunction analysis has been developed to avoid some of the interpretive errors that may arise when pure subtraction is applied to the analysis of imaging data (Price and Friston, 1997; Friston *et al.*, 1999a; Nichols *et al.*, 2005). Correlation analysis between external indices and intracranial voxel values during activation permit experimental designs without employing two-state subtraction paradigms (Friston *et al.*, 1994; Peltier *et al.*, 2006). In addition to hypothesis-based investigations, data-driven multivariate analyses, such as principal or individual components analysis, are applicable to functional imaging data sets and can reveal potentially latent regional correlation patterns during functional brain activation (McKeown and Sejnowski, 1998; McKeown *et al.*, 1998; Calhoun *et al.*, 2005). Recent and emerging developments include real-time fMRI, in which the

individual subject learns to control the activation within a brain structure (deCharms *et al.*, 2004; Bagarinao *et al.*, 2006), and statistical methods for detecting differences in the pattern of voxel activations within clusters of voxels. In the sample of pain-imaging studies to be discussed in this book, one should be able to appreciate the variety of options for statistical analysis in functional imaging studies.

Anatomical registration A critical aspect of functional imaging analysis is the anatomical registration of functional activation within and between subjects. There are programs that provide for the correction of the movement of a subject so that the functional activations obtained during different phases of the study can be registered with anatomical consistency. Once the within-subject anatomical locations are established, the functional activations can be co-registered on the anatomical image of that individual. The next step is to combine and register the individual functional images into a standard stereotactic space or 3D map such as the Talairach or Montreal Neurological Institute (MNI) spaces (Talairach and Tournoux, 1988; Evans *et al.*, 1992), in which the location of specific anatomical structures is given in x, y and z coordinates. Because of intersubject variance in the location of brain structures, it is necessary to employ anatomic standardization methods in which the size and skewness of the individual brain are matched linearly to a brain that provides a standard of spatial reference for cerebral structures; this can be referred to as a “standard” brain while acknowledging individual differences from a theoretical average brain (Minoshima *et al.*, 1992, 1994; Woods *et al.*, 1998a, 1998b). The Talairach Atlas is based on the application of a proportional grid system to the brain of a single individual with a brain of approximately average size and weight; the MNI reference brain has been developed from MRI scans of multiple neurologically healthy persons of both sexes. Local anatomical differences between the individual brain and the standard brain are minimized by employing a non-linear warping algorithm (Minoshima *et al.*, 1994). Most methods are fully automated and include iterative matching of an individual brain image set to a standard brain, using a mathematically defined transformation function and corresponding landmarks within the brain.

The resting brain and deactivations

The analysis of fMRI or PET studies frequently results in the appearance of activations with a negative value (deactivations). Deactivations are seen in functional imaging studies of pain, so it is important to understand the underlying mechanisms and their significance. In an analysis of nine PET studies involving a visual task, Shulman and colleagues identified several brain areas

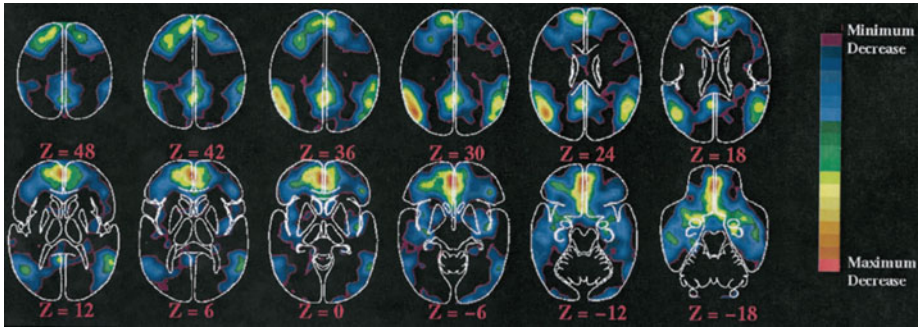


Fig. 5.9. Regions of the brain shown by Shulman and colleagues to deactivate during different visual cognitive tasks compared with passive visual fixation. Data were analyzed from nine different PET studies involving 132 individuals. The images are oriented with the left side to the reader's left. Numbers indicate mm above or below a plane connecting the anterior and posterior commissures. Note the concentration of deactivations in the medial frontal and posterior parietal regions. Adapted from Raichle *et al.* (2001) from Shulman *et al.* (1997).

that were consistently deactivated during the performance of different cognitive tasks compared with passive visual fixation on a target (Fig. 5.9) (Shulman *et al.*, 1997). The deactivated regions were located primarily within medial frontal and posterior parietal cortex and included the posterior cingulate/precuneal region, left and right inferior parietal cortex, left dorsolateral frontal cortex, left lateral inferior frontal cortex, left inferior temporal gyrus, medial frontal regions and the right amygdala.

It is unlikely that the activity of inhibitory interneurons causes these deactivations because, as discussed above, inhibitory interneurons are components of local circuits that receive excitatory synaptic input and may thus contribute to the positive hemodynamic response. Rather, the deactivations most likely reflect the withdrawal of ongoing, baseline neural activity as the brain engages new sensory, motor or cognitive tasks. Raichle and colleagues have addressed this issue in a series of PET studies designed to identify a “default” or “resting” state of the brain that provides a “true baseline” from which all activations arise (Raichle *et al.*, 2001; Raichle, 2006). These investigators obtained the oxygen extraction fraction (OEF), the ratio of oxygen used to oxygen delivered, throughout all regions of the resting brain from quantitative metabolic and circulatory measurements during PET. Because of the hyperperfusion (overshoot) response, the OEF decreases during increased neuronal activity. In healthy subjects lying quietly with eyes closed and performing no tasks, the OEF in the typically deactivated regions (Shulman *et al.*, 1997) was found to be no different from the average OEF throughout the brain during the study. The findings were

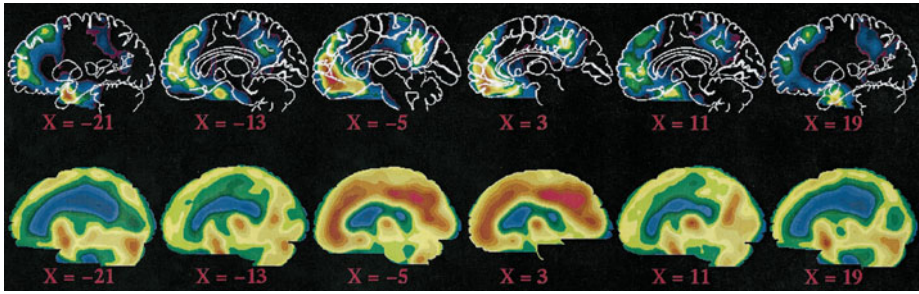


Fig. 5.10. Upper row shows a sagittal view of the deactivation data shown in Fig. 5.9. Lower row shows the rCBF of the brain of 19 healthy female subjects resting quietly while awake with eyes closed. The numbers below the images indicate mm to the right (positive) or left (negative) of the midline. Adapted from Raichle *et al.* (2001).

similar in groups of subjects with eyes open. This means that the deactivations seen in these areas when tasks are performed are reductions from ongoing activity in a resting, and not a previously activated, state. This interpretation is supported by the observation that rCBF is increased in these same areas in the resting state (Fig. 5.10). These studies show that the resting human brain is in fact highly active, consistent with its relatively high rate of oxygen consumption compared with other organs; indeed, the increase in energy consumption due to task performance is estimated to be a small fraction of that required for ongoing activity in the resting state (Raichle and Mintun, 2006).

Greicius and colleagues used connectivity analysis to demonstrate that the “default” brain regions are interconnected during the resting state and indeed form a network (Greicius *et al.*, 2003). Subsequent studies have used correlation and conjunction analysis methods to show that, in the resting state, the activity in a group of brain regions that are deactivated during task performance are correlated with one another and anti-correlated with brain regions that are typically activated during tasks (Fig. 5.11) (Fox *et al.*, 2005). Diffusion spectrum imaging-based tractography and network analysis has recently confirmed the dominant anatomical and functional interconnectedness of the medial frontal and posterior parietal components of the default resting network (Hagmann *et al.*, 2008).

Functional imaging of acute pain

Components of pain

For interpreting the physiological significance of brain activations in studies of pain, it is important to consider that some structures or activation patterns may be critical for this conscious experience and others may not.

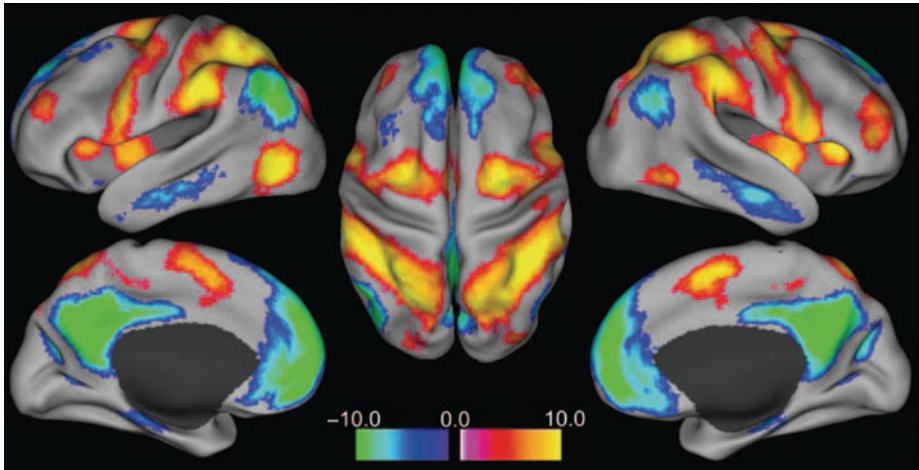


Fig. 5.11. Autocorrelation fMRI study of the resting brain of ten subjects (inflated brain view shown). Seed voxels were placed in regions typically activated (red–yellow) or deactivated (green–blue) during task performance. Colored areas represent the correlation coefficients obtained by monitoring resting BOLD fluctuations among the selected areas. The typically activated areas correlate with one another and are anti-correlated with areas that are typically deactivated during task performance. Similarly, areas of deactivation correlate with one another and are anti-correlated with activated regions. Similar results were obtained when resting subjects had eyes open or closed. Adapted from Fox *et al.* (2005).

As mentioned in [Chapter 4](#), pain is widely accepted as an experience with sensory (discriminative), hedonic¹ (affective) and cognitive (contextually dependent) components (Melzack and Casey, 1968; Merskey and Bogduk, 1994; Fields, 1999; Price, 2000). It is therefore reasonable to expect that brain activations during pain could reflect any combination of these components. It is certain that the activation of more than one cerebral structure is necessary for the experience of each pain component. It is also possible that the activation of an anatomically distinct structure could reflect the participation of that structure in more than one aspect of pain. Those currently engaged in pain imaging² are generally aware of these issues as revealed in the sample of imaging investigations presented here. In many instances, these imaging experiments have been designed to tease out a component of pain that has produced a particular imaging result.

As discussed in [Chapter 6](#), the input from nociceptors activates endogenous modulatory mechanisms in addition to structures that participate in the conscious experience of pain. In many instances, the same structure participates in both perceptual and modulating processes. For example, thalamic activation could reflect either excitatory ascending spinothalamic input, the cortical

excitation of inhibitory inputs from the thalamic reticular nucleus, or the contribution of both activities. It is important also to consider that some brain activations may be related to subconscious processes that normally accompany pain but are not critical determinants of the conscious experience. These consequences of noxious stimulation include somatic reflexes, autonomic responses and neuroendocrine reactions that are generated during central nociceptive processing.

Pain psychophysics and imaging

To discriminate among components of pain or to achieve a more detailed analysis of some aspect of each component (e.g. anxiety, anticipation or expectation aspects of cognition), the proper application of psychophysics is critical. There is an extensive literature on pain measurement (see Stevens, 1971; Engen, 1972a, 1972b; Chapman, 1978; Chapman *et al.*, 1985; Handwerker and Kobal, 1993; Gruener and Dyck, 1994; Gescheider, 1997; Craig, 1999; Gracely, 1999; Katz and Melzack, 1999; Price, 1999) so we will focus on those aspects of psychophysics of particular relevance for pain imaging studies.

Different forms of noxious stimulation (cutaneous thermal, mechanical or electrical stimulation; stimulation of viscera or muscle; ischemia) excite different combinations of peripheral receptors, afferent fibers and presumably different but variably overlapping central pathways and mechanisms; this is expected because of differences among pain experiences and should result in different brain activation patterns, also with variable overlap. These pain experiences may differ because of differences in the spatial and temporal characteristics of the stimulus, the evoked hedonic component, or many other cognitive modulating variables. Most pain imaging studies make some effort to control for multiple variables in the study design and by using sophisticated analysis procedures as discussed above. However, the variables both within and between pain imaging studies limit the validity of comparisons of the results obtained in different investigations.

Other considerations specifically related to pain

Davis (2003) has summarized some anatomical and physiological variables that deserve special consideration in imaging studies of pain. As discussed in Chapters 2–4, somatic and visceral stimuli excite neurons with a range of stimulus response thresholds extending from well below to well above a psychophysically determined pain threshold. As Davis points out, a voxel includes thousands of neurons, some of which may respond only to innocuous contact (low threshold only; LT), others only to noxious stimuli (nociceptive specific; NS), and others that respond to innocuous stimuli but show increasing activity as

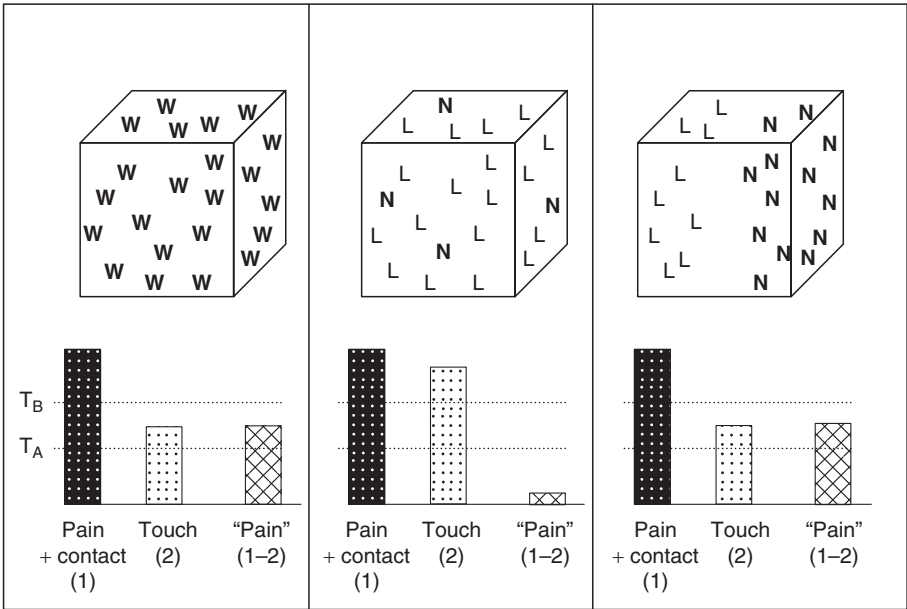


Fig. 5.12. Possible misleading results of pure subtraction in pain imaging. The three cubes represent hypothetical voxels that include a different mix of neuronal types ranging from low threshold (L) to nociceptive specific (N) and including neurons with a wide dynamic range of responses (W) from innocuous through the noxious range. The bar graphs below each voxel depict the results of a subtraction analysis in which the image signal (BOLD or rCBF) response (stimulus-baseline) to skin contact (touch; stippled bars) is subtracted from the response to painful contact (pain + contact; black bars). Even when the statistical threshold is low (T_A), the presence of a small proportion of N neurons may be undetected (middle panel) and the distinction between populations of W and N + L neurons (right and left panels) is missed. At higher thresholds (T_B), no nociceptive responses are detected. Adapted from Davis (2003).

stimulus intensity extends into the noxious range (wide dynamic range or WDR cells). As shown in Fig. 5.12, a simple subtraction analysis of an imaging study can lead to erroneous conclusions about the properties of the analyzed voxel(s). Specifically, subtracting the innocuous from the noxious responses of a voxel cluster with a small proportion of NS or WDR compared with LT neurons may lead to the conclusion that there are no nociceptive neurons in that sample of brain tissue. Other mixtures of LT, NS and WDR cells could lead to different interpretive errors. As Davis points out, and as discussed above, specific experimental designs and other statistical analysis procedures such as regression and conjunction analysis are available to assist in refining the interpretation of imaging results (Price and Friston, 1997; Friston *et al.*, 1999a; Nichols *et al.*, 2005).

A brief historical background and overview

The first functional brain images supported the theoretical foundation of pain research that had been proposed nearly 30 years before (Melzack and Casey, 1968) and later formalized in the definition of pain by the International Association for the Study of Pain (IASP) (Merskey and Bogduk, 1994). These early PET studies revealed that, during acute pain, both somatosensory (SI, primary somatosensory and SII, secondary somatosensory) and limbic (cingulate) cortical structures were active, consistent with the conceptual model that pain requires the participation of cerebral structures mediating both temporo-spatial discriminative and affective components (Jones *et al.*, 1991; Talbot *et al.*, 1991). The studies of Jones and colleagues and of Talbot and colleagues each used cutaneous noxious heat as the test condition and innocuous warmth for subtractive comparisons. Casey *et al.* (1994) subsequently confirmed and extended these observations by showing that the activations produced by the more intense stimuli were related to the perception of pain and not simply to the detection of differences in stimulus intensity; in addition, this PET study first revealed the pain-related activation of the thalamus bilaterally, cerebellar vermis, contralateral insula, and medial midbrain in the region of the periaqueductal gray (PAG).

Since these early studies, the number of publications in the field of pain imaging has increased dramatically, driven in large part by the technical development of fMRI, the application of receptor-binding studies using PET, and the increasingly sophisticated experimental designs and statistical analysis methods discussed above. The rapid growth of the field of pain imaging has prompted the publication of several reviews that have attempted a degree of consensus about the forebrain systems that are most frequently active and therefore likely to be most critical for mediating acute pain. Most of these reviews have emphasized the results of pain imaging (Casey, 2000; Casey and Bushnell, 2000; Derbyshire, 2000; Peyron *et al.*, 2000; Rainville, 2002; Porro, 2003; Apkarian *et al.*, 2005; Brooks and Tracey, 2005) but some have focused on the cerebral cortex and have included evidence from a variety of experimental paradigms (Treede *et al.*, 1999; Casey and Tran, 2006). In a review of electrophysiological, anatomical and brain imaging studies of cortical mechanisms mediating pain (Treede *et al.*, 1999), the authors concluded: "The following cortical areas have been shown to be involved in the processing of painful stimuli: primary somatosensory cortex, secondary somatosensory cortex and its vicinity in the parietal operculum, insula, anterior cingulate cortex and prefrontal cortex." A diagrammatic summary of their conclusions is presented in Fig. 5.13. This conclusion has been supported and extended to include additional limbic (posterior cingulate cortex, hippocampus), parietal (inferior parietal lobule) and prefrontal

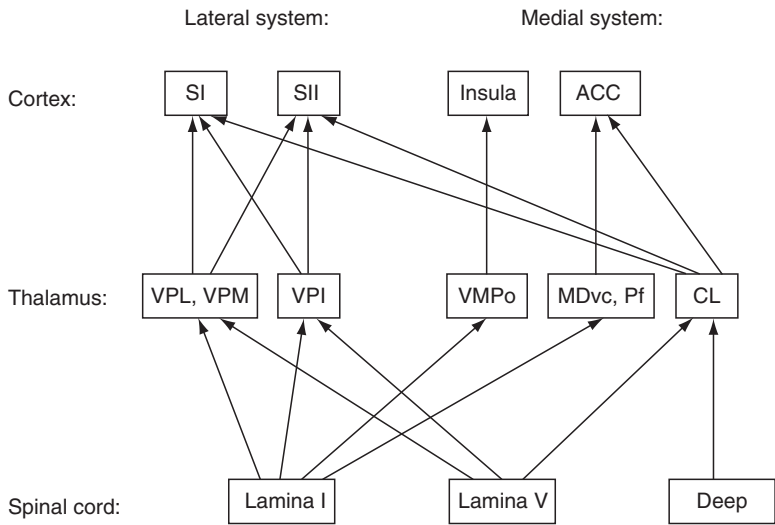


Fig. 5.13. Summary diagram of the spinal, thalamic and cortical structures and principal connecting pathways that participate in mediating pain according to a review of cortical mechanisms of pain presented by Treede *et al.* (1999) and based on combined functional imaging, electrophysiological and clinical data. Neurons in laminae 1, 5 and some deeper laminae of the spinal cord dorsal gray matter project axons as shown to various thalamic nuclei via the spinothalamic tract (a medial dorsal column pathway that is critical for visceral pain is not shown here; see [Chapters 2, 3 and 4](#)). Thalamocortical pathways are shown from the ventroposterior lateral (VPL), medial (VPM) and inferior (VPI) thalamic nuclei to the primary (SI) and secondary (SII) somatosensory cortices. Clinical and electrophysiological evidence implicates these connections in the sensory-discriminative component of pain. The central lateral thalamic nucleus (CL), shown here as unique in receiving input from the deep spinal dorsal horn, innervates the SI and SII cortices but additionally the anterior cingulate cortex (ACC), a defining component of the limbic system. The ACC also receives medial thalamic innervation from the ventrocaudal portion of the medial dorsal nucleus (MDvc) and the parafascicular nucleus (Pf). These medially located structures are considered critical for the elaboration of the affective or hedonic aspect of pain. The insular cortex, which is interconnected with the SII and ACC cortices, is shown here to receive a unique thalamic innervation from a ventromedial posterior (VMPo) nucleus (however, see [Chapters 2 and 4](#) for a reinterpretation of the posterior thalamic nuclei and related pathways) and to participate in the integration of sensory and affective components of pain and associated autonomic responses. Cognitive aspects of pain are not shown in this diagram. Adapted from Treede *et al.* (1999).

(premotor, medial, orbital, dorsolateral) cortical areas in recent reviews of cortical mechanisms (Casey and Tran, 2006; Casey, 2007) based on a broad range of experimental and clinical evidence and including a consideration of the temporal domain over which cortical activity influences pain and pain-related

behavior (Fig. 5.14). In a recent meta-analysis, which included an examination of 68 functional imaging studies, most concerning acute pain (Apkarian *et al.*, 2005), the authors concluded that “The main components of (the pain) network are: primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices (SI, SII, IC, ACC, PFC) and thalamus (Th).” (Fig. 5.15; see their table 1 for a complete list of the studies and activation patterns included in this analysis.) Thus, the general picture of the major cerebral structures mediating acute pain, as revealed by pain imaging, has remained similar to that obtained by earlier investigations and includes those participating in the elaboration of sensory-discriminative, hedonic (affective) and cognitive functions.

Because it is neither possible nor desirable to discuss all pain imaging investigations in the present format, we will consider a few studies that represent some of the questions that have been, and continue to be, addressed by applying imaging methods to the investigation of the physiological mechanisms of acute experimentally induced pain in healthy individuals. There are many unresolved issues that provide fertile ground for further exploration and continuing investigation.

The sensory-discriminative component of pain

Intensity

Which cerebral structures are responsible for the perceived intensity of acute pain? In a VOI-directed $H_2^{15}O$ PET study comparing cutaneous heat and deep cold pain (Casey *et al.*, 1996), it was shown that two levels of perceived innocuous cutaneous warmth (36 and 43 °C) differentially activated the contralateral thalamus, lenticular nucleus and cerebellar vermis and that these structures were activated also in a separate comparison of innocuous and noxious contact heat (40 and 50 °C); however, activation in the contralateral sensorimotor cortex (M1/SI) did not reach the statistical threshold for null hypothesis rejection. Two fMRI studies were among the first to address the question of intensity coding specifically. In a study designed to compare ACC activations during a language task and pain, a regression analysis revealed a positive relationship between the change in BOLD amplitude and perceived electrical (median nerve) stimulus intensity below and above the noxious range within the rostral ACC (Davis *et al.*, 1997). This finding is in general agreement with another investigation focused on the medial cortex but which included SI and other mesial structures as VOI (Porro *et al.*, 1998). These researchers injected weak acidic solutions into one foot and found positive correlations of perceived stimulus intensity in the SI, M1, SMA, medial parietal and anterior and posterior cingulate cortex. Negative correlations with perceived pain intensity were found in the medial parietal, posterior and perigenual cingulate cortex and in the medial prefrontal cortex (Fig. 5.16).

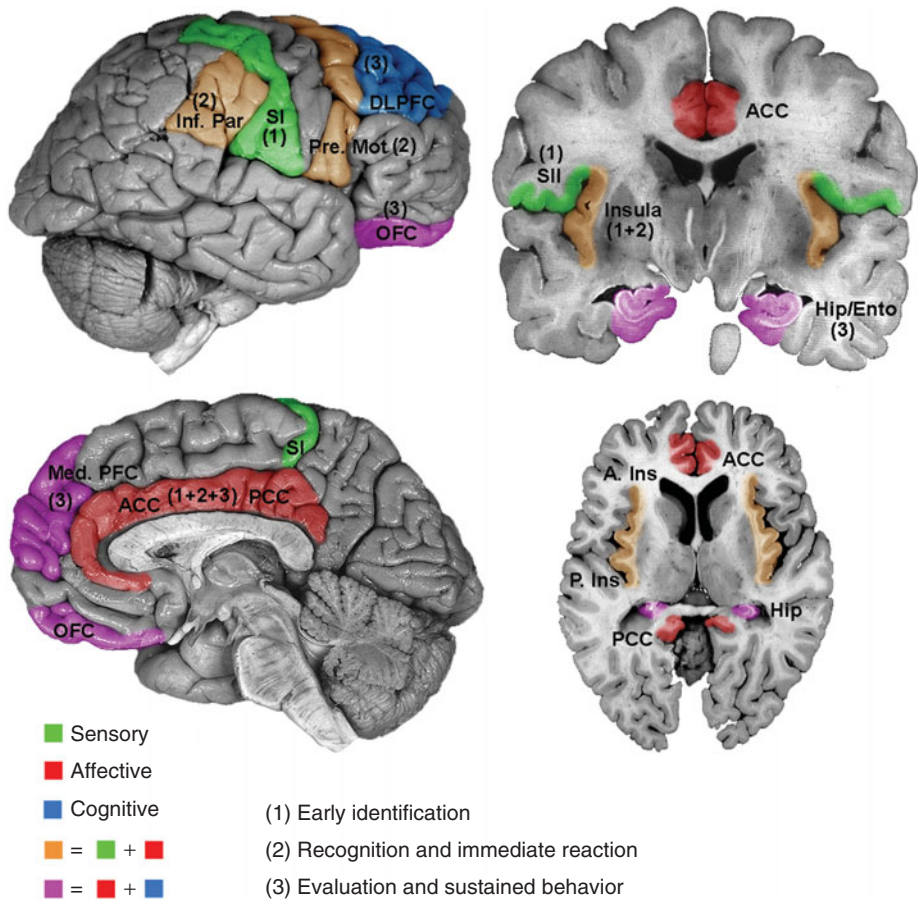


Fig. 5.14. According to a review by Casey and Tran (2006), the available evidence from multiple sources including functional brain imaging, electrophysiological recordings and clinical observations, suggests that the activity in each of the cortical areas shown here contributes to different components of the pain experience: sensory discrimination (green), affective (or hedonic) coding (red) and cognitive evaluation (blue). Some cortical areas contribute to both sensory and affective (brown) or to affective and cognitive (purple) components of pain. The suggested temporal aspect of cortical participation in pain and pain-related behavior is distributed as follows: (1) early identification; (2) recognition and immediate reaction; and (3) evaluation and sustained behavior. Although all cortical areas shown here are active early in the course of the elaboration of pain, the clinical, physiological and behavioral impact of each cortical area may vary at different times. In this figure, the major clinical, physiological and/or behavioral impact is indicated by the numbers shown within each cortical area. Thus, the sensory discriminative functions of the SI and SII cortices (#1) are most critical at the earliest stages of cortical pain processing while the cognitive processes mediated by the dorsolateral prefrontal cortex (DLPFC, #3) and the combined affective and cognitive functions of the entorhinal, hippocampal

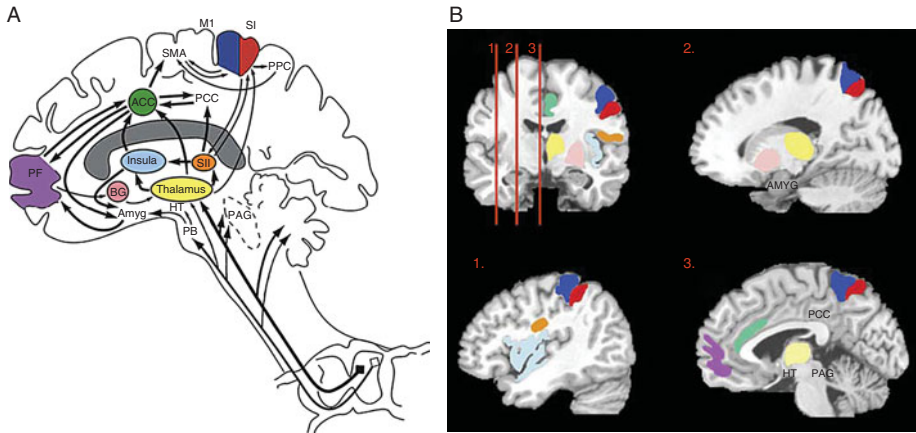


Fig. 5.15. Diagrammatic summary of brain activations (both PET and fMRI) during acute pain evoked by several different stimulation methods applied to healthy subjects. The left panel (adapted from Price, 2000), shows color-coded cortical and subcortical structures and the major pathways connecting them. The colors are applied to these same structures on an anatomically standardized brain shown in the right panel; sagittal views taken from slices indicated (1, 2, 3) on the upper left coronal view. Abbreviations: SI, primary, and SII, secondary somatosensory cortex; ACC, anterior cingulate; PF, prefrontal cortex; M1 and SMA, primary and supplementary motor cortices; PPC, posterior parietal cortex; PCC, posterior cingulate cortex; BG, basal ganglia; HT, hypothalamus; Amyg, amygdala; PB, parabrachial nucleus; PAG, periaqueductal gray. (Adapted from Apkarian *et al.*, 2005, figure 1.)

Coghill and colleagues investigated specifically the question of pain intensity discrimination (Coghill *et al.*, 1999) by applying a contact heat probe for 5 s repetitively to the skin of healthy individuals at four levels of heat intensity (35, 46, 48 and 50 °C) during the ~60 s of each H_2^{15}O PET scan. Subjects rated the

Caption for Fig. 5.14. (cont.)

(Hip/Ento, #3), medial prefrontal (Med. PFC, #3) and orbitofrontal cortices (OFC, #3) have their greatest influence on later long-term evaluations of the significance of the painful condition and the development of context-specific coping strategies. The combined sensory and affective components of the inferior parietal (Inf. Par., #2), premotor (Pre. Mot., #2), and the anterior and posterior insular (#1 and 2, respectively) cortices mediate the intermediate functions of stimulus recognition and immediate reaction. Converging lines of evidence suggest that the cingulate cortex, which integrates and mediates sensory and motor response functions, contributes to affective coding throughout the pain experience and even beyond (ACC and PCC, # 1+2+3). Adapted from Casey and Tran (2006).

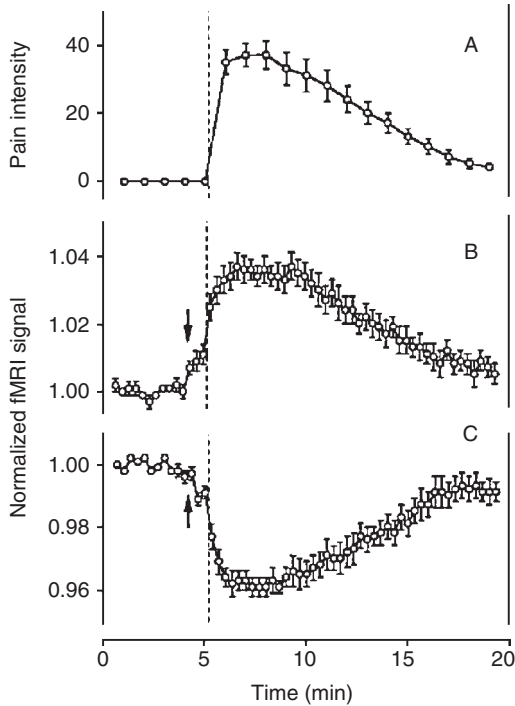


Fig. 5.16. Average ($\pm$ Se) psychophysical recording of pain intensity (A) following subcutaneous injection of mild acid into one foot of subjects during fMRI of mesial cortex. (B) Positive (upper) and (C) negative (lower) correlations of normalized BOLD signal change with perceived intensity. Positive correlations were found in SI, M1, SMA, medial parietal and anterior and posterior cingulate cortex. Negative correlations were found in the medial parietal, posterior and perigenual cingulate cortex and in the medial prefrontal cortex. Adapted from Porro *et al.* (1998).

intensity of stimulation after each scan (Fig. 5.17). Activations were compared to a rest (no heat stimulus) condition. Multiple regression analysis revealed a strong positive relationship between the intensity of activation (normalized Δ rCBF) and the perceived heat intensity bilaterally in the cerebellum, putamen, thalamus, insula, anterior cingulate cortex, and secondary somatosensory cortex, contralaterally in the primary somatosensory cortex and supplementary motor area, and ipsilaterally in the ventral premotor area (Fig. 5.18). Two regions of the right prefrontal cortex showed a response to heat stimulation that was not related to heat pain intensity. The authors interpret these results as showing that “... each cerebral hemisphere is independently capable of supporting conscious awareness of (the intensity) of a painful stimulus” and that “... pain intensity-related responses in regions important in motor control, affect, and attention suggests

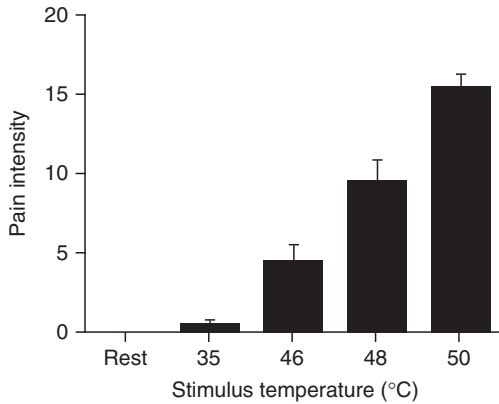


Fig. 5.17. Average ($\pm$ SE) verbal heat pain intensity ratings of 16 healthy individuals following heat stimulation while in the PET scanner. Adapted from Coghill *et al.* (1999).

that intensity-related processing can be utilized in functions other than those involved in the conscious awareness of sensory features of a painful stimulus.” In a subsequent PET activation study using similar methods of analysis, Coghill *et al.* (2001) used noxious and innocuous heat stimulation to investigate the possibility of hemispheric lateralization of pain. The results failed to identify any hemispheric lateralization of pain intensity-dependent processing; instead, pain intensity-dependent activation was detected in the same structures of each hemisphere regardless of the side of stimulation. However, the investigators found a right lateralization of both innocuous and noxious stimuli in portions of the thalamus and in the inferior parietal cortex, and in frontal cortical areas, consistent with the well-known neglect syndrome following right hemispheric lesions in humans (Heilman and Valenstein, 1972; Watson and Heilman, 1979; Stein and Volpe, 1983).

In a related fMRI study, psychophysical testing was used to separate healthy individuals into those with high or low pain ratings of heat stimulus intensity (Coghill *et al.*, 2003). The individuals with high ratings showed more frequent and more robust pain-induced BOLD responses in the SI, ACC and prefrontal cortices compared with subjects who gave low ratings; however, there was no group difference in thalamic activation.

Hofbauer and colleagues used hypnotic suggestion to modulate specifically the perceived intensity of heat pain (immersion of the hand in water) in healthy subjects and contrasted the Δ rCBF response during suggestions for increased and decreased heat pain intensity (Hofbauer *et al.*, 2001). In a VOI analysis, these investigators found a significant response increase in SI cortex during the

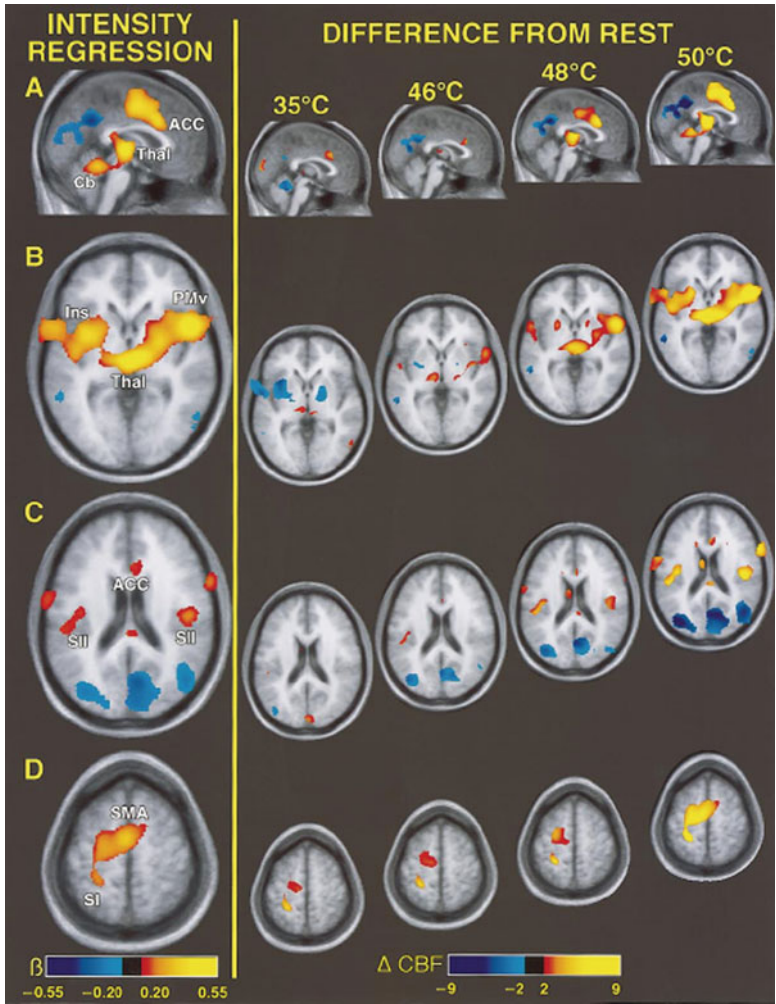


Fig. 5.18. Left panel shows the result of a multiple regression analysis of the perception of heat pain intensity with rCBF response amplitude in 16 healthy individuals; regression coefficients are color coded (red–yellow = positive, blue–violet = inverse relationship). Right panel shows regions with a progressive increase in δ rCBF with increasing stimulus temperature. The left side of the image corresponds to the subjects' left. ACC, anterior cingulate cortex; Thal, thalamus; Cb, cerebellum; Ins, insula; PMv, ventral premotor cortex; SII, secondary somatosensory cortex; SI, primary somatosensory cortex; SMA, supplementary motor area. Adapted from Coghill *et al.* (1999).

suggestion of increased pain compared with a hypnotic rest condition or compared with the suggestion of decreased pain (Fig. 5.19). These induced changes were not found in the SII or anterior cingulate cortex (ACC), but a “mixed response” was found in the contralateral insular cortex (IC), which revealed an

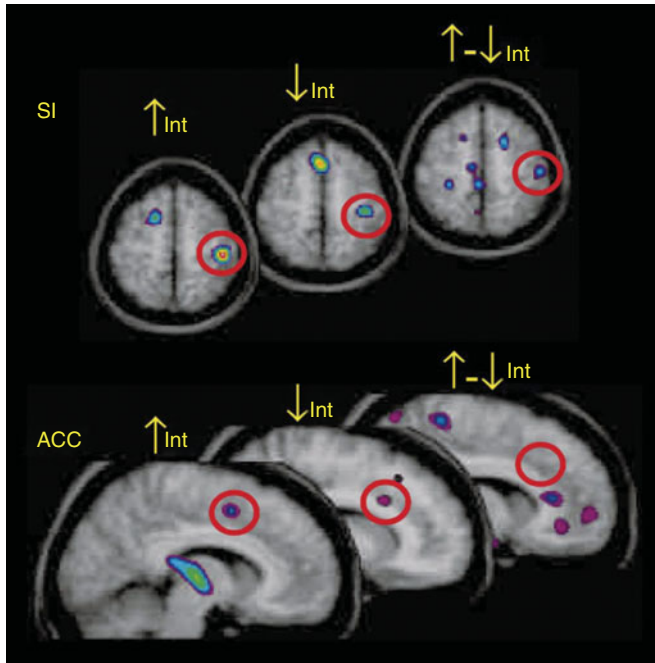


Fig. 5.19. Upper images show significant (yellow-red) regional cerebral blood flow (rCBF) changes in pain-related activity within primary somatosensory cortex (SI; red circles in right hemisphere) associated with hypnotic suggestions for increased $\uparrow$ or decreased $\downarrow$ heat pain intensity (left hand); the $\uparrow - \downarrow$ image shows the comparison of these two conditions, confirming a significant difference. (The medial frontal cortex responded only during the $\downarrow$ condition as shown in the middle image.) Lower images show similar rCBF responses in the anterior cingulate cortex (ACC); these did not reach statistical threshold. Adapted from Hofbauer *et al.* (2001).

increased response in the middle IC during suggested increased pain and in the rostral IC during suggested decreased pain.

Cutaneous infra-red laser stimuli were used in an fMRI investigation of intensity discrimination in the ACC (Buchel *et al.*, 2002). These investigators found regions in the ventral posterior ACC that did not show differential BOLD responses to innocuous stimuli, but showed a positive linear relationship with the BOLD signal amplitude during painful laser stimulation. Other regions in the ACC responded to stimulation but did not respond differentially to intensities within the noxious range. In a follow-up investigation (Bornhove *et al.*, 2002), this laboratory again used four intensities of laser stimulation to examine intensity coding in several additional cortical structures. The authors used a regression analysis to show that BOLD responses in the SI cortex followed stimulus intensity both below and within the perceived noxious range except for the highest

intensity. Responses in the insular, adjacent SII cortex and amygdala followed stimulus intensity only within the range of noxious stimuli although the latter structure also showed high responses during low-intensity trials that were not perceived, suggesting to the authors a role in encoding uncertainty. These results have been partially confirmed in an fMRI study by Alkire *et al.* (2004), who used tonic electrical stimulation to produce a sensation of deep aching pain. By modeling the BOLD response with a priori stimulus-response functions, they also obtained evidence for SI coding below and within the noxious range, graded SII responses primarily within the noxious range and ACC responses only at the highest pain intensity.

In an investigation of the mechanisms supporting the perception of the temporal summation of the intensity of the “second pain” sensation, which follows repetitive noxious contact heat stimulation, BOLD responses correlated with the intensity of this sensation were detected in the contralateral thalamus, SI, bilateral SII, anterior and posterior IC, mid-anterior ACC and the supplementary motor area (SMA) (Staud *et al.*, 2007).

In studying brain activations putatively encoding perceived pain intensity (as a sensory function) the question arises as to whether this activity may be related, in whole or in part, to the cognitive evaluation of pain (as a cognitive function only). To address this question, Kong *et al.* (2006) required subjects to delay their evaluation (cursor-indicator visual analog scale or VAS) of contact heat pain intensity until after the stimulus. During this evaluation time, the subjects could evaluate pain intensity for only half of the stimulus trials; during the other trials they were asked to move the cursor to an investigator-determined VAS target without evaluating heat intensity. Innocuous and noxious heat intensity activations were compared in contrast analyses, which included conjunction analysis. Compared with innocuous heat, activations during heat pain included the expected activation pattern of bilateral insular and opercular cortices, the ACC/medial prefrontal cortex, SII, thalamus, cerebellum and left SI (contralateral) cortex. Cognitive evaluation of pain intensity alone activated the bilateral anterior insular cortex/frontal operculum, the dorsal lateral prefrontal cortex, bilateral medial prefrontal cortex/anterior cingulate cortex, right superior parietal cortex, inferior parietal lobule, orbital prefrontal cortex and left occipital cortex. Conjunction analysis revealed that BOLD responses in both the bilateral anterior insula/frontal operculum and medial prefrontal cortex/anterior cingulate cortex were consistent with both intensity coding and cognitive evaluation of noxious heat stimulation (Fig. 5.20) (Kong *et al.*, 2006). The authors suggest that these structures may provide a bridging function that connects the encoding of the sensory aspects of pain with the cognitive evaluation of sensory input.

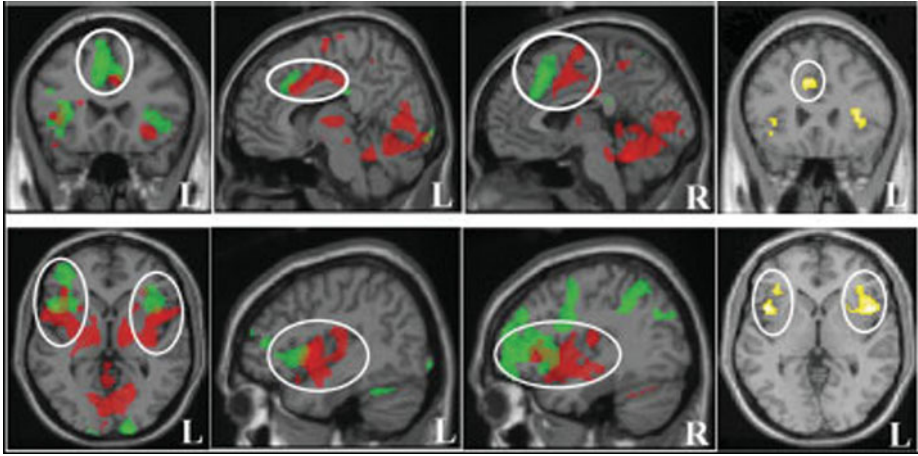


Fig. 5.20. Brain activations during the encoding of heat pain intensity (red), the cognitive evaluation of heat pain (green) and during both conditions as shown by conjunction analysis (yellow). Cingulate cortex activations are shown in top panels and insular/opercular and prefrontal activations are shown below. Adapted from Kong *et al.* (2006).

Given the overall results of the studies reviewed above, it is tempting to consider that the activation of these brain structures during pain reflects, to some degree, the intensity of activation of peripheral nociceptors and their afferent fibers. However, Craig and colleagues showed that an illusion of pain can be evoked, along with the activation of the insula and ACC, by contacting glabrous skin with closely spaced innocuous cool and warm bars (Craig *et al.*, 1996). Therefore, pain and the activation of at least these structures may not require the stimulation of high-threshold nociceptors; indeed, Green and colleagues have shown that nociceptive sensations are produced during the stimulation of low-threshold receptors for heat and cold (Green and Pope, 2003; Green, 2004; Green *et al.*, 2008).

Location and somatotopy

A PET study revealed a differential localization of activation in the area of the postcentral gyrus following the intradermal injection of capsaicin into the foot and hand (Andersson *et al.*, 1997) and intra-operative optical imaging was used in conjunction with evoked potential recording and median nerve stimulation to identify the hand area in human cortex (Shoham and Grinvald, 2001). However, the spatial resolution limitations of PET and the invasive procedure required for optical imaging place serious limitations on these methods for investigating somatotopic organization in the awake human brain. Functional

MRI has sufficient spatial resolution to reveal spatially distinct activations in SI cortex during kinesthetic and tactile stimulation. Thus, punctuate tactile stimulation activated cortical sites, corresponding to areas 6, 3b, 1 and 2 in the human precentral and postcentral gyri, but not area 3a; kinesthetic stimulation, however, additionally activated area 3a and the precentral areas 6 and 4, and the postcentral gyrus (areas 3b, 1 and 2) (Moore *et al.*, 2000). These results suggest that similar results are at least possible when noxious stimuli are used.

Based on the results of previous neurophysiological and anatomical studies (Blomqvist *et al.*, 2000), Brooks and colleagues investigated the somatotopic organization of the human insular cortex using fMRI and painful heat stimulation (49.6, 48.5 and 48.5 °C) (Brooks *et al.*, 2005). Group activation maps suggested a somatotopic organization in the contralateral posterior insula and putamen with face activations anterior to hand and foot; foot activations were medial to both hand and foot. Single subject analysis showed that the average standard space location for foot activation was 5 mm medial to that of face and hand; face activation was 3 mm anterior to hand, which was 2 mm anterior to that of the foot. These findings are in general agreement with a subsequent laser-evoked potential study showing a similar somatotopic arrangement in the insular cortex of anesthetized monkeys (Baumgartner *et al.*, 2006). Another fMRI study used non-painful and painful electrical stimulation of the median and tibial nerves to examine somatotopy in the human ACC and supplementary motor area (SMA) (Arienza *et al.*, 2006). Both non-painful and painful stimuli produced median nerve activations that were more anterior (ACC) or more inferior (SMA) than those obtained during tibial nerve stimulation. Finally, Oshiro and colleagues used fMRI in a delayed match-to-sample task to investigate activations related specifically to discriminating between locations of a noxious contact heat stimulus (Oshiro *et al.*, 2007). Subjects were required to determine whether the locations of two temporally separate painful heat stimuli were different (Fig. 5.21). In their analysis, the investigators used a regressor that compared brain activity during the second stimulus (the time of the spatial discrimination task) with that during the first stimulus (before the spatial discrimination task). Activations related only to pain were also examined. Activations related specifically to discriminating between the locations of painful heat stimuli were found in the prefrontal, anterior cingulate and posterior parietal cortices: subcortical activations were in the thalamus and caudate (Fig. 5.22). Similar results were obtained during the discrimination of innocuous cool stimuli. Notably, no discrimination-related activations during heat pain or innocuous cool stimulation were found in the SI, SII or insular cortices. As the authors point out, this discrimination task "... does not allow the identification of brain mechanisms that contribute to basic awareness of the spatial location of a single stimulus ..."

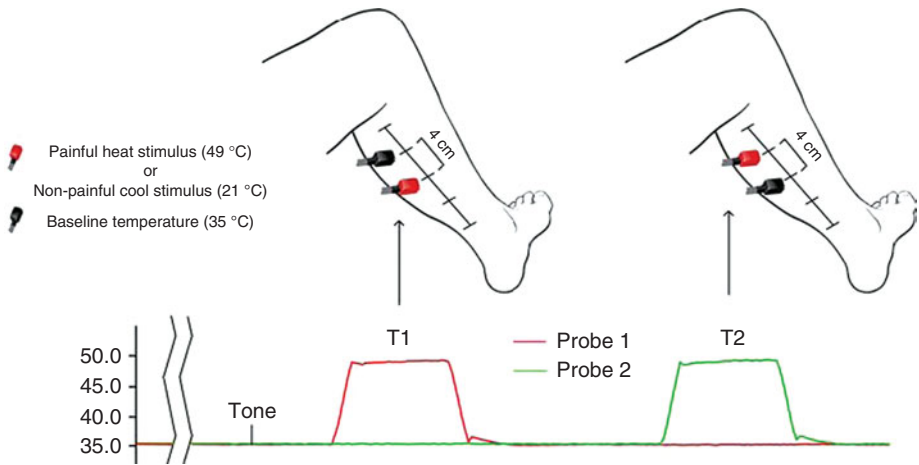


Fig. 5.21. Delayed matching-to-sample task used to identify brain activations during spatial discrimination of noxious heat or innocuous cool stimuli. Heat stimulus intensity ($^{\circ}\text{C}$) is shown at the lower left. Following a comparison stimulus (T1), the subject must indicate whether the test stimulus (T2) is at a different location; the response must be given before the end of the T2 period, during the discrimination decision. Adapted from Oshiro *et al.* (2007).

but it does show that information related to detecting spatial differences is distributed among cortical and subcortical structures that are not associated with a refined somatotopic organization or with the ability to localize somatic stimuli as determined by cellular recording or lesion studies.

Temporal characteristics

What forebrain mechanisms are responsible for the ability to detect the duration and frequency of noxious stimuli and the accompanying perceptual changes? Derbyshire and Jones addressed this question directly using H_2^{15}O PET and comparing the cerebral activation pattern obtained during the immersion of one hand (for the 2 minutes of the scan) in hot (compared with innocuous warm) water with the activations observed in six previous studies using the phasic (brief repetitive) application of noxious heat to the skin (Derbyshire and Jones, 1998). The resulting activation pattern was similar to that obtained with phasic heat stimulation, showing bilateral responses in the anterior cingulate cortex, contralateral responses in the lentiform nucleus and posterior insula, and ipsilateral responses in the thalamus, cerebellum, prefrontal and anterior insular cortex. The authors interpreted these findings as demonstrating "... general agreement between the main areas of cerebral activation during both phasic and tonic pain."

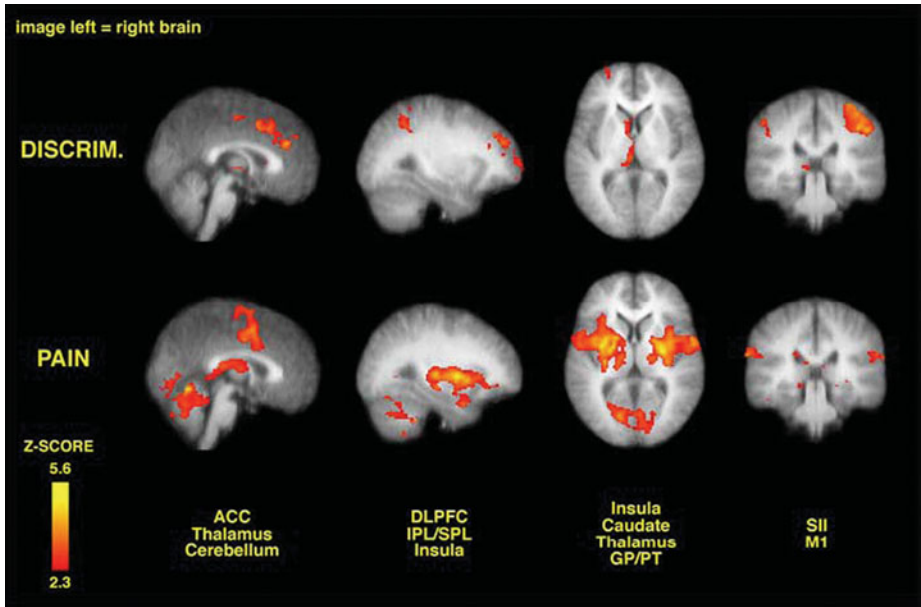


Fig. 5.22. Upper images show brain activations appearing specifically while subjects detected spatial differences between noxious heat stimuli (see Fig. 5.20). Lower images show brain activations during the perception of heat pain without regard to stimulus location. Adapted from Oshiro *et al.* (2007).

In an fMRI investigation related to the coding of intensity during prolonged stimulation, Chen and colleagues compared the time courses of the BOLD responses in the SI and SII cortices (VOI analysis) to 9 seconds of repetitive tactile brushing (at 2 Hz; contrasted with rest) and cutaneous contact heat (45–46 °C; contrasted with innocuous warmth). The participants perceived the brushing as having a constant intensity throughout the stimulation and the BOLD response showed, following the expected delay, a constant level of activation throughout but not beyond this period. The heat stimulus, however, was perceived as increasing in intensity during and slightly beyond the thermode contact period; accordingly, the BOLD response showed a delay in the maximum peak response, which persisted following stimulus withdrawal (Fig. 5.23) (Chen *et al.*, 2002). Because they observed these responses in both SI and SII cortices, the authors conclude that both structures encode the changes in perceived intensity associated with increasing durations of noxious stimuli.

In a subsequent fMRI study, Moulton and colleagues applied three intensities of noxious contact heat (41 °C and two noxious temperatures 1 and 2 °C below “tolerance”) for 16 seconds to investigate the BOLD responses in VOI within the

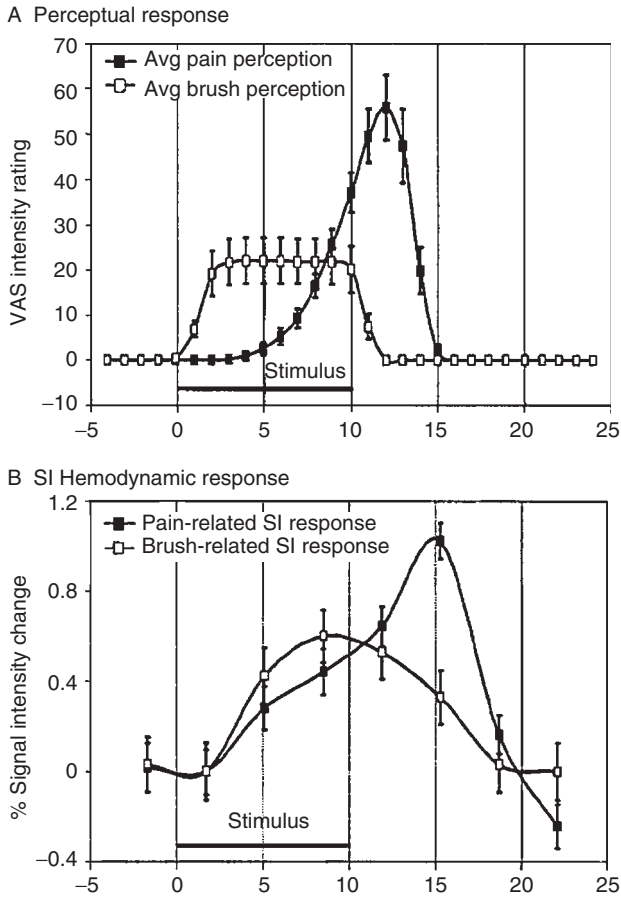


Fig. 5.23. Perceptual (A) and BOLD (B) responses in SI cortex to tactile (open squares) and noxious contact heat stimuli (filled squares). Abscissa: peristimulus time in seconds. The delay in BOLD response is consistent with the hemodynamic response delay. Adapted from Chen *et al.* (2002).

SI, SII, insular, ACC, inferior frontal and SMA cortices (Moulton *et al.*, 2005). Their analysis detected responses to both innocuous and noxious stimuli in the contralateral SI, the mid-ACC and SMA; only noxious stimuli activated the insula. In a subtraction contrast, the peak BOLD response to noxious stimulation was delayed 6–8 s from the innocuous response and a more prolonged response to the most noxious stimulus was detected only in the SI cortex, suggesting a temporal component of intensity coding (Fig. 5.24). The authors suggest that several cortical areas can encode a temporal distinction between innocuous and noxious stimuli but that the SI cortex response suggests that SI best encodes differences in the intensity of noxious stimuli.

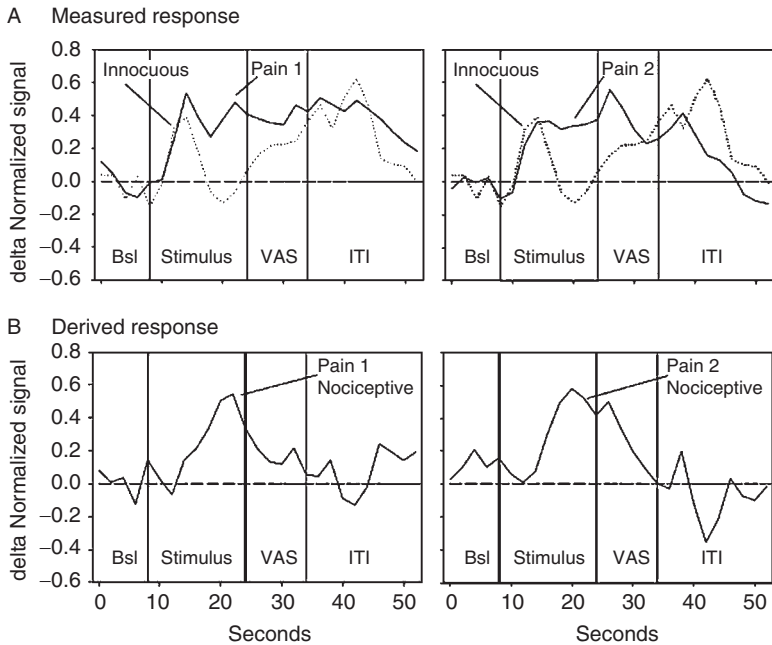


Fig. 5.24. BOLD responses in SI cortex to 16 seconds of innocuous (broken lines, top panels) and noxious heat stimulation (solid lines). Bsl, baseline; VAS, poststimulus visual analog scale rating; ITI, inter-trial interval. The top panels (A) show the response to both stimulus intensities; the lower panels (B) show the results of subtracting out that portion of the response during innocuous stimulation. The response to “Pain 2” (right lower panel), the more intense noxious stimulus, is more prolonged than that to “Pain 1,” the less intense noxious stimulus (left lower panel) although the stimulus durations are identical, suggesting a temporal component of intensity coding. Adapted from Chen *et al.* (2002).

We are not aware of imaging studies that have investigated specifically the question of encoding the frequency of noxious stimuli. However, Staud and colleagues have used fMRI and contact heat to examine the cerebral mechanisms underlying the temporal summation of the perceived intensity of the “second pain” sensation that follows the brief repetitive application of noxious contact heat to the skin (Staud *et al.*, 2007). The critical stimulus frequency for contact heat pulses of 3 s duration is 0.33 Hz, so this critical frequency was contrasted with stimulation at 0.17 Hz in a VOI analysis (Fig. 5.25). Activations in the thalamus, and the SI, SII, anterior insular and anterior cingulate cortices correlated with pain intensity ratings; additional activations included the peri-aqueductal gray, cerebellum, posterior insula, mid-anterior cingulate and pre-frontal cortex, and the supplementary motor areas (Fig. 5.26). This study shows again the multi-regional distribution of information about perceived stimulus

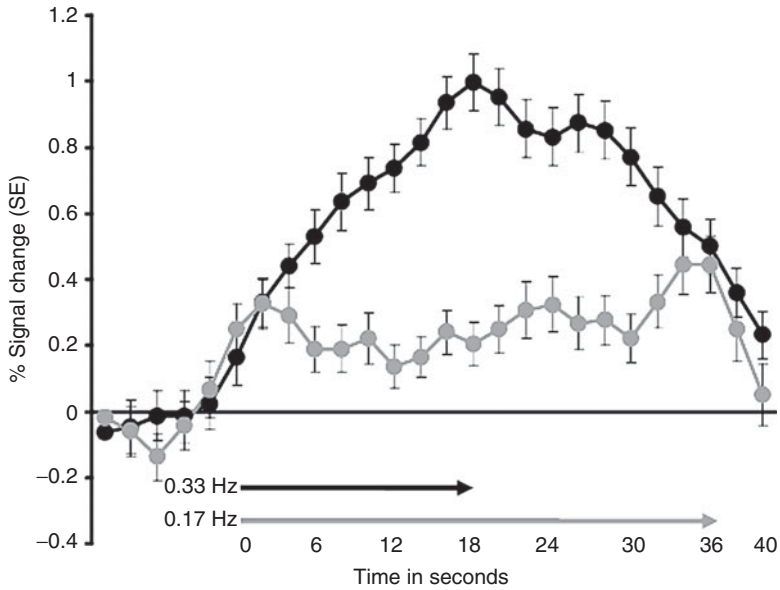


Fig. 5.25. BOLD signal increase during the perceived temporal summation of six noxious heat pulses applied to the skin at 0.33 Hz (black circles and arrow) or at 0.17 Hz (gray circles and arrow). The enhanced activation persists following the end of the 0.33 Hz, but not the 0.17 Hz, stimulus, which is consistent with the poststimulus persistence of heat pain following the higher frequency stimulus. Adapted from Staud *et al.* (2007).

intensity, the activation of structures shown elsewhere to be active during cognitive evaluations (Kong *et al.*, 2006), and suggests a temporal limit for the frequency discrimination of a type of pain thought to be mediated by unmyelinated (C) fibers.

If either innocuous or noxious stimuli are delivered repetitively during an experimental session or on repeated days, there is a decline in perceived stimulus intensity and in the amplitude of cerebral-evoked potentials; this habituation is attributable to peripheral and central mechanisms (Bjerring *et al.*, 1988; McLaughlin and Kelly, 1993; Greenspan and McGillis, 1994; Greffrath *et al.*, 2007). Bingel *et al.* (2007) investigated habituation mechanisms following the repetitive application of noxious heat to healthy individuals for 20 minutes on eight consecutive days. In a selected VOI analysis of fMRI activations, they tested the hypothesis that, over this eight-day period, brain regions known to attenuate pain perception would become more responsive to the stimulation while brain regions known to respond differentially to noxious stimuli would become less responsive. As expected, the participants gave decreased VAS pain ratings to physically identical heat stimuli as the trial period progressed and the BOLD

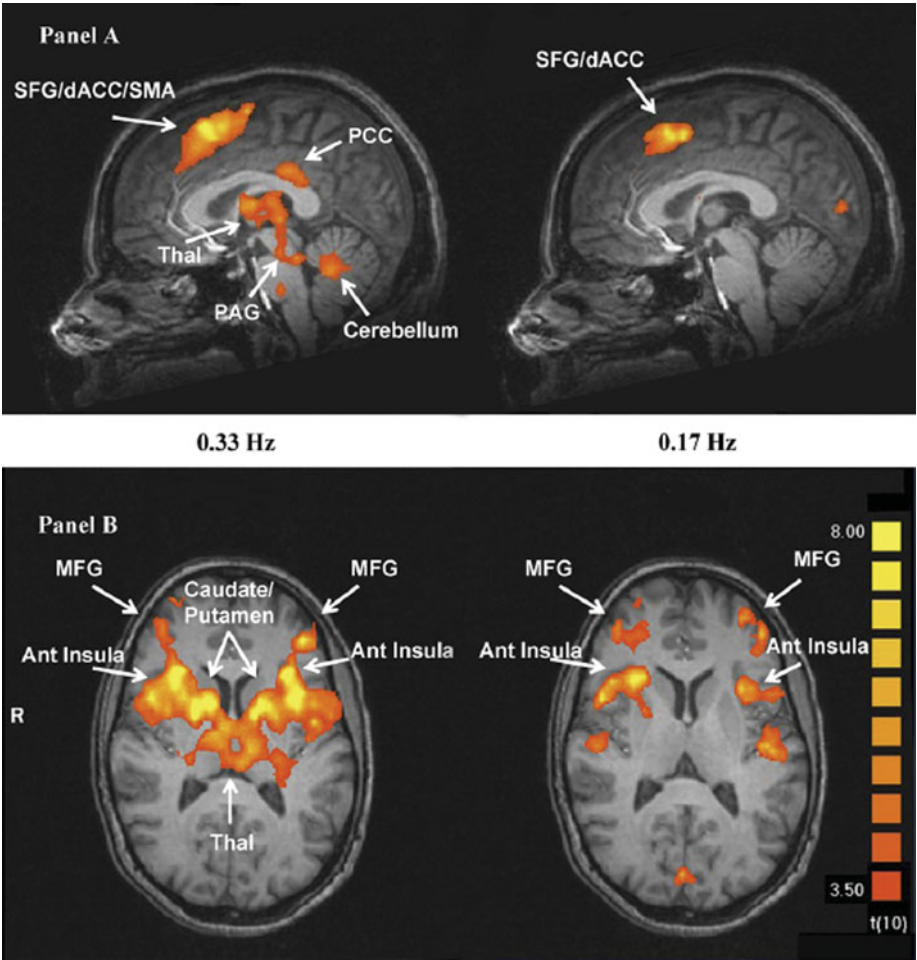


Fig. 5.26. Brain activations during the perceived temporal summation of heat pulses delivered at 0.33 Hz (left) or 0.17 Hz (right). Activations show the differences between the last stimulus of short (two stimuli) and long trains (six stimuli) at 0.33 Hz (left) and 0.17 Hz (right) (t values indicated by color bar). (THAL, thalamus; SFG, superior frontal gyrus; dACC, dorsal anterior cingulate cortex; PCC, posterior cingulate cortex; SMA, supplemental motor area; PAG, periaqueductal gray; MFG, middle frontal gyrus. Adapted from Staud *et al.* (2007).

responses in the thalamus, insula, SII cortex and putamen decreased accordingly. BOLD responses in the subgenual ACC, however, increased during this period, consistent with evidence that this region participates in the attenuation of responses to nociceptive stimuli (Casey *et al.*, 2000; Bantick *et al.*, 2002; Rainville, 2002).

The investigations reviewed above concentrated on activation differences within pain-activated structures. However, do the cerebral structures activated during acute pain maintain their level of activity over time; or does the pattern of activation among structures change with the duration of the stimulus? Noxious stimulus durations of 60 and 100 s were compared in a H_2^{15}O PET study by applying repetitively 5 s duration noxious (50°C) or innocuous (40°C) contact heat stimuli during different phases of PET data acquisition (Casey *et al.*, 2001). In a separate psychophysical session, participants gave increased verbal scale ratings of heat pain intensity and increased graphical ratings of heat pain unpleasantness to the last 5 of 20 repetitive 50°C but not 40°C stimuli. These stimuli were then applied throughout every scan and began either within ~ 10 s of the onset of PET data acquisition (early scans) or for 40 s before the scan (late scan). Data acquisition time (~ 60 s) was equal for the two conditions (Fig. 5.27). In the contrast analysis (40 – 50°C), several structures showed either increasing or exclusive activations only during the late scans (more prolonged stimulation); these included the contralateral M1/SI cortex, bilateral SII and mid-insular cortex, contralateral VP thalamus, medial ipsilateral thalamus and the vermis and paravermis of the cerebellum (Fig. 5.28A, B). These structures are presumably participating in the encoding of the perceptual differences detected in the psychophysical study. Structures that were equally active during both conditions (contralateral mid-ACC and premotor cortex) and those with significant or borderline activation only during the early scans (ipsilateral premotor cortex, contralateral pregenual anterior cingulate, lateral prefrontal and anterior insular cortex) may mediate pain-related attentive or anticipatory functions but are less likely participants in the changes in perceived intensity or unpleasantness that occur over this ~ 40 s time period. The combined results of this study and of those reviewed above show that the perception of heat pain and the pattern of brain activation within and among forebrain structures both change as the duration of noxious heat stimulation increases.

Summary

Given current imaging technology and the inertia of the hemodynamic response, it is not possible to achieve the physiological, spatial or temporal resolution that is available with neurophysiological studies such as evoked potential, magnetic, or single and multiple cellular analysis. For example, Ploner and colleagues were able to show, using magnetoencephalographic (MEG) analysis, that noxious laser stimulation activates a spatially specific region (area 1) of the SI cortex that is distinct from that responsive to tactile stimulation

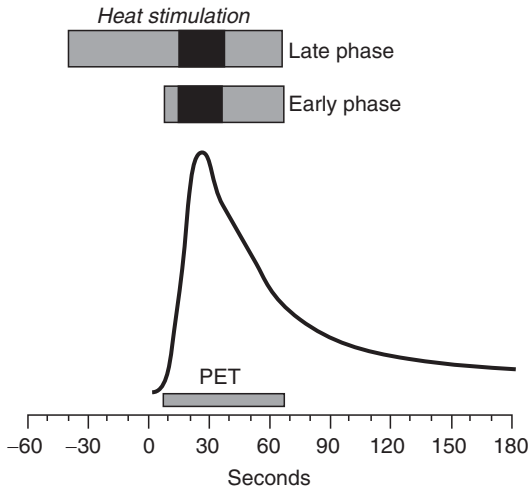


Fig. 5.27. Timing of “early” and “late” scans with respect to heat stimulation. Time course of radiation count at the subject’s head is shown from time of arrival of the tracer bolus at 0 s. Time of positron emission tomography (PET) data acquisition is shown below this input function (PET). For the late scans, PET data were collected during the late phase of heat stimulation (top bar), which began 40 s before bolus arrival at the head and continued for the duration of the scan. Early scans began at the early phase of heat stimulation (bottom bar), which began at the time of bolus arrival. Dark sections of the stimulus bars show the period of maximum signal-to-noise ratio for PET acquisition. Adapted from Casey *et al.* (2001).

(Ploner *et al.*, 2000). In contrast, contemporary functional imaging cannot identify the critical and unique physiological and anatomical characteristics of brain structures that explain the ability of humans to detect accurately the intensity, location and timing of noxious cutaneous, muscular and, to a lesser but clinically significant degree, visceral stimuli (Schnitzler *et al.*, 1999; Schlereth *et al.*, 2001; Quevedo and Coghill, 2007). However, the review above shows that information about the relative intensity, location and temporal characteristics of noxious stimuli is distributed, albeit unevenly, among several cortical and sub-cortical structures in the primate brain including the cerebellum, thalamus, putamen, primary (SI) and secondary (SII) somatosensory cortices, primary motor, premotor and supplementary motor cortices, the anterior and posterior cingulate cortex, the anterior, middle and posterior insula, and the medial and lateral prefrontal cortices. With the exception of the cingulate cortex, these areas of the cerebral cortex are included in Fig. 5.14 as participants in sensory (green) or combined sensory and affective functions (brown); this depiction is based on combined imaging, electrophysiological and clinical information,

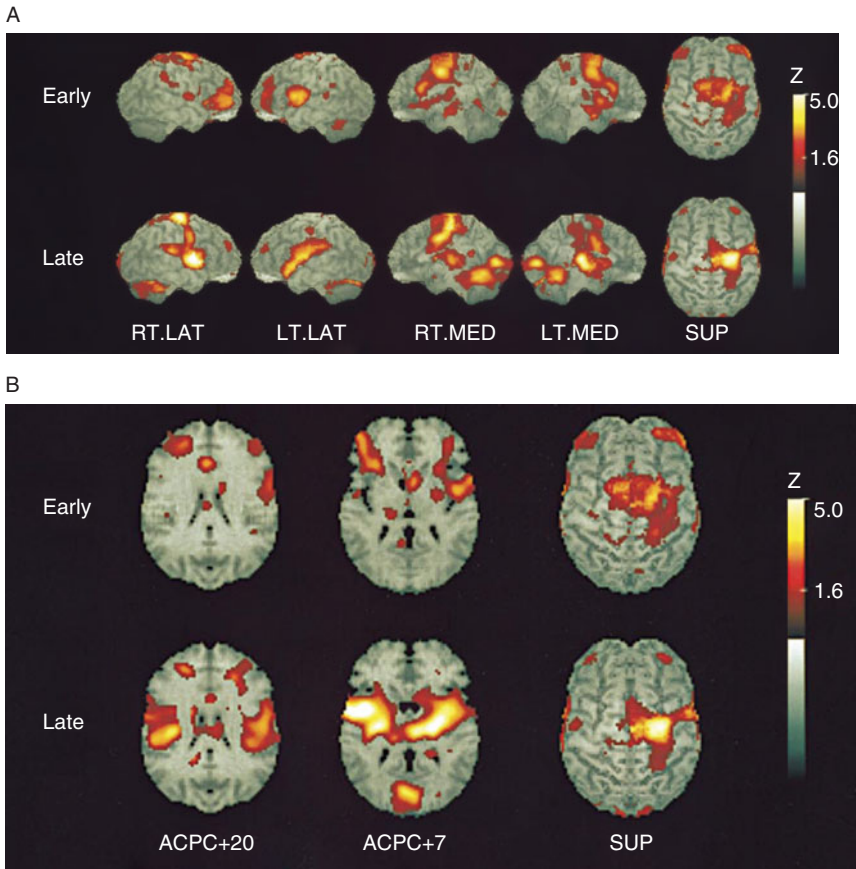


Fig. 5.28 A. Surface-rendered subtraction images of activation patterns obtained with early (top) and late (bottom) PET scans. Right hemisphere is contralateral to the heat stimulation. Flame bar shows color coding of Z-scores, indicating the statistical deviation of regional cerebral blood flow (rCBF) increase from mean global blood flow when the effect of repetitive innocuous warm stimulation (40°C) is subtracted from the effect of repetitive painful heat stimulation (50°C). Scans that began at the onset of painful heat stimulation (early scans) reveal activity bilaterally in the right medial (upper convexity; SUP view) and left lateral (frontal operculum) premotor cortex, the mesial contralateral mid-anterior and perigenual cingulate cortex, and in the right (ipsilateral) lateral prefrontal cortex. Scans that began after 40s of noxious heat stimulation (late scans) show, in this view, responses bilaterally in the mid-anterior cingulate cortex, mid-insula, thalamus and cerebellum. Late contralateral responses in the sensorimotor and premotor cortices are seen best in the superior (SUP) view. B. Transverse and superior (SUP) images of responses shown in the same format as Fig. 4.28A. Transverse levels are indicated as millimeters above a plane connecting the anterior and posterior commissures (AC-PC). This view shows best the significant and borderline bilateral insular, thalamic, lenticular nucleus and cerebellar responses that occur only in the late scans. A and B adapted from Casey *et al.* (2001).

which suggests that the cingulate cortex mediates predominantly the affective aspect of sensation and behavior. Sensory information is presumably used differently by component members of the network of structures activated during pain. Additional studies are needed to determine how each structure uses sensory information; these would include analyses of patterns of within-cluster voxel activation and other methods that complement functional imaging.

The hedonic (affective) component of pain

Conceptual considerations

Recent discussions about this topic have concerned refinements to our understanding of this term (Clark and Yang, 1983; Wade *et al.*, 1996; Fields, 1999; Price, 1999, 2000; Price and Verne, 2002). There is general agreement that a negative affective experience accompanies pain, meaning that pain is normally unpleasant; this is expressed in the definition of pain proposed by the International Association for the Study of Pain (IASP) and shown below:

(Pain is) An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. (bold underlining added)

Does the hedonic component *follow* pain and is therefore the consequence of an independent sensory experience or do the sensory and hedonic components occur *together* and are physiologically inseparable? The evidence, some of which is presented below, supports the view that the unpleasant aspect of pain is experienced as both temporally contiguous and delayed. Fields has referred to the former as “primary unpleasantness,” to be regarded, in part, as a sensory function (Fields, 1999). (He proposed the term “algoty” to refer to the stimulus-bound nature of this aspect of unpleasantness as combined with sensory discrimination.) The delayed component has been called “secondary unpleasantness” (Fields, 1999), which develops during and following an analysis of the immediate and historical context of pain by derivative cortical processes; therefore it is a cognitive process. By designing experiments that alter the context in which a noxious stimulus is delivered, pain imaging studies can reveal structures that are active primarily and perhaps exclusively during the cognitive evaluation of the stimulus, including “secondary unpleasantness.” However, as discussed above, only electrophysiological studies, combined with psychophysical analysis, have the temporal resolution to show that some hedonic and sensory-discriminative components of pain are activated in parallel and nearly simultaneously (see below and Ploner *et al.*, 1999; Schnitzler and Ploner, 2000).

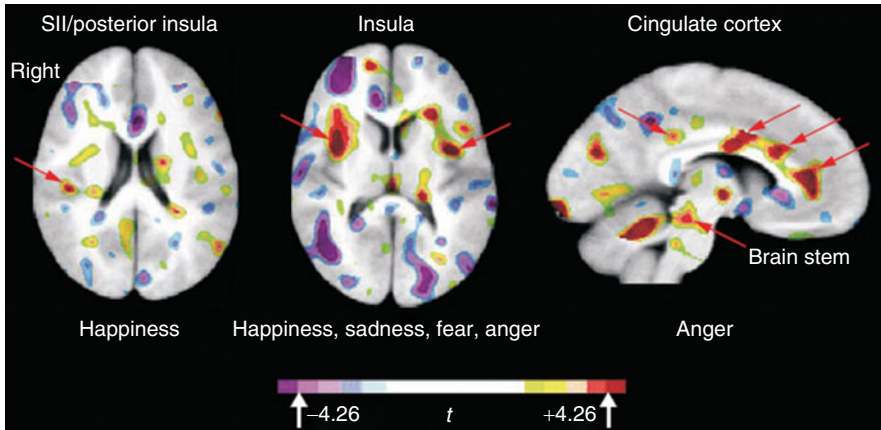


Fig. 5.29. Brain activations (PET, significant increases in red) during self-generated feelings of recalled happiness (left image) or anger (right sagittal image) compared with hedonically neutral recall. Middle image shows insular activations during each of the emotional states examined. Adapted from Rainville (2002) from Damasio *et al.* (2000).

Separating the hedonic and sensory components in functional imaging

To identify brain regions that are active specifically during an hedonic experience, Damasio and colleagues performed a H_2^{15}O PET study of individuals who re-experienced emotional states, including happiness, sadness, fear and anger, during the recall of earlier emotionally charged events (Damasio *et al.*, 2000). Autonomic monitoring (heart rate, skin conductance) was used to corroborate reports of the emotional experience. Although the resulting activations were complex and included several structures not typically activated during pain studies, the upper midbrain, thalamus, cingulate (primarily anterior), insular, SII and orbitofrontal cortices were prominently, and often specifically, activated during sadness and anger (Fig. 5.29). Similar results, with the addition of medial thalamic activation, were obtained during externally and internally evoked emotion by Reiman *et al.* (1997). Although not specifically included in recent reviews of pain-activated structures (Treede *et al.*, 1999; Apkarian *et al.*, 2005), the orbitofrontal cortex (OFC) participates in the elaboration of both negative and positive hedonic experiences as part of a punishment–reward mechanism (Rolls, 2000) and is activated during studies of heat (Craig *et al.*, 2000) and visceral (Derbyshire, 2003) pain and in simulated pathological pain states (Lorenz *et al.*, 2002). Thus, several of the structures active during pain-independent negative hedonic states, as identified by Damasio *et al.* (2000), are active also during pain (Rainville, 2002). The activation of the insular cortex during emotional states

and pain is consistent with functional imaging evidence (Critchley *et al.*, 2004) and Craig's hypothesis that the insular cortex is a critical component of a cerebral network (including somatomotor cortex and the ACC) mediating interoceptive states, feelings and homeostatic functions generally (Craig, 2002, 2003a, 2003b).

Rainville and colleagues were the first to demonstrate an anatomical and physiological separation of hedonic and sensory-discriminative aspects of pain (Rainville *et al.*, 1997). Normally, it is difficult, if not impossible, to uncouple these pain components. However, this uncoupling can be accomplished with hypnosis. In this PET study, psychophysical analysis showed that, during the appropriate hypnotic suggestion, subjects perceived noxious contact heat of equal intensities as having increased or decreased unpleasantness. The hypnotic state alone had no effect on the perception of pain or brain activation in this study. However, as perceived unpleasantness, but not intensity, increased under hypnosis, activation increased within the mid-anterior cingulate cortex, but not within the SI cortex (Fig. 5.30A, B). Vogt has recently refined the functional localization of pain and emotion within the context of cytoarchitectural information (Vogt, 2005).

In a follow-up PET study, hypnotic modulation specifically of perceived heat intensity increased in SI, but not ACC activation (Hofbauer *et al.*, 2001). In the study of unpleasantness modulation, the authors suggest that the hedonically related ACC activation may reflect "... the emotional experience that provokes our reactions to pain," thus favoring a "secondary unpleasantness" interpretation. It is notable, however, that MEG analysis shows the response latencies of the human ACC and SI/SII cortices to be approximately equal for the "first pain" sensation although the SII cortex and ACC show unique delayed "second pain" responses (Ploner *et al.*, 2002). Moreover, simultaneous recordings of laser-evoked potentials directly from the human SI and medial frontal cortices (including ACC) show that the latencies of both N and P components are within 10–20 ms of one another (Ohara *et al.*, 2004).

In another effort to uncouple the hedonic and sensory aspects of pain, Tolle *et al.* (1999) applied triplets of cutaneous noxious heat, innocuous heat and neutral stimuli repetitively and asked participants to provide separate ratings of perceived intensity and unpleasantness after each triplet. The unpleasantness, but not the perceived intensity, of only the noxious stimulus increased following the later applications. A regression analysis of the PET activations and the ratings revealed a significant positive and unique relationship between unpleasantness and activity in the ACC, but in a location that is caudal to the activation found by Rainville *et al.* (1997).

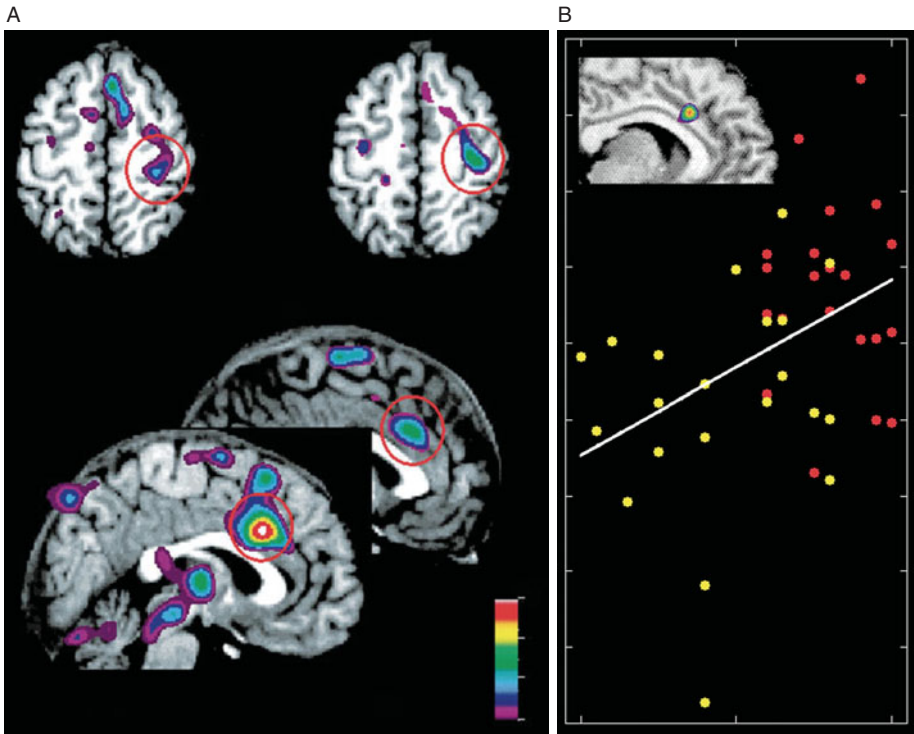


Fig. 5.30. A. Position emission tomography images obtained during the hypnotic suggestion that the unpleasantness of an equally intense noxious heat stimulus was increased or decreased. Activation of the SI cortex (upper panels) did not change but the activation in the mid-ACC increased during increased perceived pain unpleasantness (lower panels, lower of the paired sagittal images). B. Correlation analysis of activation levels (ordinate, % residual rCBF) in the mid-ACC during increasing levels of perceived unpleasantness (abscissa, ratings 0–100). A and B adapted from Rainville *et al.* (1997).

On the hypothesis that intramuscular pain is more unpleasant than intracutaneous pain, Schreckenberger *et al.* (2005) used FDG PET to compare the regional cerebral metabolic activity in three groups of subjects receiving 30-minute intracutaneous or intramuscular infusions of a painful acidic or neutral solution. At comparable levels of perceived intensity, the intramuscular infusion was more unpleasant. A direct comparison of the intramuscular and intracutaneous conditions (minus the painless infusion) failed to show a significant activation; however, the pain-related insular activation correlated with both perceived intensity and unpleasantness, suggesting, given the psychophysical analysis, a specific role for the insula in hedonic coding.

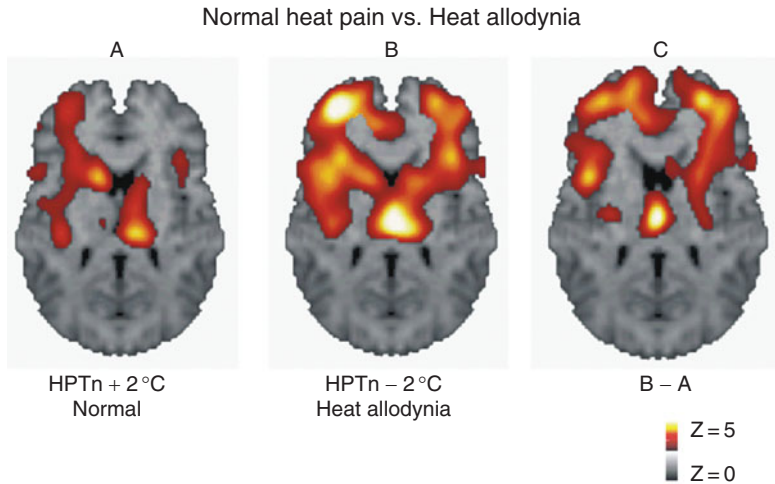


Fig. 5.31. Activation of the medial thalamus and orbitofrontal cortex (OFC) during heat allodynia. H_2^{15}O PET study of normal subjects with skin sensitized by topical capsaicin. (A) Cutaneous contact heat applied 2°C above heat pain threshold to normal skin (HPTn) evokes activity in the thalamus, insula and putamen. (B) Heat applied 2°C below HPT on sensitized skin produces the same perceived heat intensity but enhances thalamic and OFC activation. (C) Subtraction analysis reveals the activation of the medial thalamus and OFC due to the allodynic effect of topical capsaicin. During heat allodynia, the perceived unpleasantness was increased significantly more than perceived intensity, suggesting a greater role for the medial thalamus and OFC in hedonic, rather than intensity, coding. Adapted from Lorenz *et al.* (2002).

In a related H_2^{15}O PET study, Svensson and colleagues found no reliable psychophysical or brain activation differences between noxious cutaneous laser and electrical intramuscular stimulation but unpleasantness was not specifically investigated (Svensson *et al.*, 1997b). However, heat allodynia, induced in normal individuals by topical capsaicin, increases perceived unpleasantness more than perceived intensity and is associated, during intensities perceived as equal, with an allodynia-specific activation of the medial thalamus and OFC (Fig. 5.31) (Lorenz *et al.*, 2002). This finding is in general agreement with the results of a subsequent fMRI study by Rolls *et al.* (2003) who found OFC activation specifically during the perception of a tactile stimulus (rough sandpaper rotated on the palm) that was perceived as uniquely unpleasant. In comparing the brain activations during capsaicin-induced thermal and mechanical allodynia, Maihofner and Handwerker (2005) observed that during thermal hyperalgesia of equal intensity, the relative increase in the activation of the ACC and contralateral anterior insula and medial frontal cortex was correlated specifically with higher ratings of unpleasantness. Therefore, the negative hedonic state during pain may

be mediated by a slightly different network of structures during qualitatively different pain states dominated by unpleasantness.

The anticipation of pain has been used to identify brain activations during what can be presumed to be a negative hedonic experience. When differently colored lights signal an impending warm or painfully hot stimulus, the activations during the anticipation of pain are located anterior to activations during the actual pain experience in the ACC and insula; they are posterior and unilateral to pain activations in the cerebellum (Ploghaus *et al.*, 1999). In addition, the BOLD signal during pain anticipation increased sequentially with pain stimulus trials. Investigators from this laboratory then examined the pain-modulating effect of the anxiety associated with pain anticipation (Ploghaus *et al.*, 2001). They used different visual cues to signal impending heat stimuli that were rated as either moderately or strongly painful; the cue for high intensity stimulation, however, could be followed unpredictably by either high or low intensity stimuli. Heart rate monitoring and interviews confirmed that anxiety was associated with the cue for high heat intensities. The lower heat stimulus was rated as more painful following the high anxiety cue. By comparing the effect of the high and low anxiety cues during the lower intensity stimulation, it was possible to show that the modulating effect of anxiety occurred during activation of the entorhinal cortex, which in turn correlated with pain-related activations in the rostral (perigenual/pregenual) ACC and mid-/parainsular cortex (Fig. 5.32A). The authors suggest that the enhanced pain perception during anxiety is mediated by entorhinal/hippocampal amplification of the pain-related activations in the insula and ACC. In a follow-up of this experiment, investigators from this facility examined this hypothesis by focusing on brainstem activations during both heat pain and the anticipation of pain (Fairhurst *et al.*, 2007). Higher levels of pain anticipation (and presumed anxiety) correlated with higher pain intensity ratings; and conjunction analysis revealed that the PAG, thalamus, ACC and premotor cortex were active during both pain and anticipation (Fig. 5.32B). In addition, high activity in the ventral tegmental area and entorhinal cortex predicted increased activity in the insular cortex. These results and interpretation are consistent with the results of a related study by Sawamoto *et al.* (2000), who found, consistent with psychophysical assessment, that ACC and insular BOLD responses to a laser stimulus that was unpredictably noxious were increased relative to a predictably innocuous stimulus.

The close physiological relationship between pain and hedonic states is highlighted by the findings of Becerra and colleagues, who found that the activations during heat pain followed the activations of structures that have been identified in other studies as forming the “reward circuitry” of the brain (see Fig. 5.33) (Becerra *et al.*, 2001). The authors suggest that information from nociceptors is

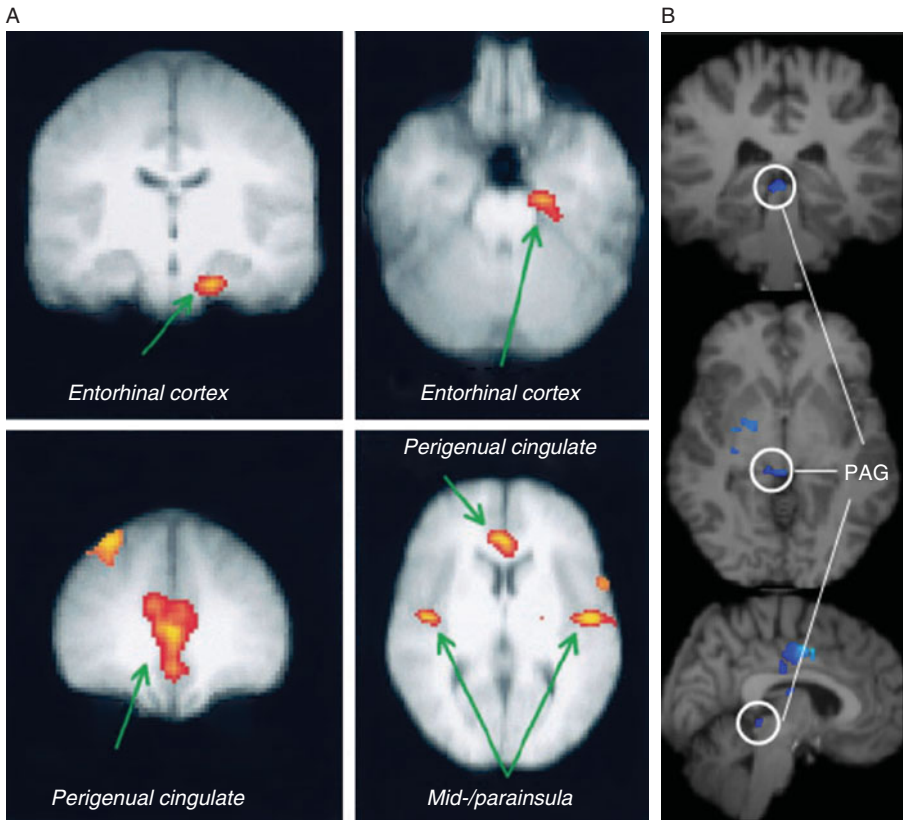


Fig. 5.32. A. Anxiety-related activations in the entorhinal cortex (upper panels) correlate with pain-related activations in the perigenual and mid-/parainsular cortex. (Adapted from Ploghaus *et al.*, 2001.) B. Conjunction analysis of the two contrasts “pain – baseline” and “anticipation – baseline,” showing activation of the PAG and ACC during both pain and the anticipation of pain. Additional activations in this analysis include the thalamus and premotor cortex (not shown). Adapted from Fairhurst *et al.* (2007).

processed early by brain structures that detect and assign hedonic valence; this information then influences the activation of structures mediating the somato-sensory and cognitive aspects of pain. Thus, the cerebral responses to nociceptive input are modulated by limbic structures that also receive nociceptive information and are active during emotional states.

The cognitive component of pain

Cognition refers to the act or process of knowing. As a determining component of pain, cognition implies that information about the excitation of

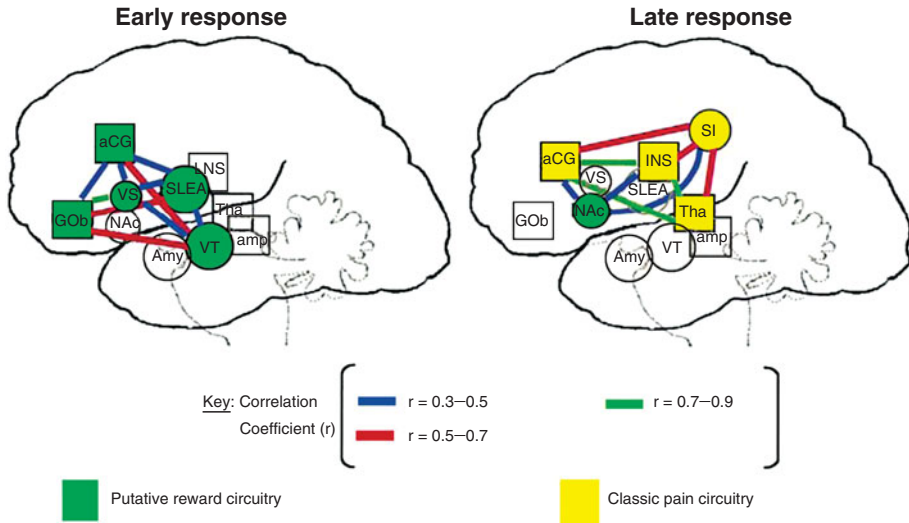


Fig. 5.33. During the perception of heat pain, the activation of structures that have been associated with reward (green) is early and significantly inter-correlated (see correlation coefficients and interconnecting colors). The correlated activation of pain-associated structures (yellow) occurs later but also includes a reward-related structure, the nucleus accumbens (NAc). GOB, basal orbital gyrus (part of OFC); aCG, anterior cingulate cortex; VS, ventral striatum; SLEA, extended sublentiform amygdala; VT, ventral tegmentum; INS, insula; Thal, thalamus; SI, primary somatosensory cortex; Amy, amygdala. Adapted from Becerra *et al.* (2001).

nociceptors (such as location and intensity), the immediate environmental and historical context of this excitation, and the hedonic strength and valence assigned to this input is used to determine how, or even whether, pain is perceived. Because this background information must be gathered before being applied to the processing of nociceptive information, the development of the cognitive component of pain precedes, accompanies and follows sensory-discriminative and hedonic processes to determine how pain is perceived. For example, Lorenz and colleagues used $H_2^{15}O$ PET to show that, during experimentally induced heat allodynia, activity in the right and left dorsolateral PFC (DLPFC) correlated negatively with perceived intensity and unpleasantness. During high left DLPFC activity, the inter-regional correlation of midbrain and medial thalamic activity was significantly reduced (Fig. 5.34) while high activity in the right DLPFC was associated with a weakened correlation of anterior insular activation with both pain intensity and affect (Lorenz *et al.*, 2003). These results suggest that the DLPFC controls pain by modulating pain-activated cortico-subcortical and cortico-cortical pathways. This formulation is in general

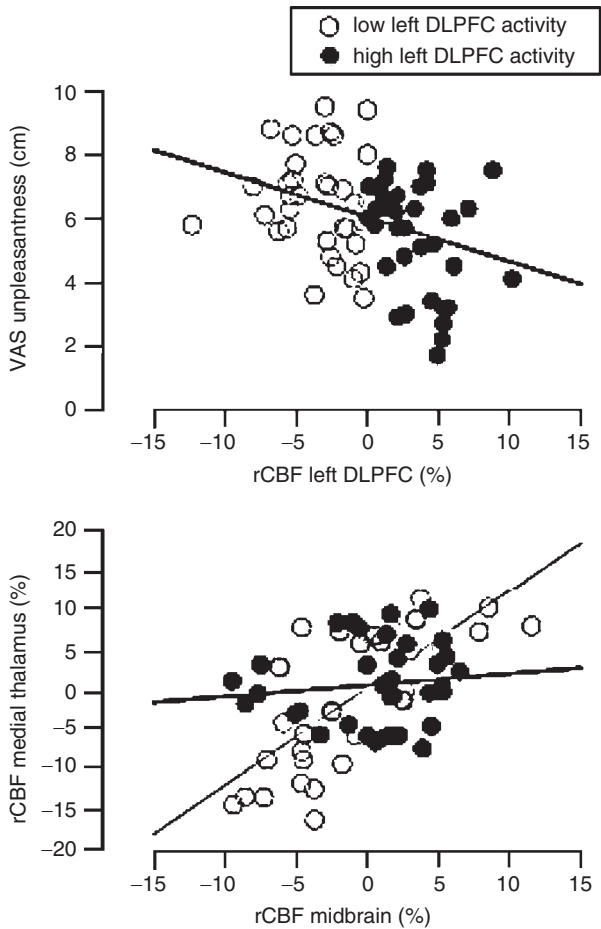


Fig. 5.34. Upper panel: high levels of left DLPFC activity (filled circles) are associated with lower ratings of unpleasantness during heat allodynia. Lower panel: during high levels of left DLPFC activity, when perceived unpleasantness is attenuated, the correlation between medial thalamic and midbrain activity is reduced. Adapted from Lorenz *et al.* (2003).

agreement with the evidence presented by Koechlin and colleagues showing that the lateral prefrontal cortex (IPFC) is organized hierarchically to assert cognitive control over motor responses to stimuli (Koechlin *et al.*, 2003). Medial prefrontal cortical areas also participate in the modulation of pain as shown by the modulation of heat pain intensity by the voluntary control of the intensity of BOLD activation in the mid-ACC (deCharms *et al.*, 2005). In this real-time fMRI experiment, participants were instructed to increase or decrease the perceived intensity of constant-intensity noxious repetitive contact heat stimuli while viewing a representation of their BOLD responses in the ACC. Pain intensity and

unpleasantness correlated positively with the amplitude of the ACC response; other structures showing a similar correlation included the insular and SII somatosensory cortex. As shown in the examples to follow, brain structures receiving nociceptive input, including components of the limbic system and endogenous opioid mechanisms (Pert and Snyder, 1973; LaMotte *et al.*, 1978; Sadzot *et al.*, 1990; Bencherif *et al.*, 2002), join the PFC to participate in the modulation of pain during cognitive processes.

Expectation and attention

In an fMRI study, the expectation of heat pain intensity was manipulated to reveal that the DLPFC and several other pain-activated structures, including the anterior insula and ACC, participate in the attenuation of perceived pain and brain activations during pain (Koyama *et al.*, 2005). Expectancy of pain intensity was also manipulated in a similar study in which the effect of expectancy was shown to be associated with activations in the caudal ACC but also with subcortical activity in the caudate nucleus, cerebellum and nucleus cuneiformis, confirming the participation of cortical and subcortical pain-activated structures in pain modulation (Keltner *et al.*, 2006). In an experiment related to the effects of expectation and PFC control, real-time fMRI (rtfMRI) was used to provide direct feedback to subjects trained to activate the mid-ACC to increase or decrease perceived heat pain (deCharms *et al.*, 2005). As voluntary changes in ACC activation were achieved, pain intensity and unpleasantness increased or decreased in positive correlation with mid-ACC activation. This experiment suggests that medial PFC brain activation is perhaps most susceptible to voluntary control for pain modulation.

Habituation to a noxious stimulus is another, perhaps contrasting, way of changing expectation. As discussed in the preceding section on the sensory-discriminative aspects of pain, this effect was explored by Bingel and colleagues, who demonstrated a decline in perceived noxious heat intensity when the stimulation was applied repetitively in divided sessions over 8 days (Bingel *et al.*, 2007). Noxious heat-evoked activations decreased in the thalamus, insula and ACC but activity in the rostral (subgenual) ACC increased, suggesting that this part of the medial PFC mediates this habituation or hypoalgesic-related effect (Fig. 5.35). It is notable that this rACC activation is anatomically quite separate from the more caudal mid-ACC region used for pain control in the experiments of deCharms *et al.* (2005), consistent with contrasting functional differences among regions of the cingulate gyrus.

Davis and colleagues were among the first to examine the effect of attentional state on ACC pain activations using fMRI. Painful electrical stimulation activated an ACC region caudal to that activated during an attention-demanding word

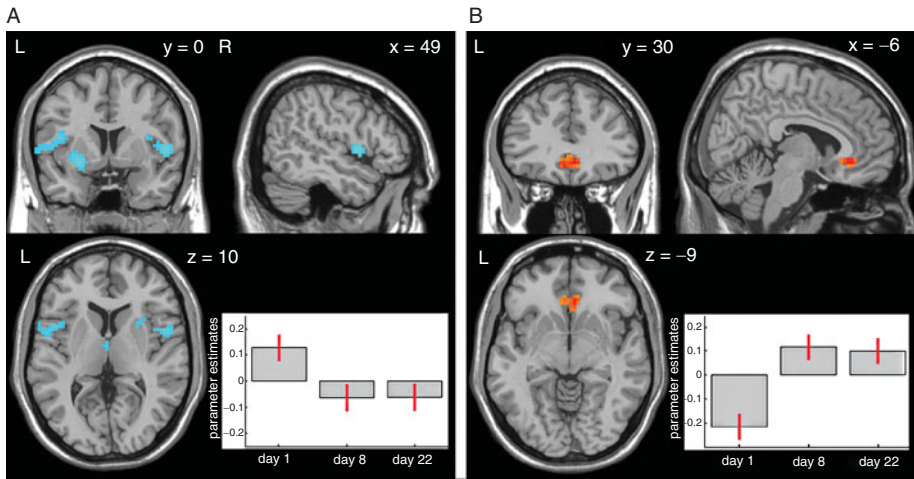


Fig. 5.35. A, Decreases in heat pain activations (thalamus, insula, putamen, SII cortex) following an eight-day period of repetitive stimulation in divided sessions during which pain ratings decreased and threshold increased. Inset shows parameter estimates (regression coefficients) for insular activation during the days indicated. The effect persisted for 22 days. B, During this same period, pain-related activation increased in the subgenual ACC (parameter estimates from this site are shown in the inset). Adapted from Bingel *et al.* (2007).

task (Davis *et al.*, 1997). Two subsequent experiments revealed additional mPFC participation in pain modulation during attention. In a PET study, Petrovic and colleagues found that pain during the “cold pressor” pain test was reduced during a maze distraction task and the pain-related activations in the SII cortex and PAG were decreased while lateral OFC activity increased (Petrovic *et al.*, 2000). Similarly, Bantick and colleagues found that the distraction of a Stroop word color conflict task reduced heat pain and the activation of the thalamus, insula and mid-ACC; in contrast, the rostral (pregenual) ACC and OFC were more active during this period (Bantick *et al.*, 2002).

Evidence for brainstem participation in attention-mediated pain modulation was obtained by a directed study of PAG activation during distraction compared with attention to heat pain. As expected from studies of rodent pain models, PAG activity correlated with reduced pain intensity during distraction (Tracey *et al.*, 2002). These results were confirmed and elaborated in another fMRI investigation that used heat pain (contrasted with warmth) and the Stroop distraction task (Valet *et al.*, 2004). The participating subjects reported, retrospectively after the scanning, significant reductions of both pain intensity and unpleasantness during distraction; unpleasantness was the most reduced. There was a marked

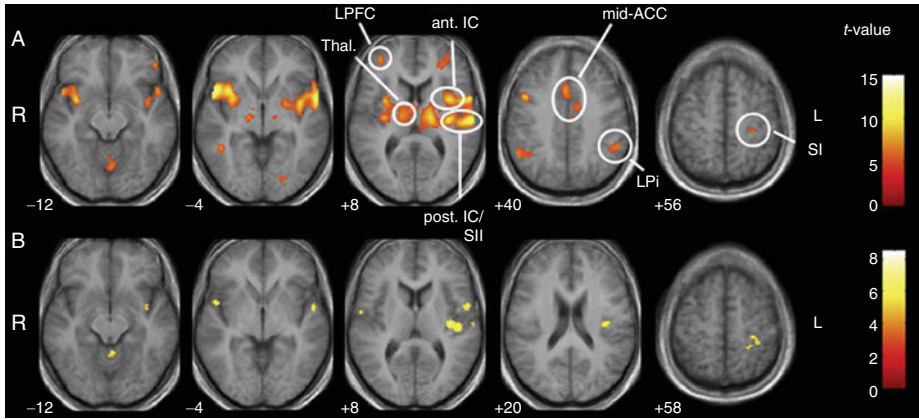


Fig. 5.36A. Effect of distraction (Stroop task) on heat pain activations. Top row shows the heat pain activations without distraction in the anterior and posterior insula (ant., post. IC), lateral prefrontal cortex (LPFC), thalamus (thal), mid-ACC and inferior parietal lobule (LPI). Bottom row shows the activations during the same stimulus intensity but during distraction; only the SI and posterior insular cortex survived analysis threshold. Adapted from Valet *et al.* (2004).

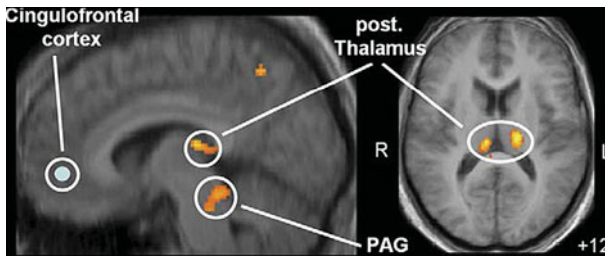


Fig. 5.36B. Covariation analysis of the study shown in Fig. 5.36A. The rostral (pregenual) ACC (cingulo-frontal cortex in the figure) was active specifically during the distraction task. Therefore, this activation was used in this covariation analysis, which shows that this prefrontal activation covaries with activity in the posterior thalamus (VPL/pulvinar) and PAG, forming a circuit that could mediate the pain-attenuating effects of distraction.

reduction in pain-related activations during distraction (Fig. 5.36A) while the pregenual rostral ACC was active. Subsequent covariance analysis showed that the pregenual rostral ACC activity covaried with activity in the posterior thalamus and PAG, suggesting that this circuit mediates the pain-attenuating effect of distraction (Fig. 5.36B).

Hoffman and colleagues have shown the significant therapeutic effects of distraction by using a 3D “virtual reality” illusion (floating in an icy canyon and shooting

snowballs) during painful clinical procedures (wound care of burn patients) (Hoffman *et al.*, 2000). These investigators have used fMRI to show that heat pain activations are markedly reduced during “virtual reality” distraction (Hoffman *et al.*, 2004). Whether this therapeutic effect is mediated through the limbic cortical and subcortical circuits discussed above is unknown at this time. Nonetheless, these results show that pain imaging lends clinical credibility to pain-relieving measures that otherwise might have been dismissed as lacking a physiological basis.

Placebo analgesia

The placebo effect or response, and particularly placebo analgesia, has a long history (Beecher *et al.*, 1953; Beecher, 1955, 1956, 1960). The discovery of endogenous opioids opened up the possibility of identifying a physiological mechanism for placebo analgesia (Snyder, 1977) and indeed subsequent experiments provided strong evidence that this phenomenon was mediated, at least in part, by endogenous opioid mechanisms (Levine *et al.*, 1978; Gracely *et al.*, 1983). Nonetheless, doubts remained concerning the physiological reality of the placebo effect in general (Hrobjartsson and Gotzsche, 2001).

Casey and colleagues investigated the specific effect of the μ receptor agonist fentanyl on the perception and brain activation produced by noxious cold (cold pressor test) and vibratory stimulation (Casey *et al.*, 2000). As expected, fentanyl markedly attenuated cold pain and cold pain activations but had no effect on vibratory sensation or activation. However, subtraction analysis revealed that the mid- and rostral (pregenual) ACC was strongly activated during the fentanyl condition in the absence of pain. This finding is consistent with the observations discussed above, showing that the rACC participates in the active production of endogenous analgesia and that this area of the ACC is rich in opiate receptors (Frost *et al.*, 1985; Sadzot *et al.*, 1990).

In a direct examination of the activation of endogenous opioid mechanisms, Zubieta and colleagues estimated the binding potential of ^{11}C carfentanyl to show that, during the sustained pain produced by the intramuscular infusion of hypertonic saline, there is reduced opioid binding (hence, increased opioid receptor occupancy, consistent with endogenous release) in structures that are active during pain including the thalamus, insula and PFC as well as the amygdala. Moreover, there was a strong correlation between the level of perceived pain intensity or unpleasantness and the level of endogenous opioid release (Zubieta *et al.*, 2001) (Fig. 5.37A, B).

Petrovic and colleagues then used PET to test the hypothesis that placebo analgesia and exogenous opioids activate the same set of brain structures (Petrovic *et al.*, 2002). In the placebo condition, participating subjects were told that they were receiving an intravenous infusion of a powerful analgesic when in

A

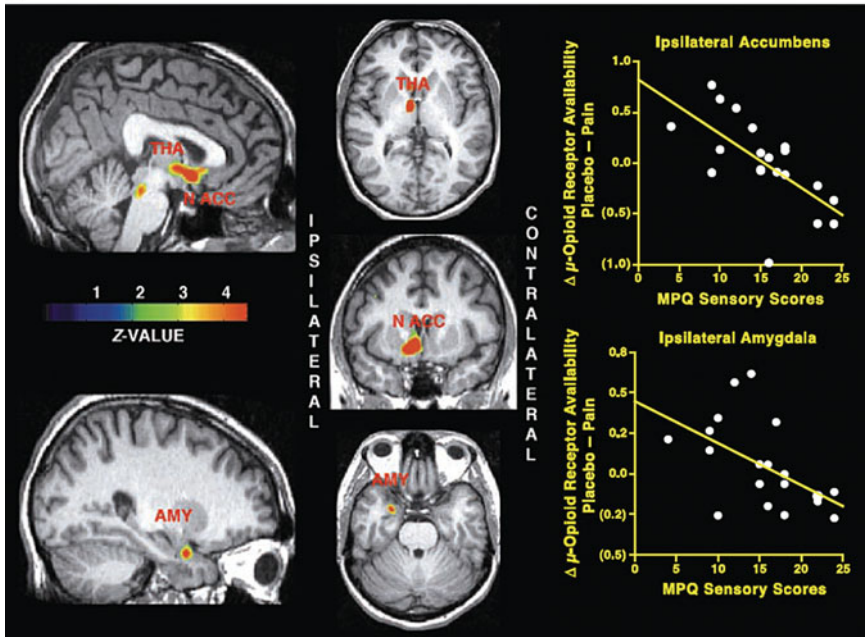


Fig. 5.37A. Regions in which reduced ^{11}C carfentanyl binding during sustained muscle pain (painless “placebo” – painful hypertonic saline) is negatively correlated with perceived pain intensity in: thalamus, THA; n. accumbens, N ACC; and amygdala, AMY.

B

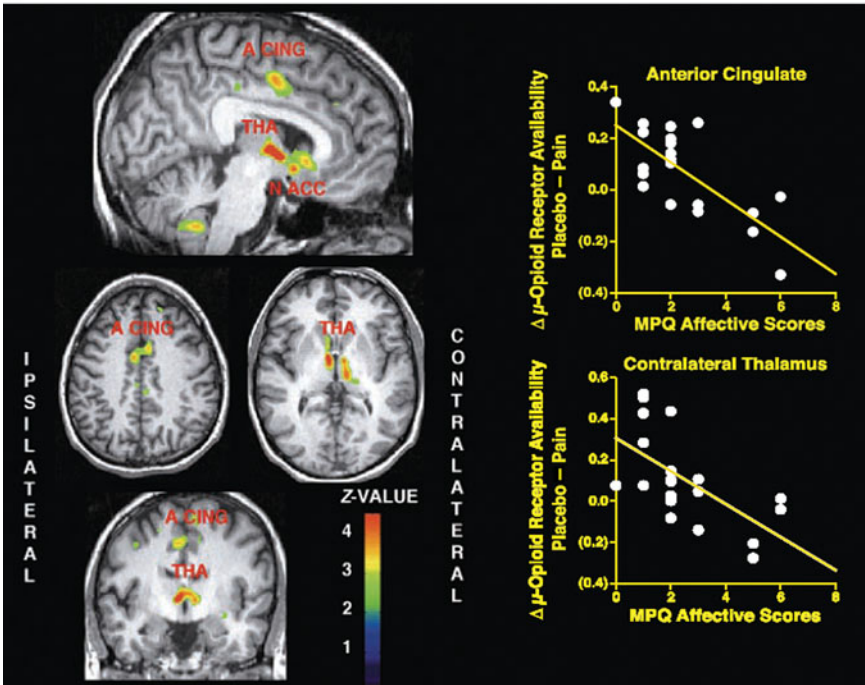


Fig. 5.37B. Same as Fig. 5.37A except that the correlation with pain unpleasantness (affect) is shown in the images and graphs. Anterior cingulate cortex, A CING.

fact the infusion was saline; remifentanyl, a μ receptor agonist, was given as the active agent. Those subjects responding with the most reductions in perceived contact heat pain showed activation of the rACC, overlapping the same area activated during remifentanyl analgesia. As in the subsequent fMRI study by Valet *et al.* (2004), covariance analysis revealed evidence for functional connectivity between the rACC and the midbrain in the region of the PAG during both placebo and opioid analgesia. These studies set the stage for a more detailed examination of the mechanisms mediating placebo analgesia.

Experiments by Price and colleagues revealed the importance of expectation in evoking placebo analgesia (Price *et al.*, 1999). This led to the use of expectation and stimulus manipulation to study the physiology of placebo analgesia using fMRI (Wager *et al.*, 2004). A collaborative investigation was conducted at two institutions, one using electric shock (study 1) and the other contact heat (study 2) as noxious stimuli. A major goal of these investigations was to obtain evidence for a decrease in pain-related activations during the activation of structures in the placebo condition. In both studies, a cream was applied to the skin stimulation site and, in one phase of each study, the subjects were told that the cream was a powerful analgesic. In study 2, the expectancy of analgesia was enhanced by lowering heat stimulus intensity following application of the cream (the manipulation phase); this was followed by another test in which the “analgesic” cream was applied and the stimulus temperature maintained at a level previously determined to be quite noxious; this tested the analgesic effect of the expectation-enhanced placebo. In both studies, placebo analgesia was observed and correlated with reductions in the activation of rACC, thalamus, insula and parahippocampal cortex (Fig. 5.38A). In study 2, it was possible to demonstrate that the BOLD response in the thalamus and insula was reduced in the placebo condition compared with the control (Fig. 5.38B). During stimulus anticipation in the placebo condition, there was activation of the DLPFC, OFC and midbrain (in the PAG region), consistent with the interpretation that these structures mediate the reduced pain activations during the placebo condition (Fig. 5.38C). Price *et al.* (2007) have subsequently confirmed these results in a group of patients with irritable bowel syndrome (IBS) and have shown that the placebo-related reductions in pain activation (rectal balloon distention) occur throughout the noxious stimulation period. They observed reductions in pain and pain activations in the thalamus, SI and SII cortices, insula and ACC. A follow-up of this investigation in IBS patients is discussed in Chapter 8.

Subsequent investigations of the placebo mechanism have provided additional information but are generally supportive of the formulation that, during placebo analgesia, there is an attenuation of pain-related activations accompanied by the activation of a functionally interconnected prefrontal and limbic

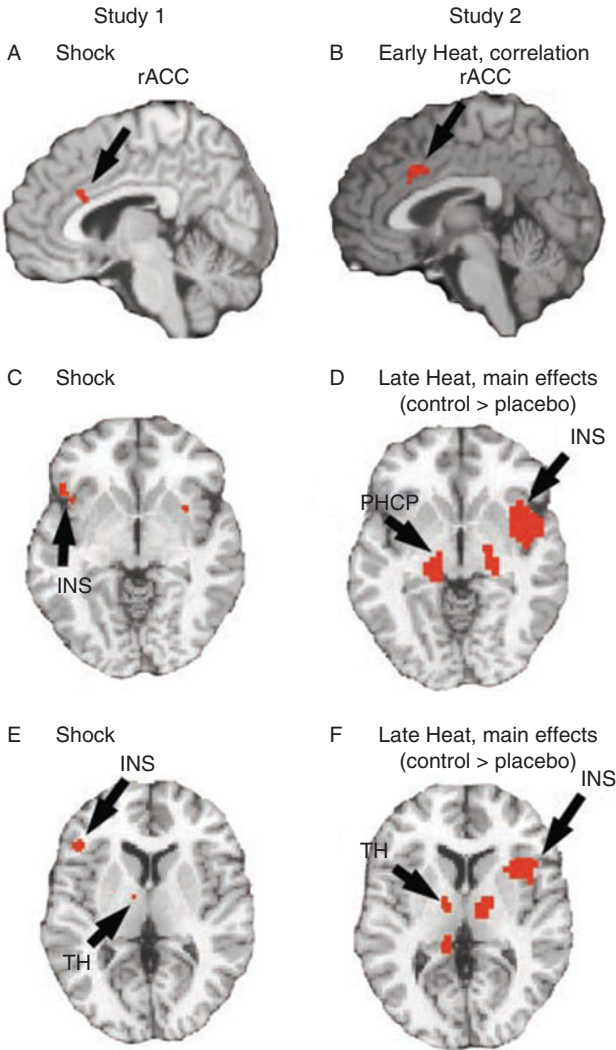


Fig. 5.38A. Structures with positive correlations between the magnitudes of the placebo effect and reductions in brain activation (BOLD amplitude) in pain-responsive regions in studies 1 and 2. rACC, rostral ACC; INS, insula; PHCP, parahippocampus; TH, thalamus. Adapted from Wager *et al.* (2004).

circuit that implements the pain modulation. Bingel and colleagues, for example, used painful and painless laser stimulation in a site-specific expectation placebo paradigm to show, with connectivity analysis, that the placebo condition was uniquely associated with conjoint activity in the rostral ACC, both amygdalae and the midbrain PAG (Bingel *et al.*, 2006).

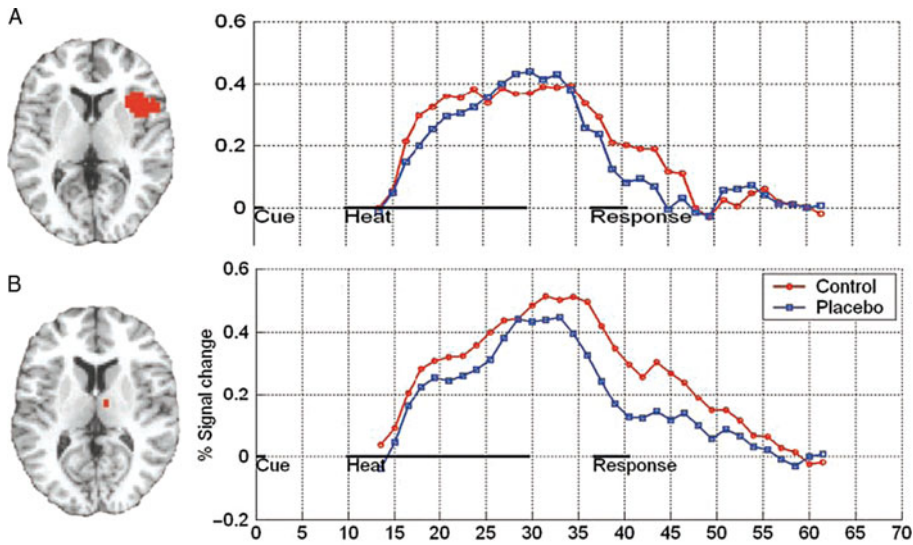


Figure 5.38B. BOLD signal changes in the insula (A) and thalamus (B) during the control period (red lines) and during the placebo period (blue lines) in study 2. The subject's heat pain rating was reported during the response period following the heat stimulus. Adapted from Wager *et al.* (2004).

Endogenous opioid mechanisms appear to play a major role in mediating the placebo analgesia effect. Zubieta and colleagues, for example, found evidence for endogenous opioid release in the rACC (pre- and subgenual), DLPFC, insula and nucleus accumbens during placebo analgesia (Zubieta *et al.*, 2005). Kong and colleagues observed a unilateral placebo analgesic effect during placebo acupuncture; this was accompanied by rACC activation that correlated with the strength of placebo analgesia, again consistent with the active participation of rACC in placebo analgesia. To further directly support the involvement of endogenous opioid mechanisms in placebo analgesia, Wager and colleagues used ^{11}C carfentanyl to show that, during placebo analgesia, μ opioid receptor occupancy is increased in the PAG, dorsal raphe, nucleus cuneiformis, amygdala, orbitofrontal cortex, insula, rACC and OFC (Wager *et al.*, 2007). The opioid activation in some of these regions appeared to be related to pain anticipation and others to the pain stimulus itself. Connectivity analysis revealed an increase in the functional connectivity of the PAG and rACC, consistent with the observations discussed above. It appears that collectively the investigations cited above have begun to identify the neurochemical and neurophysiological basis for placebo analgesia and to relate it directly to cognitive processes associated with expectation.

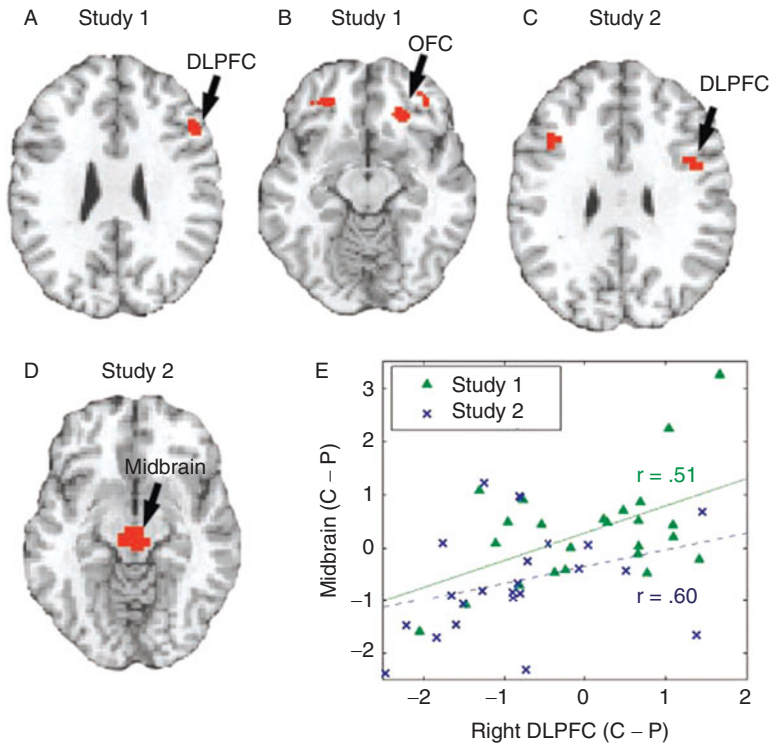


Figure 5.38C. Structures activated during the anticipation period in the placebo condition. In study 1 the activations correlated with the strength of the placebo response; subjects were not preselected for showing a placebo response. In study 2 subjects were preselected for showing a placebo response, so only the main effect of placebo-control is shown. The dorsolateral prefrontal cortex (DLPFC) is active in both studies (A and C) and the orbitofrontal cortex (OFC) shows the correlation in study 1 (B). The area of the PAG is active in study 2 (D). The graph (E) shows the correlation between midbrain and DLPFC activation magnitude during the placebo condition, suggesting a functional link between these structures during placebo. Adapted from Wager *et al.* (2004).

In addition to opioid-based endogenous pain modulatory mechanisms, Hagelberg and colleagues have presented evidence, based on earlier animal studies, that dopamine receptors, specifically the D2 receptor, participate in endogenous analgesia (for review, see Hagelberg *et al.*, 2004; Pertovaara *et al.*, 2008). In an ^{11}C raclopride PET investigation, D2 binding potential in the right putamen was inversely correlated with cold pain threshold (ice water immersion) and, in the right medial temporal cortex, with cold pain tolerance (Hagelberg *et al.*, 2002). Furthermore, heat pain threshold elevation induced by

concurrent cold pain (the DNIC effect) was directly correlated with D2 binding potential in the left putamen.

Differences among acute pains

Sex differences

Psychophysics Several psychophysical studies have revealed sex differences in the perceived intensity or affective quality of noxious stimuli. Some of these differences and their origin have been reviewed (Berkley, 1997). In a meta-analysis, the effect size of sex was large to moderate depending on the measurement (tolerance or threshold) and method of stimulation. The authors concluded that the effect size (0.55 to 0.57 for threshold and tolerance, respectively) would require 41 members of each sex to achieve a power of 0.70 in most studies (Riley III *et al.*, 1998). For experimentally applied noxious stimuli, the physical characteristics of the stimulus appear to be important in some studies. In a study comparing the perceived intensity of noxious cutaneous electrical stimulation with contact heat pain, women judged the electrical stimuli to be significantly higher than men but there were no sex differences in heat pain intensity (Lautenbacher and Rollman, 1993). During noxious pressure, women gave higher pain ratings and showed greater pupillary dilation than men, suggesting a physiological difference in nociceptive processing at least within the autonomic nervous system (Ellermeier and Westphal, 1995). The female menstrual cycle may be a significant variable also, but this may depend on the type of stimulation because ischemic, but not heat, pain intensity appears to be reduced during the midfollicular phase of the cycle (Fillingim *et al.*, 1997). The timing of the stimulation may be important because the temporal summation of heat pain, but not the perceived intensity of brief pulses, is greater in women than in men (Fillingim *et al.*, 1998). In contrast, the spatial summation of heat pain does not appear to be different across sexes although the heat pain threshold in both sexes is inversely related to stimulus area in both sexes (Lautenbacher *et al.*, 2001).

The affective dimension of the pain experience may be another important measure of sex differences. Sarlani and colleagues (Sarlani *et al.*, 2003) evaluated the sensory and affective experiences of healthy men and women while their hands were immersed in water at temperatures ranging from 10 to 47.8 °C. Women gave higher ratings for both pain intensity and affect at the more extreme temperature ranges. One possible neurobiological explanation for these sex differences is that women might have less robust pain modulatory mechanisms. Because noxious stimuli activate endogenous pain modulatory systems (Chapter 6), France and Suchowiecki (1999) examined changes in the threshold excitability of a flexion reflex in men and women while their forearms were

rendered ischemic by a pressure cuff or concurrent noxious electrocutaneous stimulation. There was no significant sex difference in the degree of flexion reflex attenuation during concurrent noxious stimulation, but, as the authors comment, other forms of endogenous pain modulation that are not activated specifically by nociceptive input could show sex differences.

Imaging Sex differences in the response to noxious stimuli could reflect baseline (resting) differences in brain metabolism or resting blood flow. In an analysis of the resting cerebral metabolic rate of glucose utilization (CMRglu), there was a trend for greater global CMRglu in women than in men, this regional difference being significant in the orbitofrontal area (Andreason *et al.*, 1994). However, a subsequent PET study of healthy individuals showed that men had higher resting glucose metabolism than women in temporal-limbic regions and cerebellum but lower metabolism in the cingulate cortex (Gur *et al.*, 1995). In studies of responses to noxious stimuli, these resting metabolic differences should be accounted for by the methods of contrast (rest vs. stimulation) or correlation analysis described in previous sections. However, given the importance of the affective dimension of pain in sex differences (Sarllani *et al.*, 2003) it is important to consider underlying sex differences in the brain responses to emotionally charged stimuli. In a meta-analysis of 65 neuroimaging studies that included negative or aversive emotions such as fear, anxiety, anger and guilt, but specifically excluded pain, Wager *et al.* (2003) found that women activated the cerebellum, midbrain, thalamus and subgenual anterior cingulate cortex more than men; with the exception of the thalamus, activation of these structures was more likely to be associated with aversive experiences or negative emotions. One might expect, therefore, that imaging studies of pain, and specifically the affective dimension of pain, might reveal consistent sex differences in the brain responses in these structures; this has not been the case, however.

In the first PET rCBF study of sex differences in brain activation, women gave higher intensity ratings to 50 °C, but not 40 °C, contact heat stimuli and showed greater activations to 50 °C in the contralateral (right) prefrontal cortex, insula and thalamus; a direct VOI comparison also suggested greater activation of the contralateral insula and thalamus (Paulson *et al.*, 1998). In a subsequent PET study, the pain evoked by brief infra-red laser stimulation of the hand was equalized across participants (Derbyshire *et al.*, 2002). The women showed a greater activation of the pregenual anterior cingulate but less activation than men of the contralateral (left) prefrontal, parietal (Brodmann areas 7 and 40), insular and somatosensory primary (SI) and secondary (SII) cortices. In a VOI-directed fMRI examination of the BOLD signal during contact (16 s) heat that was

perceived equally painful between sexes (Moulton *et al.*, 2006), men showed greater BOLD response amplitude bilaterally of the primary somatosensory (SI) and mid-ACC cortices. An examination of negative BOLD response amplitude (deactivations) in adjacent voxels showed no sex differences. The affective dimension of pain was not specifically measured and the phase of the menstrual cycle was not controlled in these aforementioned studies.

De Leeuw *et al.* (2006), upon reviewing the variable results of the effect of sex hormones on pain, used fMRI to study the heat pain responses (contrasted with innocuous warmth) of nine women at different times following the onset of menstruation, a low estrogen phase (28 pg/ml 17 β estradiol) 2–3 days post-onset and a high estrogen phase (79 pg/ml) 11–12 days post-onset. The estrogen, but not progesterone, levels (progesterone: 0.59 and 0.62 ng/ml, respectively) were different between conditions. In both conditions, and consistent with previous studies, heat pain activations appeared bilaterally in the insula, thalamus and cingulate gyrus, contralaterally in the middle and inferior prefrontal cortex, inferior parietal lobule and cuneus region, and ipsilaterally in the precentral gyrus. Although there was no difference in the ratings or threshold of heat pain or in measures of anxiety between these conditions, the bilateral pregenual anterior cingulate cortex, right (contralateral) precuneus region, and left cerebellum showed a greater response during the low estrogen phase. The contralateral cerebellum was the only activation unique to the high estrogen condition.

Zubieta *et al.* (2002) used ^{11}C carfentanyl binding potential during PET to examine sex differences in the activation of endogenous opioid mechanisms during the infusion of hypertonic saline (compared with isotonic saline) into the masseter muscle. The women were examined during the follicular phase of their menstrual cycle and had estrogen levels (43.7 pg/ml) in the mid-range of those measured in the study by de Leeuw and colleagues. The intramuscular infusion was controlled so that the intensity and affective experiences were not different between sexes; nonetheless, men showed greater activation of the endogenous opioid system in the anterior thalamus, ventral basal ganglia and amygdala and women had a decreased opioid system activation in the nucleus accumbens. Thus, men may activate the endogenous opioid mechanism more robustly than women in the low estrogen phase of their menstrual cycle but it is not currently possible to predict the brain activation differences that could explain the variable sex-related perceptual differences that are sometimes detected. It is possible, as Berkley (1997) suggests, that the sex-related differences in pain perception are sufficiently small, and the variables with large effects on pain perception so numerous, that the experimental paradigms applied thus far cannot detect consistently the salient physiological differences.

Skin pain and itch

Nearly all imaging studies reviewed thus far used skin as the afferent source for input from nociceptors. The pattern of brain activation from cutaneous sources dominates the results of the meta-analysis conducted by Apkarian *et al.* (2005); an estimated 53 of the 67 studies (79%) listed in their table 1 used some form of cutaneous stimulation. The percentage of activations from all sources ranges from 94% (anterior cingulate cortex) to 68% (SII somatosensory cortex) and includes the primary (SI) somatosensory cortex (69%), insular cortex (88%) and thalamus (84%) (their table 2); their designation of prefrontal cortex (39%) includes various prefrontal regions on the medial and lateral aspect of the hemisphere. The cerebellum is activated in 16 (24%) of the 67 listed studies and the skin was stimulated in all but two of these. Because the structures listed above are representative of brain activations from noxious cutaneous stimulation (see also Casey and Tran, 2006), we will consider only a few additional studies related to nociceptive sources from the skin.

Itch, to paraphrase a dictionary definition, is a (usually) localized uncomfortable cutaneous sensation (or state of having the sensation) of some combination of pricking, crawling or stinging accompanied by the desire to relieve the experience by scratching the affected site. Itch therefore has qualities that overlap almost completely with pain, except that itch is not generally associated with tissue damage or described in terms of tissue damage. Psychophysical and human neuronographic recording studies identified C fibers as the primary afferent source mediating the sensation of prickle or itch (Van Hees and Gybels, 1981; Garnsworthy *et al.*, 1988; Handwerker *et al.*, 1991). Some of these afferents could be activated by other forms of noxious chemical stimulation that evoked a burning sensation without a significant change in firing pattern (Handwerker *et al.*, 1991). In subsequent investigations, a small population of C fibers ($N = 8$) was found to respond to cutaneous histamine that induced itching; five of these fibers also responded to heat and all had large receptive fields up to 85 mm in diameter (Schmelz *et al.*, 1997). Subsequently Andrew and Craig (2001) identified spinothalamic tract neurons in lamina I of the cat dorsal horn that responded to histamine but not to heat or mechanical stimulation.

Imaging itch Hsieh *et al.* (1994) used $H_2^{15}O$ PET to examine the cerebral activations produced by cutaneous histamine-induced itching; they found activation bilaterally in the supplementary motor area (SMA) and dorsal premotor cortex (Brodmann area 6), in the contralateral (left) anterior cingulate cortex (ACC), ipsilateral inferior posterior parietal cortex (Brodmann areas 39 and 40) and dorsolateral prefrontal cortex (Brodmann area 46), and the midbrain and

cerebellum. Activations in the somatosensory cortices (SI, SII) or the thalamus were not detected. A similar PET activation study compared histamine-induced itch with saline controls and performed both subtraction and correlation analyses (Darsow *et al.*, 2000). Subtraction analysis of the main effect revealed the following predominantly or exclusively contralateral (left) activations: SI somatosensory and motor cortices, supplementary and premotor cortices, anterior cingulate, orbitofrontal and superior temporal cortices. Perceived itch intensity correlated with activation of the contralateral somatosensory and motor areas. Activation of several areas including the contralateral insula, somatosensory association (Brodmann areas 2 and 5), posterior parietal (Brodmann area 19) and prefrontal areas (Brodmann area 10) correlated with wheal, flare and temperature reactions of the skin (Darsow *et al.*, 2000). This group obtained similar results in a follow-up PET study, commenting on the similarity of itch and pain activations except for a more predictable activation of motor-related structures during itch and a lack of itch-related thalamic activity (Drzezga *et al.*, 2001). However, thalamic activation was observed in a PET study of itching induced by histamine iontophoresis (Mochizuki *et al.*, 2003). In that investigation, perceived itch intensity and itch-related activation of the anterior cingulate, parietal, premotor and dorsolateral prefrontal cortices was reduced while PAG activation appeared during counterstimulation with cold or itch stimulation. A subsequent fMRI study by this group compared within-subject brain activations during equal periods of contact cold pain and itching induced by histamine iontophoresis (Mochizuki *et al.*, 2007). Group-wise comparison showed that thalamic activation was present only during pain but BOLD activity was greater during itch in the posterior cingulate and posterior insular cortices; activity in these latter structures correlated with itching but not pain. The SII cortex, ACC, anterior insula, basal ganglia and SMA were active in both conditions.

In two fMRI studies, *deactivations* (negative BOLD signals compared with baseline) were observed specifically during itching. Herde *et al.* (2007) used histamine iontophoresis but truncated the itching period (~3 min) with the infusion of lidocaine. In a group comparison of itching and 28 s of contact heat pain, they found unique, itch-related deactivations bilaterally in the subgenual anterior cingulate cortex and amygdala. Other salient differences included a more symmetrical bilateral activation of the anterior insula and thalamus during itch. The authors suggest that the itch experience may be more stressful than heat pain because of its longer duration. Itch-specific deactivations were also observed by Valet *et al.* (2008). They used fMRI and controlled the duration and intensity of itching by thermal modulation of the histamine site. Under the conditions of their experiment, cooling enhanced and heating attenuated histamine-induced

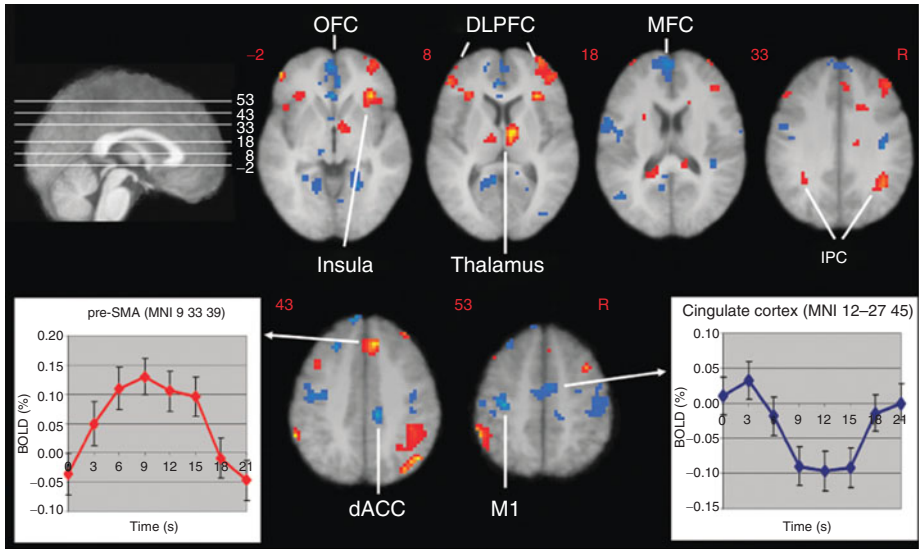


Fig. 5.39. Activations (red-yellow) and deactivations (blue) during 8 s periods of itching induced by thermal modulation of cutaneous histamine. BOLD signal changes shown for the supplementary motor area (SMA, right inset) and the dorsal mid-cingulate cortex (left inset). Adapted from Valet *et al.* (2008).

itch and allowed itching to be increased and decreased in ~ 20 s cycles. During the first 8 s of the most intense itching, the main effects contrast revealed thalamic activation in addition to activation of the supplementary motor area, anterior insula, inferior parietal and dorsolateral prefrontal cortices. Most notably, itch-specific deactivations appeared in the orbitofrontal, medial frontal, mid-cingulate and primary motor cortex (Fig. 5.39); the authors suggest that this deactivation may reflect a disinhibition that permits the itching to occur (Valet *et al.*, 2008). As discussed earlier in this chapter, deactivations occur against the background of ongoing activity. Both studies reporting deactivations used methods that limit the duration of itching, perhaps introducing another variable, such as the anticipation of itching relief, that may be related to this unique BOLD response. It is therefore notable that, in an investigation comparing the effect of histamine and allergen-induced pruritis, itching was prolonged, lasting throughout the 17 min of fMRI acquisition, and no deactivations were reported (Leknes *et al.*, 2007). Instead, the authors comment on the consistent activations, during histamine and allergen-induced pruritis, in structures associated with establishing hedonic and motivational valence such as the ventral striatum (n. accumbens), pregenual ACC and orbitofrontal cortex (see also Becerra *et al.*, 2001).

Tooth pain

Jantsch *et al.* (2005) used fMRI to compare the pain following electrical stimulation of tooth pulp with brief, painful mechanical stimulation (impact of a pneumatically driven cylinder) of the hand. Impedance and current monitoring were used to assure that the tooth stimulation was confined to the tooth pulp. Both types of stimuli were adjusted to approximate equal perceived intensities and both activated the somatosensory (SI and SII), insular and anterior cingulate cortices; the precentral, orbital, inferior frontal, medial frontal and superior frontal gyri responded also. In the group contrast analysis, mechanical pain evoked larger BOLD responses in the posterior part of the anterior cingulate cortex; tooth pain was associated with larger responses in the insula and in the motor and medial frontal areas. In post-scan interviews, tooth pain was judged to be more unpleasant at the beginning of the 20 s stimulation period and hand pain was more unpleasant at the end; whether there is a direct relationship between these perceptual and brain activation differences has not been determined.

Muscle pain

Psychophysics Muscle pain can be induced experimentally most specifically (without cutaneous stimulation) by direct electrical stimulation within the muscle or by the infusion of algogenic substances, most commonly hypertonic saline (Giamberardino *et al.*, 1988; Vecchiet *et al.*, 1988; Zhang *et al.*, 1993; Graven-Nielsen *et al.*, 1997a, 1997b). Psychophysical studies show that experimentally induced muscle pain, like muscle pain in clinically painful conditions, is perceived as deep, aching, usually dull, poorly localized compared to skin pain, and commonly referred to beyond neighboring myotomes (Kellgren, 1938). In the intramuscular hypertonic saline model, pain intensity and area increases with repeated infusions and appears to be mediated by receptors responding to both mechanical and chemical (ionic) stimuli (Graven-Nielsen *et al.*, 1997a, 1997b). Although the exponent of the log-log plot of the psychophysical curve for intramuscular electrically induced pain is significantly lower than for cutaneous infra-red laser pain, at any given intensity intramuscular pain is rated as more unpleasant (Svensson *et al.*, 1997c); and unpleasantness increases with pain duration in the hypertonic saline model (Stohler and Kowalski, 1999). Intraneural microstimulation and recording in human muscle afferent nerves shows that muscle pain is mediated by activity in slowly conducting A δ and C fibers (Simone *et al.*, 1994; Marchettini *et al.*, 1996). The cerebral potentials evoked by painful intramuscular electrical stimulation are also consistent with the participation of A δ afferent fibers in

intramuscular pain and include frontal activity that is not evoked by noxious cutaneous infra-red laser stimulation at any perceived intensity (Svensson *et al.*, 1997a). Consistent with the finding of diffuse noxious inhibitory controls (DNIC) in animal and human studies (Le Bars *et al.*, 1979a, 1979b; Bouhassira *et al.*, 1993), experimentally induced muscle pain in humans elevates the pressure pain threshold at heterotopic sites (Graven-Nielsen *et al.*, 1998) and is likewise attenuated by either painful or painless heterotopic stimulation (Svensson *et al.*, 1999).

Imaging muscle pain Svensson *et al.* (1997b) used H_2^{15}O PET to compare the cerebral activations evoked by ~100 s of painful constant electrical intramuscular and repetitive (0.5 Hz) infra-red laser stimulation. Pain intensities were not different between the two forms of stimulation. In contrast with innocuous stimulation, cutaneous laser stimulation activated the contralateral thalamus, and the SII, anterior insular, prefrontal (Brodmann areas 10/46) and inferior parietal (Brodmann area 40) cortices; the ipsilateral premotor cortex (Brodmann area 6) was activated also. During intramuscular, but not cutaneous pain, the contralateral anterior cingulate and ipsilateral cerebellum responded; no response was detected in the anterior insula, thalamus, prefrontal or premotor cortices but the ipsilateral cerebellum was activated. Despite the differences in the pattern of activation among structures, a VOI-directed comparison failed to detect significant differences in the pain-related responses of any of these structures; this is probably due primarily to the presence of subthreshold activations that rendered within-VOI across-condition comparisons (anterior cingulate cortex, for example) statistically insignificant. In any case, these results suggested that the perceived differences between these muscular and cutaneous pains are mediated by within-structure differences in neuronal activity rather than in the unique activation of separate brain structures. In another PET activation study, Kupers and colleagues injected hypertonic saline into the masseter muscle, producing moderate to severe pain (Kupers *et al.*, 2004). A fixed-effects analysis revealed bilateral responses in the dorsal-posterior insula, anterior cingulate and prefrontal cortices, right posterior parietal cortex, brain-stem (in the area of the PAG) and cerebellum. Hyperesthesia induced by tactile stimulation over the painful muscle was rated just near pain threshold and was associated with activation in the subgenual cingulate gyrus and the ventral and dorsal medial thalamus; however, there was no direct comparison of cutaneous and muscle pain of similar intensities.

Schreckenberger and colleagues used ^{18}F fluorodeoxyglucose PET in 40 healthy individuals to compare the glucose metabolic responses to equally intense longer duration cutaneous and muscular pain induced by the infusion of an

acidic solution (Schreckenberger *et al.*, 2005). This approach has the advantage of applying similar stimuli and may avoid autonomic responses to repetitive pulsatile stimuli. However, radiation safety considerations limit the number of experimental conditions to which each individual may be exposed. Accordingly, for this comparison, the participants were divided into three groups: a pain group (two scans each with painful skin and muscle stimulation), a sham group (two scans each with painless infusions of skin and muscle) and a control group ($N = 20$) without stimulation. The analysis was restricted to VOI based on previous pain imaging studies. During both skin and muscle pain, glucose uptake in the bilateral insular cortex correlated with unpleasantness. Compared with the sham group, only the muscle pain group showed more glucose uptake bilaterally in the medial frontal gyrus and insula. The comparison of skin and muscle pain (within the pain group) revealed that, during the 20 s of each condition, the bilateral medial prefrontal cortex (Brodmann area 10) and the contralateral precentral gyrus and medial dorsal thalamus were activated more by intramuscular than cutaneous pain. But when the activations produced by the sham stimulation (sham group) were considered in comparing skin and intramuscular pain, there was no difference in glucose metabolism among any of the regions investigated. In accord with Svensson *et al.* (1997b), the authors concluded "... that superficial and deep pain processing may recruit very similar anatomic brain regions" (Schreckenberger *et al.*, 2005, p. 1181). Thus, the encoding of perceptual differences between these types of pain may occur within similarly activated brain structures. Indeed, Henderson *et al.* (2006) were able to detect within-structure activation differences in an fMRI investigation comparing equal intensities of ~4 minutes of skin and muscular pain evoked by the injection of hypertonic saline. Both types of pain evoked BOLD responses in the insular, cingulate and somatosensory cortices but the BOLD responses were different within each of these areas. In the primary somatosensory (SI), motor (M1) and insular cortices, adjacent clusters of voxels showed either no difference or an increased BOLD response to muscular, compared with cutaneous, pain. The cingulate cortex was divided into sectors according to Vogt and colleagues (Vogt *et al.*, 2003; Vogt, 2005) and BOLD activations in some voxels were greater during muscle than during skin pain in the cingulate motor region; in the perigenual sector, however, *deactivations* were associated with both types of pain, the muscle pain response being larger (Fig. 5.40). As noted previously in this chapter, *deactivations* signal a reduction in regional perfusion, perhaps related to unrecognized increased baseline activity in this region in anticipation of the noxious stimuli. In a subsequent fMRI investigation, these investigators detected a somatotopic organization (leg and forearm) of BOLD responses in the insula to skin and muscle pain with muscle pain responses in the ipsilateral anterior insula

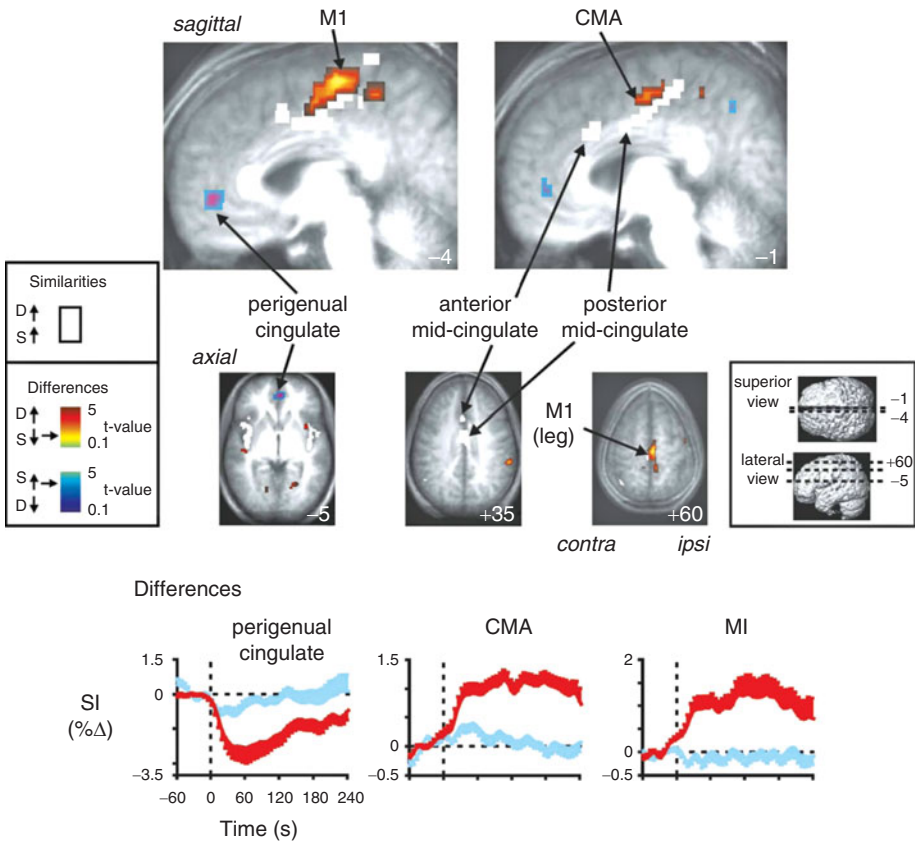


Fig. 5.40. BOLD response differences during cutaneous and muscle pain evoked by hypertonic saline. Color scale at left encodes positive (up arrows) or negative (down arrows) BOLD responses during skin (S = superficial) or muscle (D = deep) pain. Sagittal (top) and transverse or superior (middle row) brain views show voxel clusters with equal positive BOLD responses to both stimuli (white). BOLD responses during muscle pain were greater (red–yellow) than during skin pain in the primary motor cortex (M1; leg area) and the adjacent cingulate motor area (CMA) as shown by the two BOLD response graphs in the lower right and center (muscle response, red; skin response, blue). In the perigenual cingulate cortex, deactivating BOLD responses occurred during both stimuli (left graph). Adapted from Henderson *et al.* (2006).

being anterior to skin pain activations (Henderson *et al.*, 2007). In summary, current evidence suggests that the perceptual differences between cutaneous and muscular pain are most likely to be encoded by differences in the responses of neuronal groups within, rather than between or among, brain structures identified at the gross anatomical level.

Visceral pain

Psychophysics Visceral pain is commonly experienced as quite different from somatic pain. In a systematic, quantitative study of graded colonic distention in healthy volunteers, Ness and colleagues found that affective descriptors such as “unpleasant” and “annoying” were used even at low perceived intensities (Ness *et al.*, 1990). As expected, the pain has an aching or cramping quality and is perceived as deep to overlying somatic areas occupying major fractions of the body surface. Spatial summation of the pressure/pain is detected as increasing areas of pain referred to the commonly innervated somatic spinal segment. The intensity and negative hedonic quality of the sensation increases rapidly with increasing distention and, consistent with temporal summation, repeated distensions of equal intensity are perceived as increasingly intense and unpleasant (Ness *et al.*, 1990). In a subsequent study comparing the pain of esophageal distension with contact heat applied to the midline chest, Strigo and colleagues found that, in accord with the findings of Ness *et al.* (1990), the threshold for pain intensity during esophageal distension was higher than for unpleasantness; this was not true for contact heat pain (Strigo *et al.*, 2002). In addition, the ratio of unpleasantness to intensity was higher, at all intensity levels, for esophageal pain than for heat pain. As discussed in Chapter 3, visceral pain is mediated primarily through postsynaptic neurons in the medial part of the spinal cord dorsal columns (see also Willis *et al.*, 1999) and there is considerable convergence of somatic and visceral inputs onto neurons in the spinal cord, dorsal column nuclei and ventral posterior lateral thalamus in rodents and primates (Berkley *et al.*, 1993; Brüggemann *et al.*, 1994; Berkley and Hubscher, 1995; Lenz *et al.*, 1997; Al Chaer *et al.*, 1998, 1999; Foreman, 1999; Zhang *et al.*, 2002). Given the unique perceptual characteristics of visceral pain and the pathways mediating it, it is reasonable to expect consistent differences in the pattern of cerebral activation during visceral pain; however, the degree of convergence at the cellular level would argue for considerable overlap of cerebral responses given the level of spatial resolution in functional imaging.

Imaging visceral pain Although the gut is the visceral organ most intensively studied with functional imaging, there are a few investigations related to the issue of chest pain caused by cardiac ischemia. Rosen *et al.* (1994) used the dobutamine stress test during $H_2^{15}O$ PET to induce angina in 12 patients with known coronary artery disease. During angina (dull retrosternal chest pain) with electrocardiographic evidence of myocardial ischemia, there were blood perfusion increases in the hypothalamus, midbrain (PAG), bilateral thalamus and in the lateral prefrontal and anterior cingulate cortices. The thalamic, but not the

cortical, activations persisted after the angina subsided, suggesting to the authors that the thalamus may have a gating or modulatory function on the cortical responses because thalamic activity was uncoupled from the pain. This hypothesis was supported in a subsequent PET study that included patients with painless (silent) myocardial ischemia (Rosen *et al.*, 1996). In contrast with patients experiencing cardiac pain, the patients without pain showed only right frontal activation and reduced activation in the basal forebrain and cingulate cortex during myocardial ischemia; the thalamus, however, was activated bilaterally equally in both groups. Given the regularity with which the insular cortex is activated during pain, it is notable that insular activation is not reported in the above studies. Critchley and colleagues, for example, observed activity in the insula in addition to the somatosensory and cingulate cortices in healthy individuals who were instructed to monitor accurately their own heart beat (Critchley *et al.*, 2004). Nonetheless, the results reported by Rosen and colleagues suggest that painless myocardial ischemia, which had been considered a sign of impaired cardiac innervation, may be caused by an unusually robust thalamocortical inhibitory gating mechanism in some individuals (Casey, 1996; Rosen and Camici, 2000).

Imaging studies during gut distension reveal little that is surprising in view of the known convergence of somatic and visceral inputs at the cellular level. In a PET activation study by Aziz and colleagues the bilateral insular, primary somatosensory (SI) and frontoparietal opercular cortices were activated during either painless or painful esophageal distention; during painful stimulation, however, only the right anterior insular and anterior cingulate cortices were active. There was no comparison of the responses during somatic stimulation (Aziz *et al.*, 1997). In a subsequent fMRI investigation (Aziz *et al.*, 2000), painless distension of the proximal esophagus resulted in a different cerebral activation pattern than painless distension of the distal esophagus. With proximal distension, the sensation of fullness was localized to the upper chest and the brain activation appeared in the trunk region of the left primary somatosensory cortex (SI); the right mid-anterior cingulate was activated also. In contrast, distal esophageal distention was more diffusely localized to the lower chest and was associated with activations at the junction of the primary and secondary (SII) somatosensory areas bilaterally, in the perigenual region of the cingulate cortex, and in the cerebellum. The authors relate their findings to the magnetoencephalographic (MEG) studies of Schnitzler and colleagues, who found that the relatively poorly localized esophageal sensations were related to MEG responses in the SII cortex whereas well localized somatic sensations were represented by responses in the SI cortex (Schnitzler *et al.*, 1999). In reviewing 15 functional brain imaging studies of visceral sensation through May 2002, Derbyshire (2003) commented

that "... (there is) considerable consistency in the activation of prefrontal, primary and secondary sensory, mACC (mid-anterior cingulate cortex), SMA (supplementary motor cortex), pACC (posterior anterior cingulate cortex), orbitofrontal, and insular cortices during stimulation of the viscera" (p. 16, parentheses added). In particular, he noted the activation differences during stimulation of the rostral (esophageal) and caudal (rectal) portions of the gastrointestinal tract and the possible relationship of these differences to the discriminative and affective dimensions of visceral sensation.

In the first brain imaging study to compare directly visceral and cutaneous pain, Strigo and colleagues compared the fMRI BOLD responses to painless and painful distention of the distal esophagus with those evoked by painless and painful contact heat stimulation of the midline chest (Strigo *et al.*, 2003). The perceptual differences between visceral and cutaneous stimuli were consistent with the psychophysical findings discussed above; at any given perceived intensity, the relative unpleasantness was greater during the visceral stimulation. A direct VOI comparison of structures responding differentially to the noxious levels of stimulation shows that, at equal levels of perceived intensity, visceral, but not cutaneous, pain was accompanied by bilateral activity in the inferior primary somatosensory (SI) and primary motor (M1) cortices; also, a more rostral part of the anterior cingulate cortex was activated during visceral pain. The right anterior insula responded more during cutaneous than visceral pain. Otherwise, both types of stimuli activated a network of structures that included the secondary (SII) somatosensory cortex, thalamus, basal ganglia and cerebellum. These investigators have also found differences in the location of esophageal and chest heat pain activations in the parasyllian cortex (Strigo *et al.*, 2005). Nonetheless, it is difficult to relate the activation differences found in these studies with the perceptual differences, primarily hedonic, between visceral and somatic (cutaneous) pain.

In another approach to differentiating visceral and somatic pain, Dunckley and colleagues also compared the activations associated with cutaneous heat and visceral (rectal) distension pain but at equal levels of unpleasantness; accordingly, the perceived intensity of heat pain was greater under these conditions (Dunckley *et al.*, 2005a). The activation overlap between these different stimuli was striking and included the bilateral thalamus, insular cortex, mid-cingulate cortex, supplementary motor area, globus pallidus and medial mid-brain (Fig. 5.41). In a direct VOI comparison of structural activation differences, only the bilateral perigenual, posterior cingulate and ventromedial prefrontal cortices showed a differential response and this was a greater *deactivation* during visceral, compared with somatic pain. The authors suggest that these deactivations may be related to prestimulus anticipation of the visceral stimulus. In a

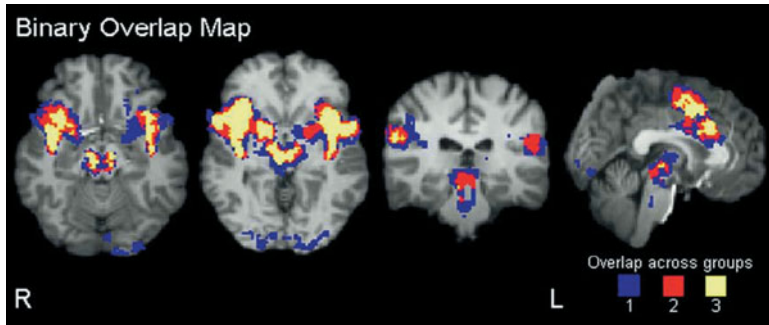


Fig. 5.41. Overlap of activations evoked by visceral (rectal balloon) or somatic (noxious heat pain to foot or low back) stimuli. Participating healthy subjects received each type of stimulation as a group member in separate fMRI sessions. Activations in one group are shown in blue, two groups in red and all three groups in yellow (color code at lower right). All three types of stimuli activated the bilateral thalamus, insular cortex, mid-cingulate cortex, supplementary motor area, globus pallidus and medial midbrain. Adapted from *Dunckley et al. (2005a)*.

related fMRI study specifically of brainstem responses, members of this group applied intensity-matched electrical stimuli to the rectum and lower abdomen. Again, both types of stimuli activated similar brainstem structures (periaqueductal gray, nucleus cuneiformis, substantia nigra and the parabrachial and red nuclei) but the visceral stimulation evoked a greater response in the nucleus cuneiformis. The authors suggest that this differential response may be related to the hedonic difference between visceral and somatic sensations (*Dunckley et al., 2005b*).

Summary

From the discussion in this chapter, it seems clear that the introduction of functional brain imaging has dramatically changed the course of pain research by providing an opportunity to examine, at a regional anatomical level, the function of a living human brain that can communicate its experience. We have learned that the change in regional blood perfusion is a useful surrogate measure of the activity of large groups of neurons and that this measure can be used to gain insight into the function of large-scale neuronal networks, the activity of which leads to the experience of pain. We have begun to learn how the brain participates actively in modulating pain, indeed in determining whether pain occurs at all. However functional brain imaging in its present form cannot alone reveal fully the neurobiological mechanisms responsible for pain (see also Logothetis, 2008); additional information must come from multiple other

sources including detailed psychophysical analyses of the effect of well-defined lesions, investigations of the neurobiology of the plastic changes that follow neurological lesions, electrophysiological studies of neuronal ensembles and their long-range connections, and the analysis of selective pain modulations caused by drugs, disease and genetic variation. However, functional imaging can help identify, at least at the neuroanatomical systems level, the critical and unique patterns of brain activity that mediate similar and different pain experiences and the neural systems that modulate them. We can anticipate that more critical information will be forthcoming as temporal and spatial resolution improves and as new imaging ligands are developed for the investigation of the central neurochemical variables affecting pain.

Endnotes

1 This word is used here as defined by definition 1b in <i>Webster's 3rd New International Dictionary</i> , G & C Merriam Company, Springfield, MA, (1971), p. 1048, to refer to	"... the psychological range of feelings from pleasant to unpleasant ..."	the term "pain imaging," but we will use it here occasionally for convenience.
2 The multidimensionality of pain calls into question the current widespread use of		

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Pain modulatory systems

Introduction

It is well known that much of the sensory input to the central nervous system can be modulated by centrifugally organized control systems that originate in the central nervous system (Head and Holmes, 1911; Hagbarth, 1960). The control mechanisms can be excitatory or inhibitory processes that may occur in the periphery or within the central nervous system. Inhibition can be at pre- and/or postsynaptic sites (Fig. 6.1(I)). Presynaptic inhibition at the first central synapse of a sensory pathway has the potential advantage of being able to reduce sensory input prior to wide dissemination of that sensory input within the central nervous system through the activation of interneuronal networks and multiple ascending pathways, for example, in the spinal cord (Schmidt, 1973; see Chapter 3).

Pre- and postsynaptic inhibition can have somewhat different effects on the stimulus-response curves of second-order sensory neurons, as shown in Fig. 6.1(II). Postsynaptic inhibition involves inhibitory postsynaptic potentials that sum with excitatory postsynaptic potentials (Fig. 6.1(IIA)). If there is a linear summation, the stimulus-response curve will be shifted to the right in a parallel fashion (Carstens *et al.*, 1980). However, if the IPSP is generated in a membrane area near that in which the EPSP is generated, the excitatory current may be shunted and the slope of the stimulus-response curve reduced, causing a reduction in the gain of synaptic transmission (Fig. 6.1(IIIB)). A similar reduction in gain can be produced by presynaptic inhibition.

Sensory modulatory pathways include what are often referred to as the endogenous analgesia system (see reviews by Mayer and Price, 1976; Basbaum and Fields, 1978; Willis, 1982). The endogenous analgesia system is accessible to

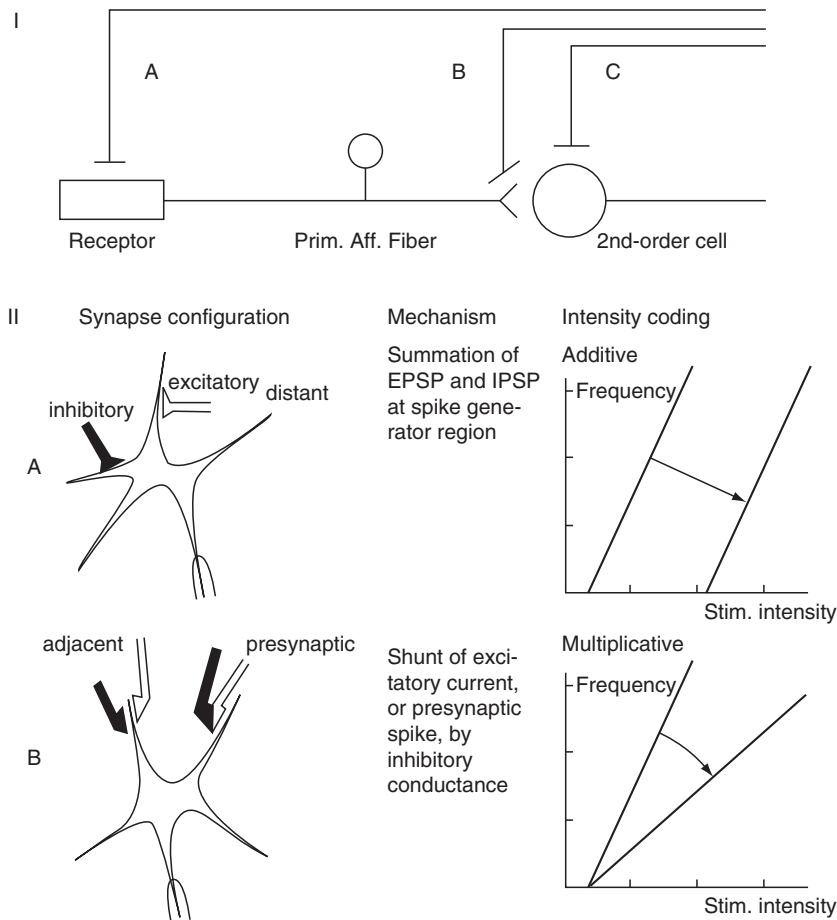


Fig. 6.1. The diagram in (I) indicates several of the sites at which a centrifugal control system originating in the central nervous system can exert its effects on an afferent pathway. In (A), the control system is shown to act directly on a peripheral sensory receptor organ. An example of this would be the action of gamma motor neurons on a muscle spindle. In (B), the control system reduces the release of neurotransmitter from the terminals of primary afferent fibers by means of presynaptic inhibition. This form of inhibition results from primary afferent depolarization. In (C), the control system employs postsynaptic inhibition to reduce the transmission of information by second-order sensory neurons. (From Schmidt, 1973.) (II) shows how different arrangements of the synapses made by a centrifugal control system can result in different effects on the stimulus-response curves of sensory neurons in the central nervous system. In (A), postsynaptic actions are exerted on different parts of the surface membrane of a central neuron. If the excitatory and inhibitory postsynaptic potentials (EPSP and IPSP) sum linearly, the IPSP will produce a parallel shift of the stimulus-response curve to the right. In (B), if an IPSP is evoked by synapses placed near those that generate an EPSP, shunting of the excitatory current may result, causing a reduction in the slope (gain) of the stimulus-response curve. Presynaptic inhibition of the excitatory pathway would have a similar effect. From Carstens *et al.* (1980).

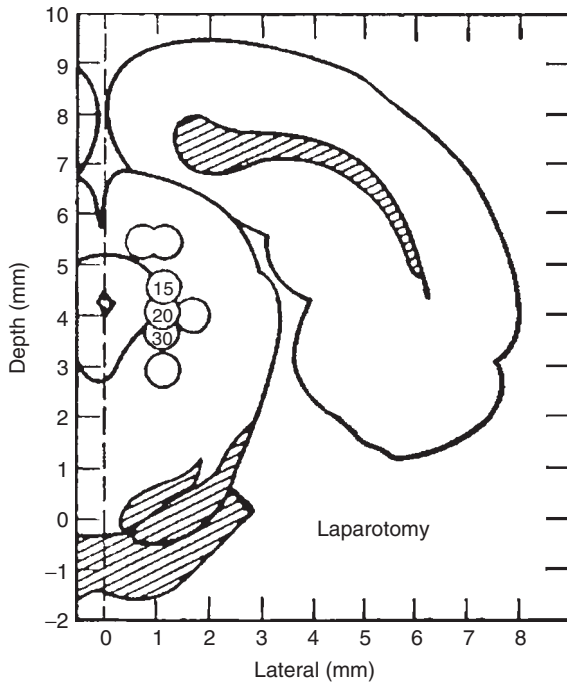


Fig. 6.2. Sites near the PAG that when stimulated electrically resulted in analgesia in rats undergoing exploratory laparotomies. Effective sites are indicated by circles containing numbers corresponding to the stimulus currents (in μA) that were used. Circles without numbers were ineffective sites even with maximum stimulus currents ($35 \mu\text{A}$). From Reynolds (1969).

therapeutic interventions for pain relief using pharmacological agents (such as morphine) that act on the appropriate receptors (e.g. μ -opiate receptors) at central synapses (Tsou and Jang, 1962; Yaksh and Rudy, 1978) or using stimuli that directly activate neural elements of the analgesia system (Besson *et al.*, 1981). Analgesia evoked by electrical stimulation within the brain is called “stimulation-produced analgesia” (SPA; Mayer and Liebeskind, 1974). The endogenous analgesia system is also likely to be engaged when psychological factors, such as stress, influence pain responses (Beecher, 1959; Bodnar *et al.*, 1978, 1980).

Many experimental studies of the endogenous analgesia system were encouraged by the seminal publication by Reynolds (1969) describing his finding that abdominal surgery could be performed on awake rats during focal electrical stimulation applied near the midbrain periaqueductal gray (PAG; see Fig. 6.2). Although the rats did not react to painful stimuli during PAG stimulation, they continued to respond to tactile stimulation, and so it could be concluded that the PAG stimulation produced analgesia, rather than anesthesia. Since the PAG

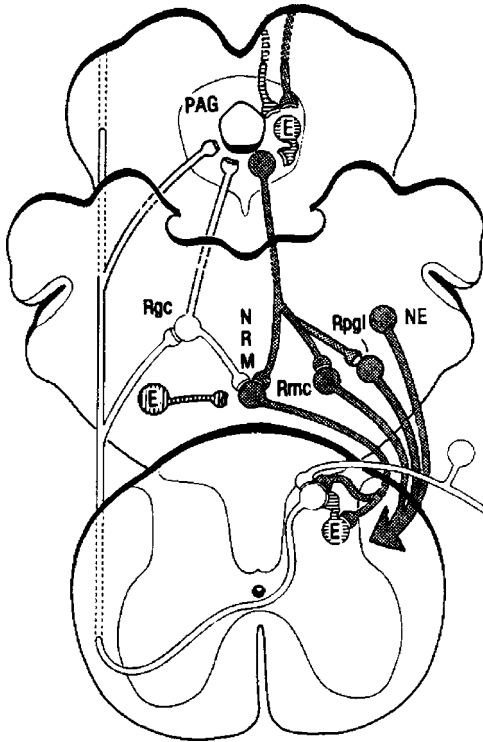


Fig. 6.3. Drawing illustrating the descending endogenous analgesia pathways centered on the periaqueductal gray (PAG). Connections are shown from the PAG to the nucleus raphe magnus (NRM), the nucleus reticularis magnocellularis (Rmc) and nucleus reticularis paragigantocellularis lateralis (Rpgl). A noradrenergic projection (NE) is also depicted, although its origin is not identified. Afferent inputs to the PAG from higher centers and from the spinal cord and brainstem are shown. Several sites proposed to involve endorphin-containing interneurons are indicated (E). From Basbaum and Fields (1984).

has few direct projections to the spinal cord, the neural pathways responsible for the analgesia were suggested to relay at a lower level of the brainstem in several nuclei of the rostral ventral medulla, including the nucleus raphe magnus (NRM) and adjacent reticular nuclei, the nucleus reticularis magnocellularis (Rmc) and the nucleus reticularis paragigantocellularis lateralis (Rpgl) (Fig. 6.3; Basbaum *et al.*, 1978; Basbaum and Fields, 1979; Behbehani and Fields, 1979; see review by Basbaum and Fields, 1984). Axonal projections from these nuclei descend in the dorsal part of the lateral funiculus, as shown by lesion studies (Engberg *et al.*, 1968; Fields *et al.*, 1977), synapse in the spinal cord dorsal horn, and inhibit nociceptive dorsal horn neurons (Fields *et al.*, 1977; Akaike *et al.*, 1978). The inhibition could be through the action of projections of bulbospinal neurons

(such as serotonergic and peptidergic projections from the NRM and other raphe nuclei; Akil and Liebeskind, 1975; Bowker *et al.*, 1981) that synapse directly on ascending nociceptive tract cells or it could be mediated by way of inhibitory interneurons, including opioid-containing cells in the dorsal horn. In addition, there is a noradrenergic bulbospinal projection which was shown to originate in the nuclei locus coeruleus and subcoeruleus and related cell groups of the dorsolateral pontine tegmentum (Westlund *et al.*, 1981). The PAG receives input both from higher centers and also from the spinal cord and lower brain stem (Fig. 6.3; Beitz, 1982). These connections provide a mechanism for the engagement of the endogenous analgesia system without external intervention.

Many of the studies done soon after the report by Reynolds involved experiments on commonly used laboratory animals, such as rats and cats, and often involved stimulation not only of the PAG but also of the nucleus raphe magnus or sites within the brainstem reticular formation (Mayer *et al.*, 1971; Oliveras *et al.*, 1974a, 1975, 1977, 1979; see also reviews by Fields and Basbaum, 1978; Willis, 1982; Jones, 1992; Willis and Coggeshall, 2004). However, some investigations were also carried out on monkeys (e.g. Beall *et al.*, 1976; Willis *et al.*, 1977; Gerhart *et al.*, 1981) and even on humans (Hosobuchi *et al.*, 1977, 1979). Deep brain stimulation in patients has since emerged as an important neurosurgical option for pain therapy (Gybels and Sweet, 1989).

In experimental animals, such as rats, it is a common practice to use flexor withdrawal reflexes (Creed *et al.*, 1932; Eccles and Lundberg, 1959a, 1959b; Holmqvist and Lundberg, 1959, 1961; Holmqvist *et al.*, 1960) as behavioral tests for the development of “analgesia” (or “antinociception”) following stimulation in a region of the central nervous system (Willis, 1982). Reflex withdrawal of a limb can be evoked by chemical or thermal stimulation of a paw (Dubuisson and Dennis, 1977; Hargreaves *et al.*, 1988) or by strong mechanical stimulation, such as by the application of stiff von Frey filaments, to produce a paw withdrawal response. Other experimentally useful flexion reflex responses include the tail flick reflex (D’Amour and Smith, 1941) and the jaw opening reflex (Mitchell, 1964; Oliveras *et al.*, 1974b). These reflexes are most readily evoked in unanesthetized animals, but at least weak responses can often be observed in lightly anesthetized animals. The function of these reflexes is to withdraw the body part from the noxious stimulus, and so the sensory consequences of at least some of these noxious stimuli are minimized in awake, behaving animals.

Another way to test for the development of an antinociceptive response due to central nervous system stimulation is to compare the responses of central neurons to noxious stimuli before and during or after the CNS stimulation. For example, if stimulation in a particular region of the brain causes a reduction in the nociceptive responses of a central sensory neuron, it can be argued that this

change in neural activity is a part of an antinociceptive response that would be manifested as analgesia in a human subject, who could report a sensory change. The kinds of nociceptive neurons that are generally tested include both wide dynamic range and nociceptive-specific dorsal horn neurons (see [Chapter 3](#)). However, the possible relationship between the activity of such neurons and the sensory experience of pain is strengthened if the recordings are made from neurons whose axonal projections are identified by antidromic activation in order to demonstrate that the neurons belong to a sensory pathway known to contribute to pain sensation, such as the spinothalamic tract (see [Chapter 3](#)). Excitation of some nociceptive interneurons, of course, would be expected to help activate nociceptive tracts that convey pain signals to higher centers. However, an unidentified interneuron could instead be inhibitory, or it could contribute to motor control, rather than to sensory experience ([Chapter 3](#)). The point is that it is difficult to determine the function of neurons that are unidentified with respect to their axonal projections.

Brain structures that, when stimulated electrically, can result in the inhibition of the activity of nociceptive dorsal horn neurons, such as monkey, cat or rat spinothalamic tract (STT) cells, include the periaqueductal gray, nucleus raphe magnus, nucleus reticularis gigantocellularis and midbrain reticular formation (McCreery and Bloedel, 1975; Beall *et al.*, 1976; Willis *et al.*, 1977; Haber *et al.*, 1978, 1980; Hayes *et al.*, 1979; McCreery *et al.*, 1979; Gerhart *et al.*, 1981a, 1984; Giesler *et al.*, 1981; Yezierski *et al.*, 1982; Ammons *et al.*, 1984; Carstens, 1988), the locus coeruleus, subcoeruleus/parabrachial region (Mokha *et al.*, 1985; Brennan *et al.*, 1987; Girardot *et al.*, 1987), ventral posterior thalamus (Gerhart *et al.*, 1981b, 1983) and somatosensory cerebral cortex (Coulter *et al.*, 1974; Yezierski *et al.*, 1983). Excitatory effects of stimulation in the PAG or the VPL thalamic nucleus on primate raphe-spinal and reticulospinal neurons have been demonstrated (Willis *et al.*, 1984), supporting the view that the more rostral parts of the endogenous analgesia system have a synaptic relay in the medulla oblongata. These observations may explain the analgesic effect of motor cortex stimulation and deep brain stimulation upon chronic pain, as described in [Chapter 9](#).

Intracellular recordings from monkey STT neurons have shown that stimulation in the nucleus raphe magnus can result in postsynaptic inhibition of nociceptive spinal cord neurons (Giesler *et al.*, 1981). For example, in [Fig. 6.4](#) are shown intracellular recordings from a monkey STT cell. The antidromic action potential in [Fig. 6.4A](#) was evoked by stimulation in the contralateral ventral posterior lateral thalamic nucleus. The background activity of the neuron of [Fig. 6.4B](#) was inhibited when a train of stimuli was delivered in the NRM ([Fig. 6.4C](#); inset shows the stimulus site). The higher gain recording in [Fig. 6.4D](#) reveals an inhibitory postsynaptic potential (IPSP) that was produced

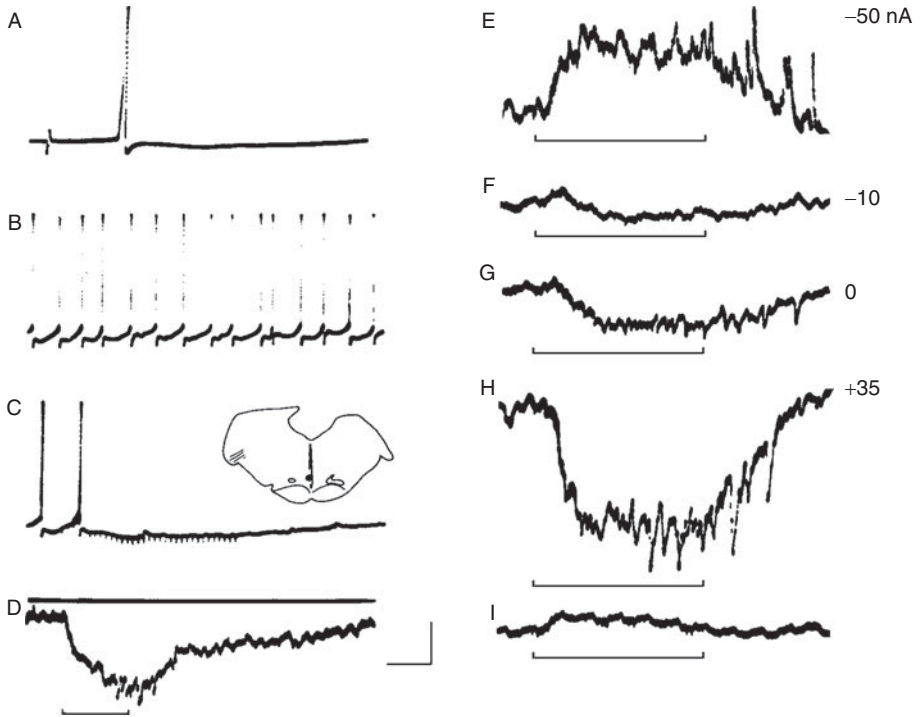


Fig. 6.4. Postsynaptic inhibition of a primate spinothalamic tract (STT) neuron evoked by stimulation in the nucleus raphe magnus (NRM). (A) is the antidromic action potential used to identify the neuron as an STT cell; the stimulus was delivered by an electrode placed in the contralateral ventral posterior lateral thalamic nucleus. (B) shows the background activity of the neuron. In (C), this activity was suppressed during repetitive stimulation at the site indicated in the inset (100 ms train of 200 μ A, 0.1 ms pulses at 333 Hz). (D) is the inhibitory postsynaptic potential (IPSP) produced by NRM stimulation and recorded at high amplifier gain. (E–H) show that the IPSP could be modified by the passage of current through the acetate-filled microelectrode used to impale the STT cell. The IPSP in (G) was recorded while no current was passed. The IPSP was reduced by a hyperpolarizing current nearly to the reversal potential in (F) and then inverted to a depolarizing potential in (E) when the current was increased. A depolarizing current increased the amplitude of the hyperpolarizing potential in (H). (I) is the field potential recorded just extracellularly. The durations of the stimulus trains are shown by the horizontal lines below the records in (D–I). From Giesler *et al.* (1981).

by the NRM stimulation. The IPSP could be affected in a predictable way when current was passed through the intracellular microelectrode (reversed in sign by a hyperpolarizing current in Fig. 6.4E and enlarged by a depolarizing current in Fig. 6.4H).

Primary afferent depolarization, which is a major factor in the mechanism underlying presynaptic inhibition (reviewed in Willis, 1999), has been demonstrated to occur in primary afferent fibers to the cat spinal cord, including nociceptive afferents, following stimulation in the medial lower brainstem in the nucleus raphe magnus (Martin *et al.*, 1979). The development of primary afferent depolarization was assessed using the excitability testing technique introduced by Wall (1958). The experimental arrangement is shown in the drawing at the top of Fig. 6.5. A stimulating electrode was placed in the spinal cord dorsal horn near the terminals of primary afferent fibers (including nociceptors) in order to test for changes in the excitability of the primary afferent fibers in response to stimulation in the brainstem. Intra-axonal recordings were made using a glass microelectrode that was inserted into the exposed sural nerve through an opening in the epi- and perineurium. A bipolar electrode placed in contact with the proximal part of the sural nerve was used to deliver stimuli that excited individual primary afferent fibers impaled by the microelectrode. Measurement of the latencies of the action potentials allowed the calculation of the conduction velocities of the afferent fibers. The conduction velocity and the receptive field properties of a given afferent fiber allowed it to be classified, for example, as a nociceptor or a mechanoreceptor (thermoreceptors were not encountered). For example, Fig. 6.5B shows the conduction velocity of an A δ -nociceptor and the location of its receptive field; the afferent fiber was found to be selectively activated by noxious mechanical stimuli applied to the receptive field. The stimulating electrode in the spinal cord dorsal horn was then used to determine the threshold of the terminals of the afferent fiber being recorded, and a firing index was calculated based on the proportion of times the afferent nerve fiber discharged following repeated spinal cord stimulation. The stimulus strength was set to result in a relatively small firing index (for example, the control firing index in Fig. 6.5C was about 20%, meaning that the axon discharged once for each five stimulus trials). After the control firing index was established, a site in the NRM was stimulated using electrical pulses of a given strength and the firing index of the afferent fiber in response to spinal cord stimulation was reassessed. In the experiment of Fig. 6.5, the firing index increased progressively with increasing intensities of NRM stimulation of 50, 100 and then 200 μ A, producing a progressive increase in primary afferent depolarization and presumably the strength of the consequent presynaptic inhibition.

In some instances, excitation rather than inhibition of monkey or cat spinothalamic neurons has been observed following stimulation in certain parts of the brain, including the nucleus reticularis gigantocellularis in the medulla (McCreery *et al.*, 1979; Haber *et al.*, 1980) and the sensorimotor cortex (Coulter *et al.*, 1974; Yeziarski *et al.*, 1983). Examples are given in the next section.

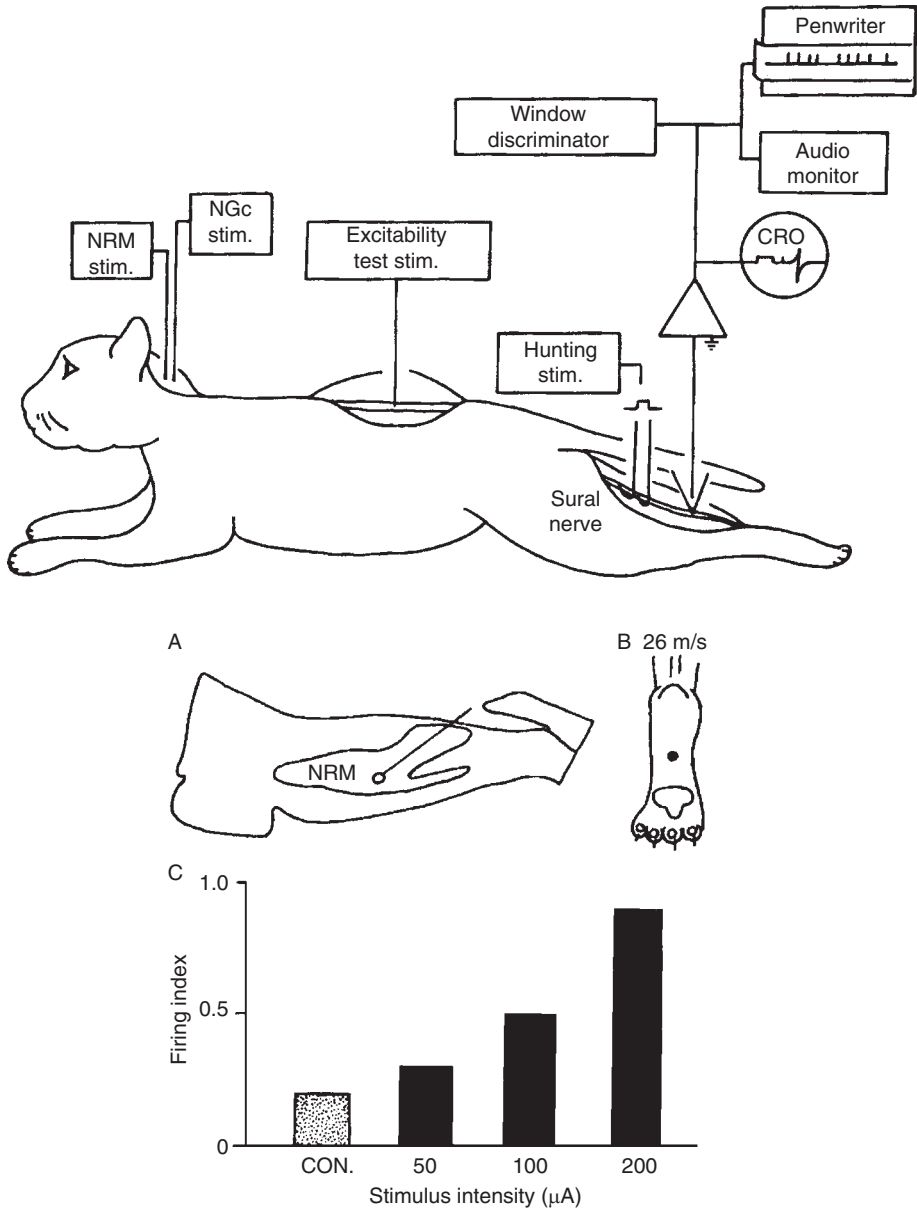


Fig. 6.5. Primary afferent depolarization (PAD) detected in nociceptive afferent fibers following stimulation in the nucleus raphe magnus (NRM) of anesthetized cats using the excitability testing technique of Wall (1958). The drawing at the top of the illustration shows the experimental arrangement. An electrode was inserted through a craniotomy into the medial brainstem to stimulate within either the NRM or the adjacent nucleus reticularis gigantocellularis (NGc). A laminectomy exposed the spinal cord so that an electrode could be introduced into the lumbar dorsal horn to activate the terminals of primary afferent fibers. The sural nerve was isolated in the left

Since interruption of the dorsolateral funiculi fails to prevent the excitatory effects of stimulation in the medullary reticular formation, the excitatory pathway must descend in the ventral quadrant of the spinal cord (Haber *et al.*, 1980).

The neurotransmitters that are released in the spinal cord following stimulation of brain structures that participate in the endogenous analgesia system include opiates, serotonin, norepinephrine and inhibitory amino acids (Oliveras *et al.*, 1975, 1977, 1979; Yaksh and Rudy, 1978; Yaksh, 1979; Hammond *et al.*, 1985; Sorkin *et al.*, 1988, 1991, 1993; Carlton *et al.*, 1991; Lin *et al.*, 1994; Cui *et al.*, 1999). Administration of these neurotransmitters, their agonists or their antagonists into the spinal cord can affect the inhibition of monkey spinothalamic neurons and other nociceptive spinal cord neurons evoked by stimulation of brain structures; evidence for excitatory actions of some of the neurotransmitters has also been noted (Yaksh and Rudy, 1976; Jordan *et al.*, 1979; Yezierski *et al.*, 1982; Hammond and Yaksh, 1984; Willcockson *et al.*, 1984a, 1984b; Peng *et al.*, 1996a, 1996b, 1996c, 2001; Lin *et al.*, 1996a, 1996b). The effects of exogenous drugs, such as barbiturates, and opioids, on the activity of monkey projection neurons presumed to be spinothalamic tract cells have also been examined (Hori *et al.*, 1984; Willcockson *et al.*, 1986).

Inhibition of monkey spinothalamic tract cells induced by stimulation in the periaqueductal gray or the ventral medial medulla oblongata

An example of the inhibition of the activity of a monkey spinothalamic tract (STT) cell during and for a short time following repetitive stimulation in the NRM or the PAG is shown in Fig. 6.6 (Yezierski *et al.*, 1982). The STT cell was

Caption for Fig. 6.5. (cont.)

hindlimb, and a bipolar stimulating electrode was placed in contact with the nerve to activate the individual nerve fibers (hunting stimulus) from which recordings were made with a glass microelectrode. The type of afferent neuron recorded from was determined based on the conduction velocity of its action potential and by its receptive field properties. The drawing in (A) in the lower panel shows the position of the tip of the brainstem stimulating electrode in a midsagittal section through the NRM. In (B), the receptive field of an A δ mechanical nociceptor is shown on a drawing of the paw, and the conduction velocity of the axon is indicated. The bar graph in (C) shows the firing index of the nociceptive afferent in the control condition (CON.) and just after a conditioning train of stimuli was delivered in the NRM (50 ms train of stimuli at 333 Hz at strengths from 50 to 200 μ A). The firing index was calculated by dividing the number of antidromic spike potentials recorded by the number of trials. The firing index was deliberately set to a low control level, since it was anticipated that the conditioning stimulation in the NRM would increase the firing index. From Martin *et al.* (1979).

classified as a nociceptive-specific neuron because when various intensities of mechanical stimulation were applied to the receptive field in the foot (Fig. 6.6B), the cell was activated strongly only by noxious squeezing of the skin (Fig. 6.6A). There was only a slight response to pinching the skin with an arterial clip that produced pain when used on the skin of the investigators, and there was no response to innocuous stimuli (Fig. 6.6A). The recording site for the neuron was in lamina I of the spinal cord dorsal horn (Fig. 6.6C). The stimulus sites in the NRM and in the PAG are indicated in Fig. 6.6D and E. Inhibition of the activity of the STT cell that was evoked by squeezing the receptive field is shown in the rate histograms in Fig. 6.6F and G.

Figure 6.7 (Gerhart *et al.*, 1981a) shows an example of the inhibition of the responses of a monkey STT cell to peripheral nerve afferent volleys during stimulation in the NRM. In this experiment, the STT cell was classified as a wide dynamic range neuron, and it was activated by electrical stimulation of the sural nerve at a strength sufficient to excite just A fibers or at a stronger intensity that also excited C fibers. The peristimulus time histogram in Fig. 6.7A illustrates the responses of the neuron to volleys in A α β and A δ fibers, whereas the histogram in Fig. 6.7C shows the additional later response when C fibers were also activated. Repetitive stimulation in the NRM at the site indicated in the drawing of a midsagittal section of the brainstem at the bottom of the figure produced a strong inhibition of the responses, especially those to the A δ and C fiber volleys. The responses to the volley in A β fibers were less affected. In a previous report, it was shown that the inhibition of monkey STT cells that is elicited by stimulation in the NRM can be blocked by a bilateral lesion of the dorsolateral part of the lateral funiculi of the spinal cord (Willis *et al.*, 1977). This indicates that the bulbospinal projection from the NRM of monkeys descends bilaterally in the dorsolateral funiculi, as in cats (Engberg *et al.*, 1968; Fields *et al.*, 1977).

Stimulation in the nucleus reticularis gigantocellularis (NG_c) of the medulla can result in either inhibition or excitation of monkey STT cells (Haber *et al.*, 1978, 1980). In Fig. 6.8(I), stimulation at several loci along a track placed vertically through the NG_c evoked an inhibition of the background discharges of a wide dynamic range STT neuron. In Fig. 6.8(II), stimulation in the NG_c inhibited not only the background activity of a wide dynamic range STT cell (Fig. 6.8(IIA)), but also its responses to hair movement (Fig. 6.8(IIB)), noxious squeezing of a fold of skin (Fig. 6.8(IIC)) and noxious heat (Fig. 6.8(IID)).

Excitation of a different monkey STT neuron during and following repetitive stimulation in the NG_c is shown in Fig. 6.9(IA). A series of stimulus trains applied at the location indicated in Fig. 6.9(ID) resulted in a progressively greater discharge or "wind-up" (Fig. 6.9(IB)). The background activity of the neuron was

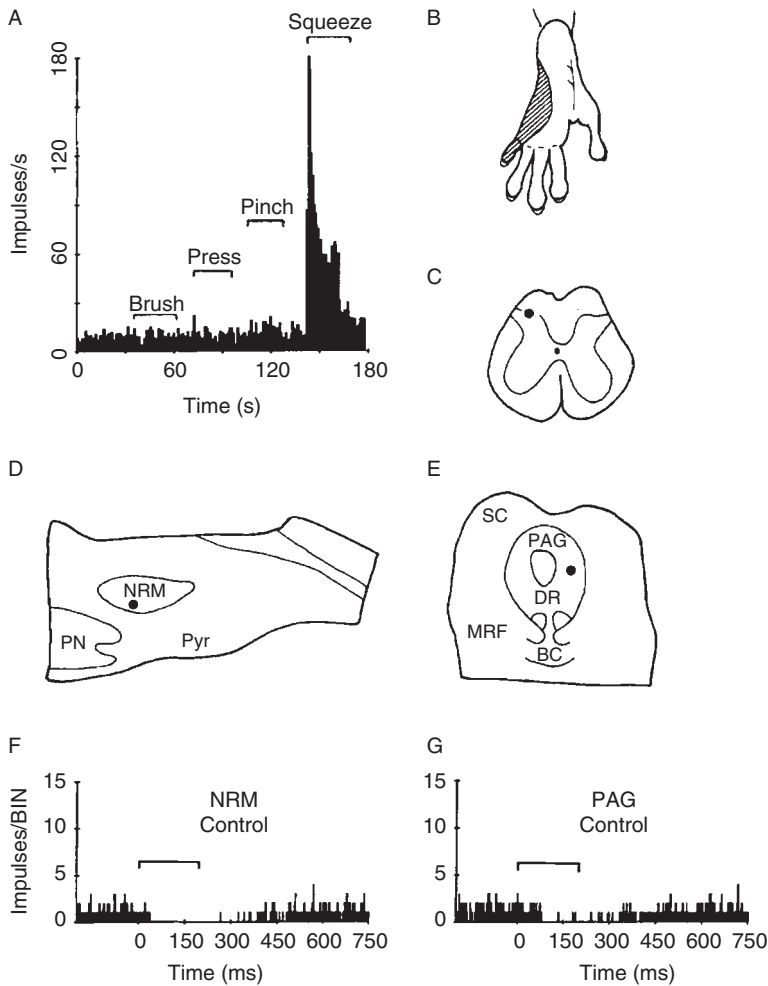


Fig. 6.6. Inhibition of the responses of a monkey spinothalamic tract cell to noxious mechanical stimulation by repetitive stimulation in the nucleus raphe magnus (NRM) or periaqueductal gray (PAG). (A) The neuron was classified as a nociceptive-specific cell based on its selective response to the most intense of the mechanical stimuli applied to the skin in the receptive field, (B). The recording site for the STT cell was in lamina I, as shown in a drawing of a transverse section of the spinal cord in (C). Repetitive stimulation was applied at the sites in the NRM and PAG shown in drawings of a sagittally sectioned lower brainstem in (D) and of a transverse section of the midbrain in (E). The STT cell was activated by squeezing the skin of the receptive field, and the NRM in (F) or the PAG in (G) were stimulated at 200 μ A during the times indicated by the horizontal brackets. Note that the inhibition outlasted the periods of stimulation. From Yeziarski *et al.* (1982).

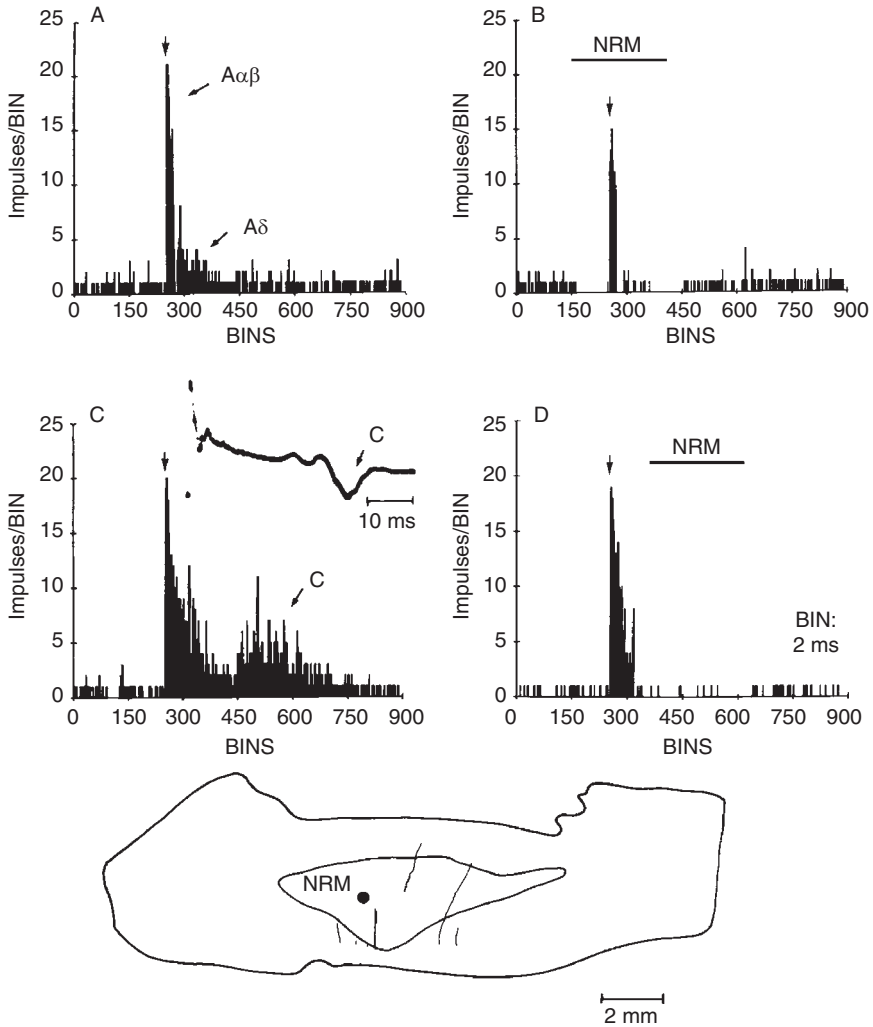


Fig. 6.7. Inhibition of the responses of a monkey STT neuron classified as a wide dynamic range cell to sural nerve volleys by stimulation in the NRM. The responses in (A) and (B) were elicited by volleys in most of the A fibers of the sural nerve. Components of the responses attributable to the $A\alpha\beta$ and the $A\delta$ fibers are indicated. In (C), the response to an additional volley in C fibers is shown, along with a recording of the C fiber volley in the sural nerve in the inset. In (B) and (D), a 500 ms train of 0.1 ms, 150 μ A pulses at 333 Hz was applied in the NRM. The times of NRM stimulation are indicated by the horizontal bars. The site of stimulation in the NRM is shown in the drawing of a midsagittal section of the lower brainstem in (E). From Gerhart *et al.* (1981a).

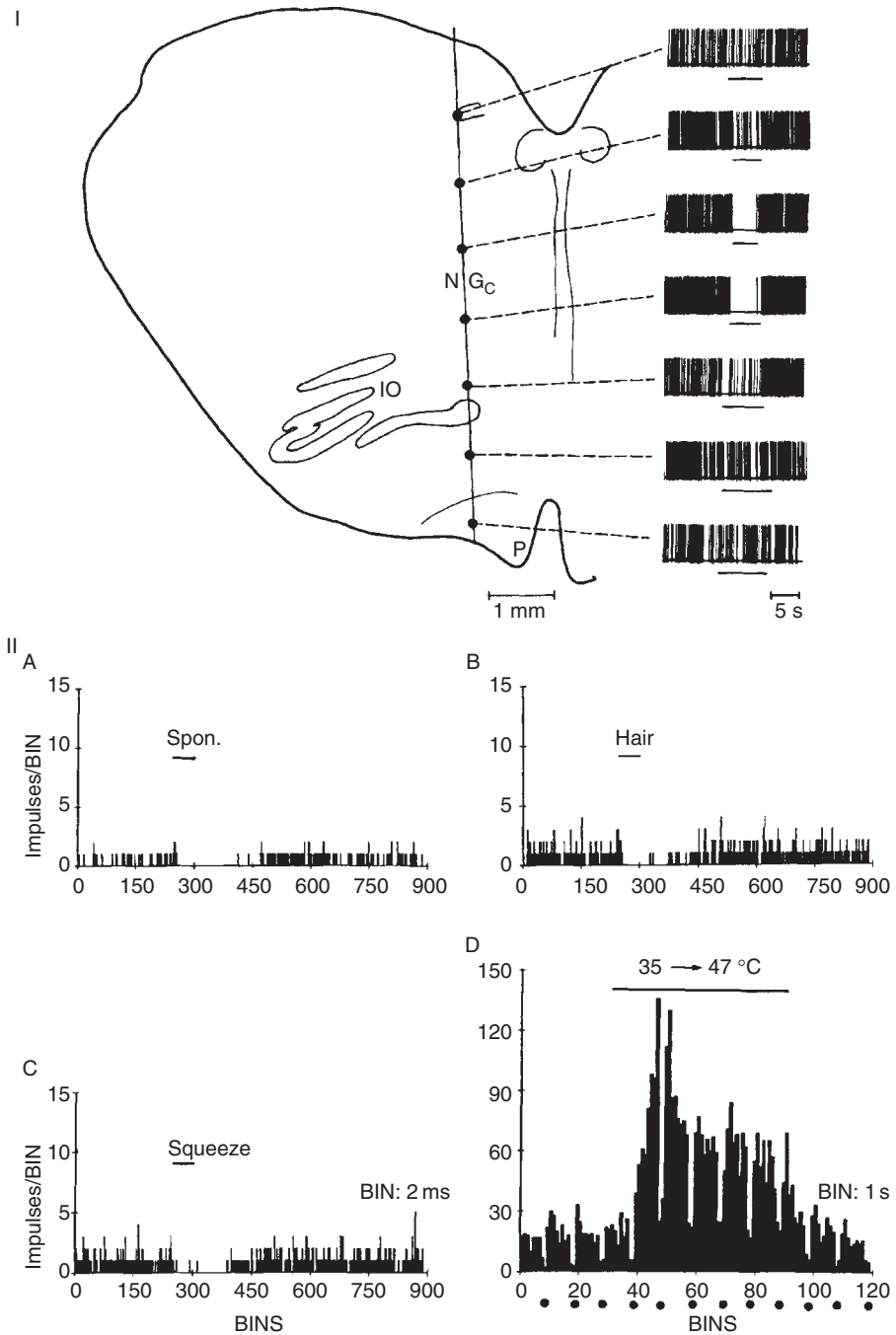


Fig. 6.8. (I) shows the inhibition of the background activity of a wide dynamic range monkey STT cell during stimulation at several loci within the medullary reticular formation (labeled NG_C). The stimulus trains were applied during the periods

inhibited when the skin of the receptive field was squeezed, as seen in Fig. 6.9(IC) (during the period between the two arrows); stimulation in the NG_c during the time indicated by the horizontal line produced a discharge of the neuron despite the inhibition due to the maintained cutaneous stimulus. In Fig. 6.9(IIA) and (B) are seen progressive increases in the inhibition of the activity of a wide dynamic range STT cell in response to a series of stimulus trains applied in the contralateral (A, CONTRA.) or ipsilateral (C, IPSI.) NG_c. The activity of the STT cell was enhanced during the period demarcated by the arrows in Fig. 6.9(IIA) by application of an arterial clip to a fold of skin in the receptive field. The progressively increasing inhibition of the cell can be termed “negative wind-up” or “wind-down” (in contrast to the “wind-up” seen in Fig. 6.9(IB) (Haber *et al.*, 1980).

Effects of stimulation of the ventral posterior thalamus and the sensorimotor cortex on monkey STT cells

Gerhart *et al.* (1981b, 1983) found that stimulation in the ventral posterior thalamic complex on either side of the brain resulted in a strong inhibition of monkey STT neurons. The inhibition was produced when applied within the ventral posterior lateral or ventral posterior medial nuclei with stimulus pulses having strengths as low as 25 μ A (Fig. 6.10). Lesions of the spinal cord white matter necessary to eliminate the inhibition produced by stimulation of the ipsilateral VPL nucleus had to include the dorsolateral funiculi bilaterally and the ventral part of the ipsilateral lateral funiculus. It was suggested that neural pathways that mediate the inhibitory effect of thalamic stimulation on monkey STT neurons might include: (1) a thalamocortical-corticofugal pathway; (2) antidromically activated STT or brainstem axons that might in turn excite descending inhibitory pathways by way of axon collaterals; and/or (3) activation of a propriospinal inhibitory system by antidromic volleys in the axons of STT cells. Since stimulation in the monkey VPL thalamic nucleus could be shown to result in the release of serotonin in the lumbar spinal cord (Sorkin *et al.*, 1992), at least

Caption for Fig. 6.8. (cont.)

indicated by the horizontal lines below the records. The stimuli were 200 μ A pulses at 333 Hz. IO, inferior olivary nucleus; P, pyramid. (IIA) shows the inhibition of the background discharge of a wide dynamic range monkey STT cell; (IIB) the response to brushing the hair in the receptive field; (IIC) the response to squeezing the skin; and (IID) the response to heating of the skin from 35 to 47 °C. The 200 ms stimulus trains applied in the NG_c were 150 μ A pulses at 333 Hz applied during the periods indicated by the horizontal lines in (A–C) and at the times of the dots below (D). From Haber *et al.* (1980).

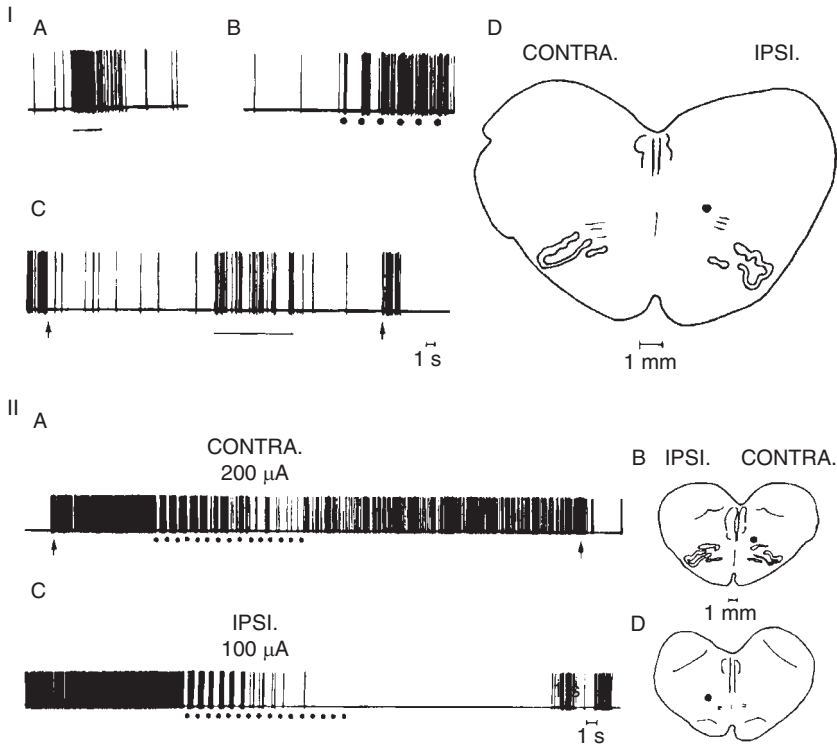


Fig. 6.9. (IA) shows the excitation of a monkey STT cell in response to repetitive stimulation in the NG_c (50 μ A pulses at 333 Hz during the period indicated by the horizontal line). In (IB), repeated stimulation using 200 ms trains of stimuli (100 μ A, 333 Hz) at the times indicated by the dots. During the time between the arrows in (IC), the activity of the cell was inhibited by squeezing the skin. Nevertheless, stimulation in the NG_c (200 μ A pulses at 333 Hz) during the period indicated by the horizontal line caused an excitation of the cell. The location of the stimulation site is shown in (ID). (IIA) and (IIC) demonstrate negative wind-up (or "wind-down") of the discharges of a wide dynamic range monkey STT cell. Prior to stimulation in the NG_c, the STT cell was strongly excited by application of an arterial clip to the skin of the receptive field during the time between the two vertical arrows. Repetitive brief trains of stimuli (200 ms trains of 200 μ A pulses at 333 Hz) were applied in the contralateral NG_c (IIB) or of 100 μ A pulses in the ipsilateral NG_c (IID) at the times indicated by the dots in (IIA) and (IIC). From Haber *et al.* (1980).

part of the inhibition evoked by VPL stimulation must have involved the excitation of serotonin-containing raphe-spinal neurons by antidromically activated collaterals of axons ascending to the thalamus. The inhibition produced by stimulation in the ventral posterior thalamic complex in monkeys may have some relationship to the ability of VPM-VPL stimulation in patients to produce

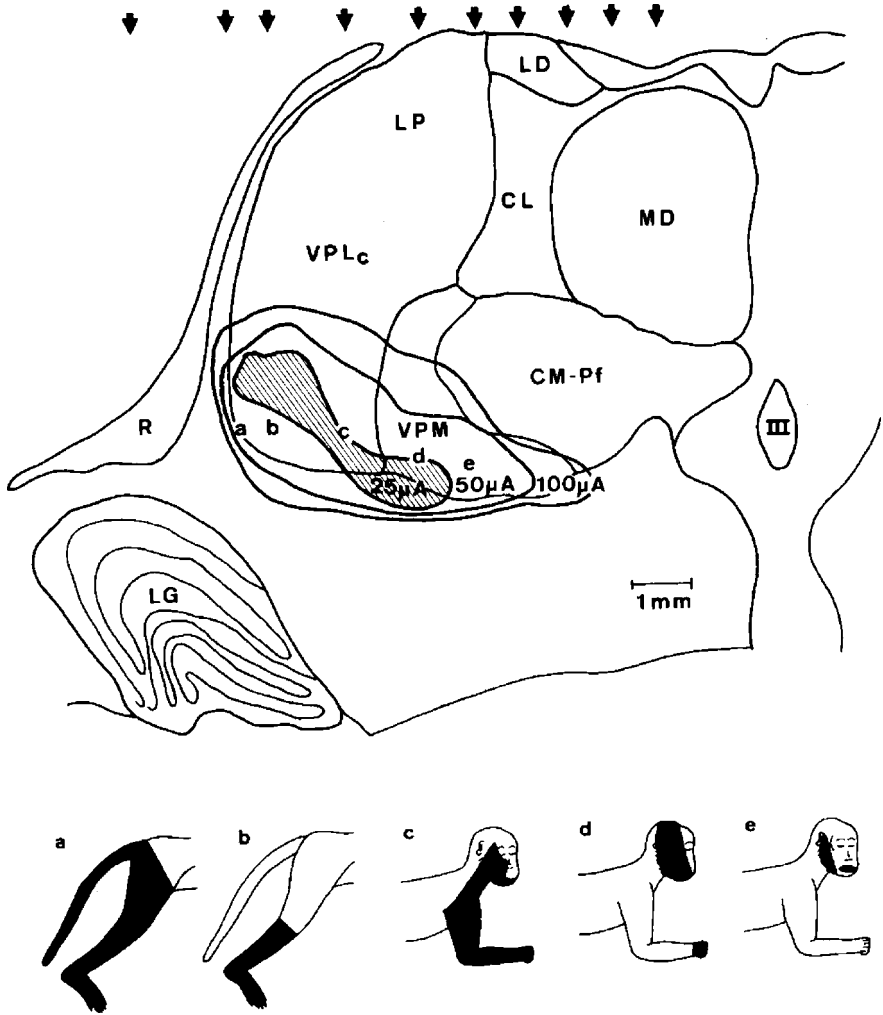


Fig. 6.10. Map of the region of the thalamus that when stimulated electrically produced an inhibition of the activity of a wide dynamic range monkey STT cell. The stimulating electrode was moved systematically across the thalamus ipsilateral to the STT cell. The tracks were directed vertically at each of the lateral/medial positions indicated by the arrows at the top of the illustration. Stimulus trains of several seconds duration (200 μ A, 100 μ s pulses at 333 Hz) were delivered at 1 mm intervals along each track. When inhibition of the STT cell was observed, lower stimulus strengths were tried. The outlined areas that overlap the VPL and VPM nuclei are regions in which stimuli at intensities of 100 μ A or less were effective in inhibiting the STT cell. In the cross-hatched area the threshold for inhibition was less than 25 μ A. Multiunit receptive fields were mapped at the recording sites indicated by the letters a-e, and the receptive fields are shown by the black areas on the corresponding figurines at the bottom of the illustration. From Gerhart *et al.* (1983).

analgesia (Gybel and Sweet, 1989) (see Chapter 9, on deep brain stimulation). However, the analgesia in humans with chronic pain is much longer-lasting than is the inhibition of nociceptive neurons in animal experiments. The reason for this difference is unclear, although the presence of anesthesia in the animal experiments could contribute.

As already mentioned, stimulation of the sensorimotor cerebral cortex can have either excitatory or inhibitory actions on monkey STT cells (Coulter *et al.*, 1974; Yezierski *et al.*, 1983) (see Chapter 9, on motor cortex stimulation). This is illustrated in Fig. 6.11. In Fig. 6.11(IA) and (IC) are the responses of a wide dynamic range monkey STT cell to electrical stimulation of the motor cortex and the medullary pyramid, respectively. Stimulation at either site resulted in a short-latency excitation of the cell. By contrast, stimulation of the SI somatosensory cortex (Fig. 6.11(IB)) produced an inhibition of the background activity of the STT neuron. The sites in the sensorimotor cortex that had been stimulated are shown in Fig. 6.11(ID) to be in Brodmann areas 4 and 2. Comparable effects are illustrated for another monkey STT cell, also classified as a wide dynamic range neuron, in Fig. 6.11(II). In this case, stimulation of either the pyramid (Fig. 6.11(IIA) and (H)) or of the white matter beneath the motor cortex (Fig. 6.11(IIB) and (I), filled circle) resulted in an excitation of the neuron (followed by a later inhibition). On the other hand, stimulation of the SI cortex in the vicinity of Brodmann area 2 produced an inhibition of the STT cell (Fig. 6.11(IIC) and (I), arrow). After the initial recordings, a lesion was made in the lateral funiculus at an upper cervical level with the intention of interrupting the lateral corticospinal tract (Fig. 6.11(IIIG)). After this lesion was made, the excitatory effects of stimulation of the pyramid or of the motor cortex were eliminated and the inhibition produced by stimulation of the SI cortex was greatly reduced (Fig. 6.11(IIID–F)).

Effects of stimulation in the nucleus raphe magnus on unidentified interneurons in the monkey spinal cord

The emphasis of the study by Willis *et al.* (1977) was on the inhibition of monkey STT cells identified by antidromic activation from the thalamus that resulted from stimulation in or very near the NRM. However, similar inhibitory effects of NRM stimulation were also observed in recordings from individual unidentified dorsal horn interneurons (Fig. 6.12(IA–D)), as well as of the interneuronal population responses to volleys in A δ afferent fibers, the cord dorsum N2 and N3 waves (Fig. 6.12(I) and (II); Beall *et al.*, 1977). For example, in Fig. 6.12(IA) are seen several bursts of action potentials that were recorded extracellularly from an interneuron in the lumbosacral enlargement of the spinal cord of a monkey in response to stimulation of the sural nerve at a strength that

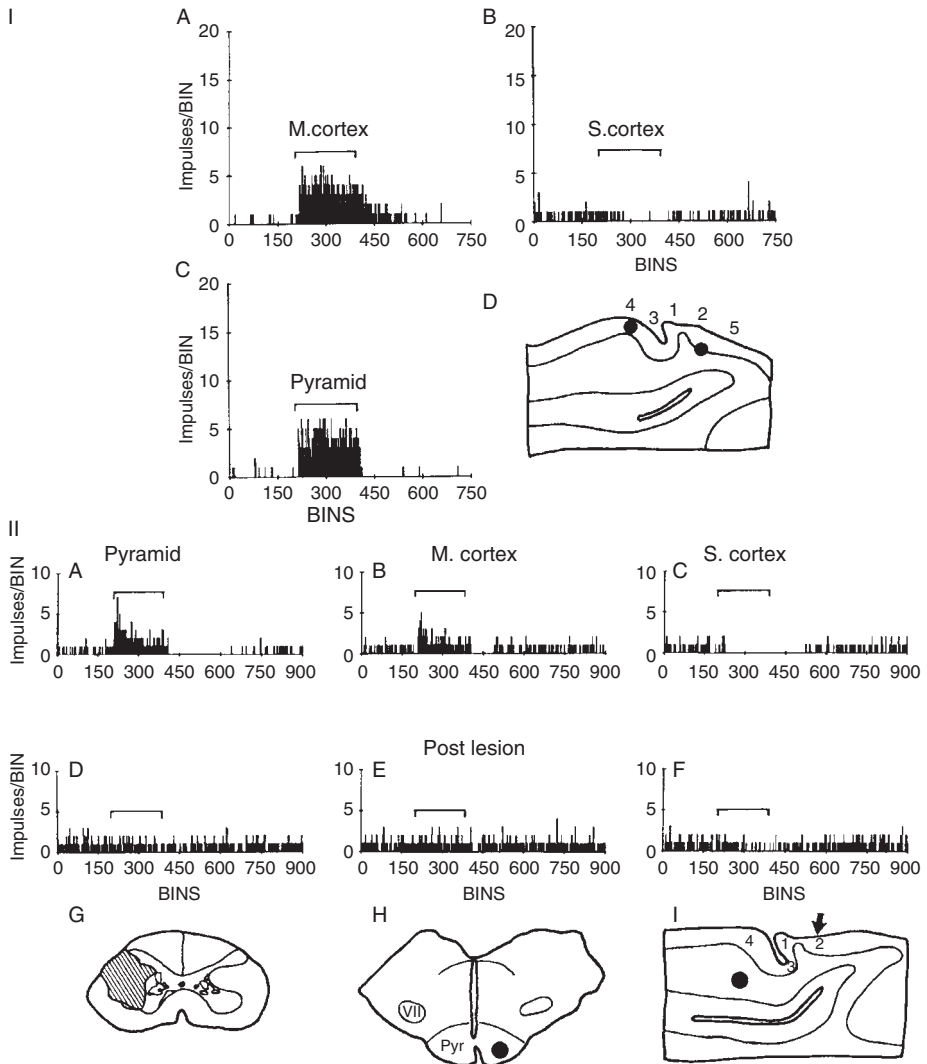


Fig. 6.11. (I) shows the effects of stimulation of the sensorimotor cortex and the medullary pyramid on a monkey STT cell. In (A) is the excitatory effect of motor cortex stimulation (200 ms trains, 100 μ A pulses) and in (B) is the inhibitory effect of SI sensory cortex stimulation (200 ms trains, 200 μ A pulses). (C) shows that stimulation of the medullary pyramid had an excitatory action (200 ms trains, 100 μ A pulses). In (D) are indicated the sites of stimulation in Brodmann areas 4 and 2. (II) documents the results of interruption of the lateral corticospinal tract on the excitatory and inhibitory actions on a monkey STT cell of stimulation of the sensorimotor cortex. (A-B) show the excitatory action of stimulation of the medullary pyramid and of the white matter just below the motor cortex, and (C) the inhibitory effect of stimulation of the SI sensory cortex. The changes produced by a lesion placed in the lateral funiculus are shown in (D-F). The lesion is indicated in (G). The stimulus site in the pyramid is shown in (H) and those in the sensorimotor cortex in (I). From Yezierski *et al.* (1983).

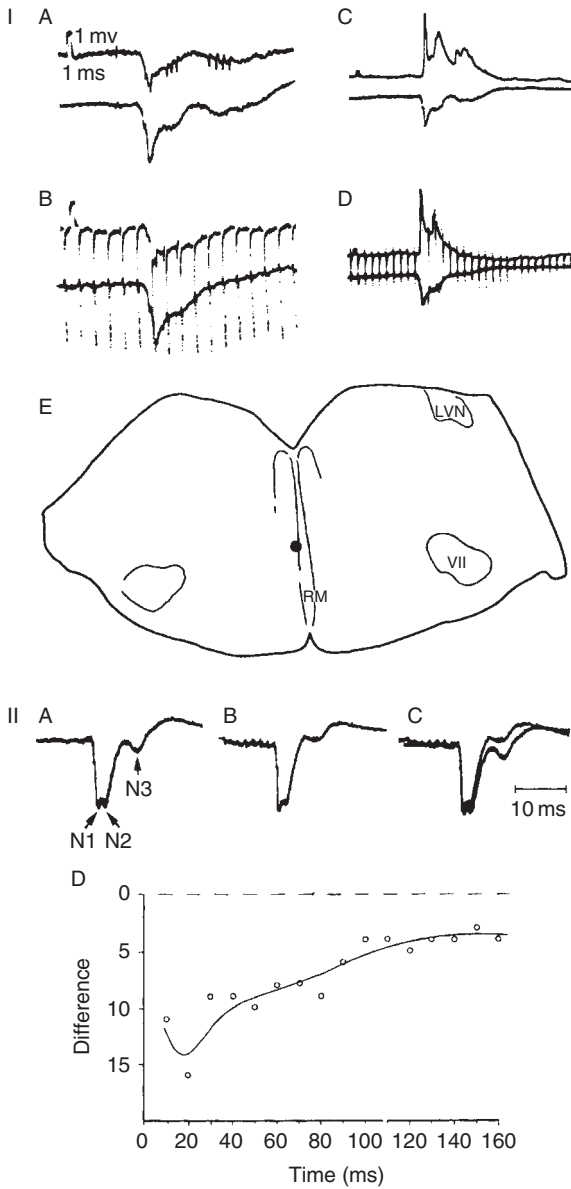


Fig. 6.12. (I) shows the responses of an interneuron in the lumbosacral enlargement of a monkey to sural nerve volleys that included both A β and A δ afferent fibers. In (IA) and (IB), the recordings were extracellular; the control responses are seen in (A) and the inhibited responses during stimulation in the NRM in (B). It is evident that the later burst of discharges was eliminated. In the cord dorsum recordings in the lower traces, it can also be seen that the N3 wave was completely eliminated during NRM stimulation (by a train of 200 μ A pulses at 333 Hz). By the time of the recording in (IC), the microelectrode had impaled the interneuron, and the sural nerve volley is shown to evoke a complex sequence of EPSPs in the cell. Stimulation in the NRM in (ID)

activated the A δ fibers in the nerve. The spikes occurred at intervals that correspond to the various components of the cord dorsum potentials seen in the lower oscilloscope trace (cf. Fig. 6.12(IIA)). In Fig. 6.12(IB), most of the action potentials of the interneuron in response to the sural nerve volley were prevented by stimulation in the NRM at the site indicated by the filled circle in Fig. 6.12(IE).

Intracellular recordings from the same interneuron are shown in Fig. 6.12(IC) and (D). The sural nerve volley evoked a complex excitatory potential, with components that corresponded to the succession of N1, N2 and N3 waves seen in the cord dorsum recording below and to the action potentials in Fig. 6.12(IA). In Fig. 6.12(ID), stimulation of the NRM is seen to inhibit completely the late component of the EPSP, as well as the N3 wave. There was a smaller degree of inhibition of the second component of the EPSP and of the N2 wave. Figure 6.12(II) again shows the cord dorsum N1, N2 and N3 waves evoked by stimulation of the sural nerve at a strength that activated its A β and A δ afferent fibers. Stimulation of NRM strongly reduced the N3 wave and slightly reduced the N2 wave. The graph in Fig. 6.12(IIID) shows the time course of the inhibition of the N3 wave.

Descending control of monkey and cat spinoreticular and spinomesencephalic tract neurons

Stimulation in the reticular formation was found to exert both inhibitory and excitatory actions on monkey spinoreticular neurons; excitatory responses were more common than inhibitory ones (Haber *et al.*, 1982). Chandler *et al.* (1989) observed that electrical stimulation in either the PAG or the midbrain reticular formation in cats produces an inhibition of the responses of spinoreticular neurons in the thoracic spinal cord to input from cardiopulmonary afferents. Injection of glutamate into the PAG had a similar effect, presumably by exciting the PAG neurons in the vicinity of the injection. However, glutamate injected into the midbrain reticular formation was ineffective. This suggests the possibility that electrical stimulation in this location activated fibers of passage,

Caption for Fig. 6.12. (cont.)

reduced the EPSP, especially its late components. (IE) shows the stimulation site in the NRM. In (IIA–C) are the monkey cord dorsum N waves (N1, N2 and N3) evoked by stimulation of the sural nerve at a strength that activates the A δ fibers in the nerve. In (IIC), a train of seven pulses at 200 μ A, 333 Hz, repeated at 1 Hz was delivered in the NRM at an interval of 20 ms before the sural nerve stimulus. It can be seen in the superimposed records of the control and conditioned responses that the N3 wave was strongly reduced by NRM stimulation. The N2 wave was also reduced slightly. The graph in (IIID) shows the time course of the inhibition of the N3 wave. From Willis *et al.* (1977).

rather than local neurons. A similar possibility should be considered in other experiments using electrical stimuli in the CNS, particularly in the brainstem reticular formation.

Fields *et al.* (1975) found that stimulation in the nucleus reticularis gigantocellularis of cats can produce a strong inhibition of spinoreticular neurons that project back to the same reticular nucleus. Reticular formation stimulation was reported to excite cat spinoreticular neurons in experiments by Cervero and Wolstencroft (1984).

Spinomesencephalic tract (SMT) neurons in rats were inhibited by electrical stimulation in the nucleus raphe magnus and the adjacent reticular formation (Men  trety *et al.*, 1980), and SMT cells in cats could be inhibited by stimulation in the PAG, midbrain reticular formation, NRM, nucleus reticularis gigantocellularis and nucleus reticularis magnocellularis (Yeziarski and Schwartz, 1986; Yeziarski, 1990).

Descending control of cat postsynaptic dorsal column neurons

Little detail is known about the structures in the brain that control the activity of cat postsynaptic dorsal column neurons. Evidently, there is a tonic inhibitory action that originates in the brain, since cold block of pathways descending in the spinal cord enhances the responses of these neurons to noxious mechanical and thermal stimulation, although not to tactile stimulation (Noble and Riddell, 1989). The source of this tonic inhibition is unclear.

Descending control of spinocervical tract and lateral cervical nucleus neurons

Activation of a pathway that descends in the dorsal part of the lateral funiculus in cats was shown to inhibit cells presumed to be spinocervical tract (SCT) neurons (Lundberg and Oscarsson, 1961). Gray and Dostrovsky (1983) observed that stimulation in the PAG, nucleus cuneiformis, NRM and medullary reticular formation produced inhibition of SCT cells. Most dorsal horn neurons were inhibited from all of these sites, and there was no difference in the responses of LT, WDR or HT cells. Kajander *et al.* (1984) observed that stimulation in the PAG or NRM also inhibits the responses of SCT cells to innocuous stimuli. Fleetwood-Walker *et al.* (1988) found that stimulation in the A11 dopaminergic cell group produces inhibition of SCT cells and that the inhibition can be blocked by an antagonist of D2 dopamine receptors.

Fetz (1968) reported that cat dorsal horn neurons with axons projecting in the vicinity of the SCT (presumed SCT cells) were usually inhibited when the pyramidal tract was stimulated, although sometimes the cells were excited and then

inhibited or occasionally were unaffected. Fetz indicated that the inhibition originated from activation of neurons in the postcruciate (sensory) cortex and the excitation from the precruciate (motor) cortex. Brown and Short (1974) confirmed that stimulation of the SI and SII areas of the cat cerebral cortex resulted in the inhibition of SCT cells. Using intracortical microstimulation, Brown *et al.* (1977) demonstrated that the parts of the cat cerebral cortex that could inhibit SCT cells included Brodmann areas 4, 3a, 3b, 1 and 5. Using intracellular recordings, Harrison and Jankowska (1984) showed that stimulation of the pyramid could produce EPSPs, IPSPs or EPSPs and IPSPs in SCT cells.

Brown (1970, 1971) observed an enhancement of the responses of cat SCT neurons when activity descending from the brainstem was blocked by cold. Stimulation of axons in the dorsal lateral funiculus or in the ventral funiculus could produce inhibition of SCT cells (Brown *et al.*, 1973a, 1973b). Cervero *et al.* (1977) confirmed that cold block of long tracts of the spinal cord revealed a tonic descending inhibition of SCT cells. Similar results were obtained by Hong *et al.* (1979).

Neurons in the lateral cervical nucleus (LCN) also appear to be subject to descending controls. For example, Dostrovsky (1984) found that LCN neurons can be inhibited by stimulation in the PAG, NRM or medullary reticular formation. However, these actions may be indirect, reflecting the inhibition of SCT neurons at a lower level of the spinal cord.

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Peripheral and central mechanisms and manifestations of chronic pain and sensitization

Neuropathic pain is pain following a disease or injury to the nervous system, and can be categorized by the location of the causative injury. Chronic pain following injury of the peripheral nervous system, distal to the oligodendroglial cell – Schwann cell junction, can be termed deafferentation pain or peripheral neuropathic pain. Chronic pain “associated with lesions of the CNS” is termed central pain syndrome (Merskey, 1986; Bonica, 1991). There are many situations in which there is injury of both the peripheral and central nervous system, particularly with injuries of the conus medullaris. In this chapter we will consider primate neuropathic pain states, beginning with peripheral neuropathic or deafferentation syndromes, and concluding with central pain syndromes.

In general terms, both central and peripheral chronic pain syndromes have similar characteristics. These include evidence of sensory loss, ongoing pain and pain evoked by stimuli that are not normally painful (allodynia or hyperalgesia). The sensory loss and hypersensitivity are demonstrated by quantitative sensory testing (QST). In addition, a number of primate models have been developed which mimic the sensory abnormalities in patients with neuropathic pain.

Clinical characteristics of peripheral neuropathic pain

The cause of most neuropathies is based on the medical history, supported by laboratory investigations (Casey *et al.*, 1996b). Diabetes is the most common cause of painful neuropathy. Generally, a progressive course suggests an inherited, metabolic or recurrent toxic etiology. In some infectious or post-infectious neuropathies, such as syphilitic polyradiculoneuropathy, the onset of symptoms is delayed because of the chronic, progressive nature of the infection

and its associated inflammatory process. Although the symptomatic presentation of painful neuropathy varies among the various causes listed above, most patients experience pain of variable intensity throughout the waking hours, often interfering with sleep. The intensity and hedonic quality of the pain may be affected by emotional and cognitive factors such as fear and attention.

In some cases, the pain occurs only in brief, intense paroxysms as in tic douloureux and tabetic polyradiculoneuropathy. Tactile and sometimes cold allodynia is present in a significant minority of patients. Evidence for neuropathy is present on routine neurological examination and the sensory examination typically reveals impaired thermal or pinprick sensation. Depending on the cause of the neuropathy, clinical evidence for large fiber (impaired vibratory sensation; depressed stretch reflexes) may be present but does not correlate with the occurrence of neuropathic pain. Indeed, the exclusive impairment of functions mediated by large diameter afferent fibers is rarely associated with painful neuropathy.

Peripheral neuropathic pain in primates

Peripheral neuropathic pain may arise from a sensory, motor or autonomic abnormality within the distribution of an anatomically identified peripheral nerve (such as the saphenous, radial or ulnar nerves), or some class of peripheral nerves (sensory, motor or autonomic), nerve roots or a plexus. The commonest cause of such pain is an abnormality of a peripheral nerve, i.e. neuropathy (Casey *et al.*, 1996b). Most neuropathies are painless, but pain may be among the presenting neurological symptoms seen on clinical examination. A mononeuropathy involves one nerve; a polyneuropathy affects more than one nerve. The sensory abnormality is most often an elevated threshold for the detection of a somatic sensation such as touch, pinprick, heat or cold (Lindblom, 1985). However, the major complaint may be that the applied stimulus is not perceived normally and often has an unpleasant quality that may be difficult for the patient to describe. The motor abnormality is usually weakness, sometimes accompanied by atrophy. Excessive or reduced sweating, increased or decreased skin temperature or cutaneous blood flow, and loss of hair are common manifestations of an autonomic abnormality.

A possible exception to this pattern is trigeminal neuralgia (tic douloureux) because impaired sensory, motor or autonomic functions are not apparent on routine clinical examination. However, sensory abnormalities may be detected, when quantitative sensory testing methods are used (Nurmikko, 1991; Bowsher *et al.*, 1997; Eide and Rabben, 1998; Nurmikko and Eldridge, 2001), and some histological studies have shown degenerative changes in the trigeminal nerve,

even in cases without evidence for vascular impingement or demyelination (Cruccu *et al.*, 1990; Klun, 1992; Hilton *et al.*, 1994; Solaro *et al.*, 2004; Obermann *et al.*, 2007).

Painful neuropathies can be produced by a wide range of etiologies (Casey *et al.*, 1996b). Traumatic neuropathies include pain due to neuroma, nerve or spinal nerve root entrapment, nerve injury (with causalgia or complex regional pain syndrome – CRPS type 2), plexus injury or spinal nerve avulsion. Toxic neuropathies include those induced by cancer chemotherapy, while metabolic or immunological neuropathies include those associated with diabetes mellitus (mononeuritis, widespread sensorimotor neuropathy, autonomic neuropathy). Vascular neuropathy is usually related to vasculitis (localized, regional or systemic). Neoplastic neuropathies are related to remote effects of tumors (paraneoplastic syndromes), or to tumor infiltration and/or compression. Infectious neuropathy may be caused by post-herpetic (zoster) neuralgia, AIDS or syphilis. Nutritional neuropathies include the polyneuropathy of chronic alcoholism. There is a variety of relatively rare hereditary sensory neuropathies, some of which (e.g. Fabry's disease) are quite painful. Finally, an idiopathic, painful, small fiber neuropathy is commonly seen in clinical neurological practice (Holland *et al.*, 1998).

We will summarize some of the evidence which suggests the mechanisms of peripheral neuropathic pain in humans (Campbell and Meyer, 2006). The specific lesion responsible for pain in neuropathy is unclear since many clinicopathological studies of diabetic neuropathy have failed to show definitive differences between painful and non-painful cases. In fact, it is unlikely that peripheral neuropathic pain has a single cause; there is evidence that some cases may be due to an idiopathic ganglionopathy of unknown cause (Gorson *et al.*, 2008). However, a common feature of painful neuropathy is the impairment of functions mediated by small diameter myelinated (A δ) or unmyelinated (C) fibers. Histological examination reveals a reduced population of these fibers, frequently with evidence for ongoing degeneration and regeneration (Dyck *et al.*, 1976). Because A δ and C fibers innervate nociceptors, it is apparent that some process associated with their degeneration underlies the generation of pain. Accordingly, the pain of neuropathy can be considered to arise as the result of two basic conditions affecting central nociceptive and pain mechanisms: (1) denervation and (2) abnormal spontaneous nerve fiber discharge. These conditions may act independently or together (Gracely *et al.*, 1992) to generate pain.

Genetic factors in peripheral neuropathic pain

A very basic question remains: why aren't all peripheral neuropathies or injuries affecting small diameter afferent fibers painful? The answer may lie in

genetic variations that affect the response to injury and the central and peripheral neural mechanisms mediating pain. Rodent models of pain have revealed no fewer than 25 specific genetic abnormalities that may alter the susceptibility to pain following inflammation or nerve injury (Mogil and Grisel, 1998). Early studies showed that mice selectively bred for showing high levels of stress-induced analgesia had elevated levels of central opioid binding. Mice with a null mutation in the gene encoding a neuronal-specific isoform of a protein kinase (PKA) subunit continue to exhibit acute pain behaviors. These mice show reduced pain-related behavior, including heat hyperalgesia, dorsal horn immunoreactivity and plasma extravasation following inflammatory tissue injury. The pain behavior produced by nerve injury, however, was unaffected in these mutant mice, suggesting that the genetic abnormality that modifies the expression of this PKA subunit specifically affects inflammation-induced pain, but not the pain of nerve injury (Malmberg *et al.*, 1997a). The specificity of genetic abnormalities in painful neuropathy is suggested additionally by studies showing that mice lacking a specific form of protein kinase C (PKC gamma) respond normally in tests of acute pain, but do not develop behaviors or dorsal horn neurochemical responses consistent with neuropathic pain following partial sciatic nerve section (Malmberg *et al.*, 1997b).

In humans, three genetic variants of the gene encoding the monoaminergic enzyme catecholamine-O-methyltransferase (COMT) are found in 96% of the human population. Five combinations of these haplotypes are strongly associated with variation in the sensitivity to experimentally applied noxious stimuli. The presence of one particular haplotype, which produces the highest levels of COMT, diminishes the risk of developing a painful disorder of the temporomandibular joint by as much as 2.3 times (Diatchenko *et al.*, 2005). In a related study, a gene (GCH1), which encodes for an essential, rate-limiting cofactor for catecholamine, serotonin and nitric oxide production (tetrahydrobiopterin or BH4), is strongly up-regulated in the rodent dorsal root ganglion after axonal injury, resulting in increased BH4 in primary sensory neurons. Notably, a haplotype of the GCH1 gene, found in 15.4% of humans, is associated with significantly reduced sensitivity to experimentally applied noxious stimuli and less pain following discectomy for persistent radicular low back pain (Tegeeder *et al.*, 2006).

Some human genetic variations are more directly related to the generation of neuronal action potentials. For example, a specific mutation in a gene encoding for the expression of a component of a voltage-gated sodium channel is associated with a familial form of what has previously been identified clinically as congenital insensitivity to pain. This particular abnormality, now considered a specific channelopathy, is an autosomal-recessive trait that maps to a

Table 7.1. *Clinical pain syndromes associated with Nav1.7 sodium channelopathy.*
(Reproduced from Waxman, 2007.)

Disorder	Inheritance	Mutation	Effects on channel	Clinical phenotype
Inherited erythromelalgia	Autosomal dominant	Missense mutations	Lower threshold for activation; slow deactivation; enhanced response to subthreshold stimuli	Attacks of burning pain and redness in distal extremities; triggered by mild warmth and exercise
Paroxysmal extreme pain disorder	Autosomal dominant	Missense mutations	Impaired inactivation; enhanced persistent current	Episodic perirectal, ocular and jaw pain accompanied by flushing and other autonomic abnormalities
Channelopathy-associated insensitivity to pain	Autosomal recessive	Nonsense mutations	Loss of function of Nav1.7	Inability to sense pain

chromosome (2q24.3) containing a gene (SCN9A) that encodes for a subunit of the voltage-gated sodium channel, Nav1.7 (Cox *et al.*, 2006). This sodium channel is strongly expressed in peripheral nociceptive neurons. The mutations present in three consanguineous families cause a loss of function of Nav1.7 as shown by electrophysiological evidence of reduced currents in cells expressing the human mutant form.

Electrophysiological studies, reviewed by Waxman *et al.* (1999), show that abnormalities in the expression of similar sodium channels underlie the hyperexcitability and spontaneous activity that appears in rodent models of nerve injury. In fact, there are multiple, physiologically distinct sodium channels in dorsal root ganglion cells, some of which may innervate nociceptors. Most critically for peripheral neuropathic pain, the expression of many of these channels is up-regulated following nerve injury or inflammation in rodent pain models.

In humans, abnormalities in the expression of the Nav1.7 channel are associated with two clinically well-defined syndromes with excessive pain (inherited erythromelalgia, paroxysmal extreme pain disorder) in addition to the congenital inability to experience pain described above (see Table 7.1) (Fertleman *et al.*,

2006; Waxman, 2007). It seems likely, then, that genetic variations are significant determinants of susceptibility to the development of chronic pain following damage to A δ and C afferent fibers in humans.

The unifying feature of painful peripheral neuropathy is damage to small-diameter finely myelinated (A δ) or unmyelinated (C) afferent fibers. Injury to these fibers has multiple effects that, individually or in combination, lead to chronic spontaneous or evoked pain or abnormal sensations so unpleasant that they produce many of the behavioral effects of pain; these effects include:

- (1) Denervation may lead to a loss of afferent-mediated inhibition as well as an anatomical and physiological reorganization of central nociceptive pathways. Denervation does not simply reduce the excitatory input to spinothalamic neurons and supraspinal nociceptive pathways; it also removes or reduces the afferent inhibition that is seen in behavioral and psychophysical studies (Vierck, Jr. *et al.*, 1974; Bini *et al.*, 1984; Milne *et al.*, 1988; Casey *et al.*, 1993; Nilsson *et al.*, 1997; Nilsson and Schouenborg, 1999; Green *et al.*, 2008) and that normally accompanies afferent input to the spinal cord, thalamus and cerebral cortex (Chapters 3 and 4) (Salt, 1989; Calford and Tweedale, 1991; Roberts *et al.*, 1992; Jones, 1993; Rasmusson *et al.*, 1993; Lund *et al.*, 1994; Xu and Wall, 1997; Willis, Jr., 1999). Acute or chronic denervation may, therefore, produce pain-related alterations in the normal neurobiology of supraspinal structures, including the cerebral cortex (Flor *et al.*, 1995) and result in the spontaneous discharge or increased excitability of spinothalamic and higher-order neurons in nociceptive pathways (Lenz *et al.*, 1994b). Denervation also reduces or removes a major trigger for activating supraspinal descending control mechanisms and endogenous pain modulation at several levels of the central nervous system (Chapter 6) (Dubner and Ren, 1999; Zubieta *et al.*, 2001; Rainville, 2002; Ren and Dubner, 2002; Edwards, 2005). Finally, denervation triggers a complex set of molecular mechanisms that underlie an adaptive or maladaptive anatomical and physiological reorganization of central nociceptive and modulatory pathways (Rausell *et al.*, 1992; Florence *et al.*, 1998; Jones and Pons, 1998).
- (2) The spontaneous activity of A δ and C afferents, either in injured or uninjured fibers, may generate pain directly through the activation of intact central nociceptive pathways or may alter these central structures so that normally innocuous inputs are perceived as painful. Data from animal models of chronic nerve injury suggest that pain may be produced by the spontaneous and abnormal discharges of A δ and C fibers arising from one or more sources: (1) acutely degenerating fibers,

(2) regenerating sprouts and/or (3) sites of injury to the nerve trunk. Acute degenerating fibers are often found in the “acute painful diabetic neuropathy” described by Archer and colleagues and in neuropathies of non-diabetic etiology but they are uncommon in biopsies from patients with chronic painful diabetic neuropathy (Archer *et al.*, 1983).

The sprouts of regenerating nerves, especially traumatic neuromas, are known to generate spontaneous action potentials, but whether these are from fibers that innervate nociceptors or are sufficient in number and frequency to cause pain or simply paresthesias is not known (Meyer *et al.*, 1985; Chung *et al.*, 1992; Tal *et al.*, 1999). Many, probably most, neuromas are painless or are painful only upon contact; however, painful neuromas in patients may show evidence for the development of excessive sodium channels that are associated with abnormal pain conditions (England *et al.*, 1996; Waxman *et al.*, 1999; Waxman, 2001).

At the site of nerve injury (infarction, trauma), inflammatory mediators such as cytokines, interleukins, nerve growth factors and tumor necrosis factor (TNF α) may lead to the generation of action potentials from nociceptive afferents (Sorkin *et al.*, 1997; Wagner *et al.*, 1998; Bennett, 1999; Djouhri *et al.*, 2006). Clinical evidence that neuropathic pain may be associated with activity in sensitized but intact afferent fibers comes from observations on patients with post-herpetic neuralgia (Rowbotham and Fields, 1996; Petersen *et al.*, 2000), many of whom had maximum spontaneous pain, hyperalgesia and allodynia in affected regions with relatively preserved sensory function. However, there is strong evidence that spontaneous and abnormal evoked pain may be associated also with activity originating in the intact uninjured C fiber afferents within the innervation territory of the injured afferent fibers (Wu *et al.*, 2001; Sheth *et al.*, 2002; Wu G. *et al.*, 2002a) as shown in recent experiments on a rodent pain model of spinal nerve injury. The exact mechanism of this phenomenon is not known; and it is possible that the nocifensive behavior associated with this abnormal afferent activity depends on central changes produced by the concurrent denervation. There is some experimental evidence in patients with causalgia with signs of sympathetic hyperactivity, now known as complex regional pain syndrome type 2 (CRPS 2), may have developed a form of distal receptor denervation hypersensitivity to circulating or local alpha-adrenergic agonists that enhances the activity of injured afferents (Moon *et al.*, 1999; Perl, 1999; Han *et al.*, 2000). However, the clinical relevance of these experimental observations remains to be determined (Verdugo *et al.*, 1994; Blumberg *et al.*, 1997; Baron *et al.*, 1999b, 1999c). Although sympathetic activation of nerve fibers in experimentally induced neuromas has been demonstrated, only a minority of patients with definite nerve

injury develop the full causalgia syndrome with swelling, abnormal regulation of skin temperature and color, motor impairment, osteopenia, severe tenderness, and both allodynia and hyperalgesia extending beyond the territory of the injured nerve (Wilkins and Brody, 1970). Less obvious cases are more common, but the overall incidence of causalgia as a complication of nerve injury is not known. Finally, whether ongoing afferent activity originates in injured, distally sensitized or uninjured afferent fibers, it is nonetheless likely to result in an afferent-dependent sensitization of central neurons mediated through NMDA and NK1 receptors as shown in both animal experiments and human studies (Park *et al.*, 1995; Yaksh *et al.*, 1999; Willis, 2002; Wilson *et al.*, 2008). Functional imaging studies show that these peripheral neuropathic changes quickly induce upstream abnormal cerebral responses that are ultimately responsible for the abnormal pain perceptions (see Chapter 8) (Hsieh *et al.*, 1995; Iadarola *et al.*, 1995, 1998; Petrovic *et al.*, 1999; Witting *et al.*, 2001; Lorenz *et al.*, 2002, 2003; Casey *et al.*, 2003; Peyron *et al.*, 2004; Maihofner *et al.*, 2005, 2007; Geha *et al.*, 2007; Moisset and Bouhassira, 2007; Seifert and Maihofner, 2007).

The interplay of peripheral nervous system pathology and the consequent central adaptation forms the basis for the multiple pathophysiological processes that underlie peripheral neuropathic pain. Superimposed on the expression of this pathology and accompanying pain is the genetic variation that determines the execution of this interplay and its outcome.

Physiology of peripheral neuropathic pain in primate models: behavior and peripheral nerve activity

There are several primate models of neuropathic pain that have been studied by activity of fibers in the peripheral nerve. These models include a neuroma model (Meyer *et al.*, 1985; Koschorke *et al.*, 1991), a nerve crush model (Dykes and Terzis, 1979) and an acute model formed by tight ligation and section of a peripheral nerve, which chronically leads to a neuroma (Koschorke *et al.*, 1991). None of these models had been studied by behavioral tests of hypersensitivity. The Chung model (reviewed below) was studied by behavioral tests of hypersensitivity in primates.

Neuromas have been generated by section of the superficial radial nerves, and have been studied in baboons 1–7 months after the nerve injury (Meyer *et al.*, 1985). Physiological tests revealed that 8–18% of the fibers showed spontaneous activity, and two-thirds of the fibers were unmyelinated. Crosstalk of action potential activity between fibers at the neuroma was demonstrated by cross-correlation of spike trains. These features may explain the spontaneous and evoked pains which are features of peripheral nerve injury.

Myelinated and unmyelinated fibers responded to mechanical stimulation of the neuroma, but not to stimulation of the normal nerve both in this study and in a more detailed study of neuromas of the superficial radial or sural nerve (Koschorke *et al.*, 1991). All myelinated afferents displayed entrainment by the vibratory stimuli applied near the nerve injury site. The minimal effective vibratory amplitude was determined or estimated, and was consistent with those of slowly adapting, rapidly adapting and Pacinian receptors. This activity may be related to the dysesthesias rather than the pain associated with chronic pain syndromes, although neuroma models have not been characterized behaviorally.

Another model of nerve injury which may be relevant to pain or dysesthesias of peripheral neuropathic pain is that of a crush injury to the ulnar nerve in baboons (Dykes and Terzis, 1979). Prior to reinnervation the conduction velocities proximal to the nerve injury were significantly decreased versus controls, but the incidence of “abnormal” response properties to vibratory stimuli was not different. The response properties of fibers reinnervating skin were similar to those in controls but both types of slowly adapting fibers displayed an increased rate of adaptation and a stronger tonic response to indentation. The submodalities of nociceptors were recognizable even while thresholds were elevated, and the receptive fields were poorly defined. These characteristics all normalized with time.

The responses to mechanical stimulation of myelinated fibers of the superficial radial or sural nerve have been studied in the anesthetized monkey immediately or 2–6 weeks after tight ligation and section of the nerve (Koschorke *et al.*, 1991). Seven days after the injury none of the ventral root A fibers that could be activated electrically at the nerve injury site were mechanically sensitive. However, approximately one half of the A fibers from the dorsal root were mechanically sensitive, which suggests that sensitivity to mechanical stimuli is specific to sensory fibers. The properties of these fibers following injury indicate that mechanical sensitivity is mediated by the protein subunits which comprise low-threshold mechanoreceptors, and which are transported to the site of nerve injury through axonal transport. As in the case of primate models described above, this model was not characterized behaviorally so it is unclear how relevant these findings are to the dysesthesias or pain of neuropathic pain syndromes.

Chung model: behavior and activity of fibers in the peripheral nerve fibers and STT cells

Among the small number of primate models of neuropathic pain which have been reported the most commonly used is the Chung model, produced by tight ligation of a lumbar spinal nerve just distal to the dorsal root ganglion. The

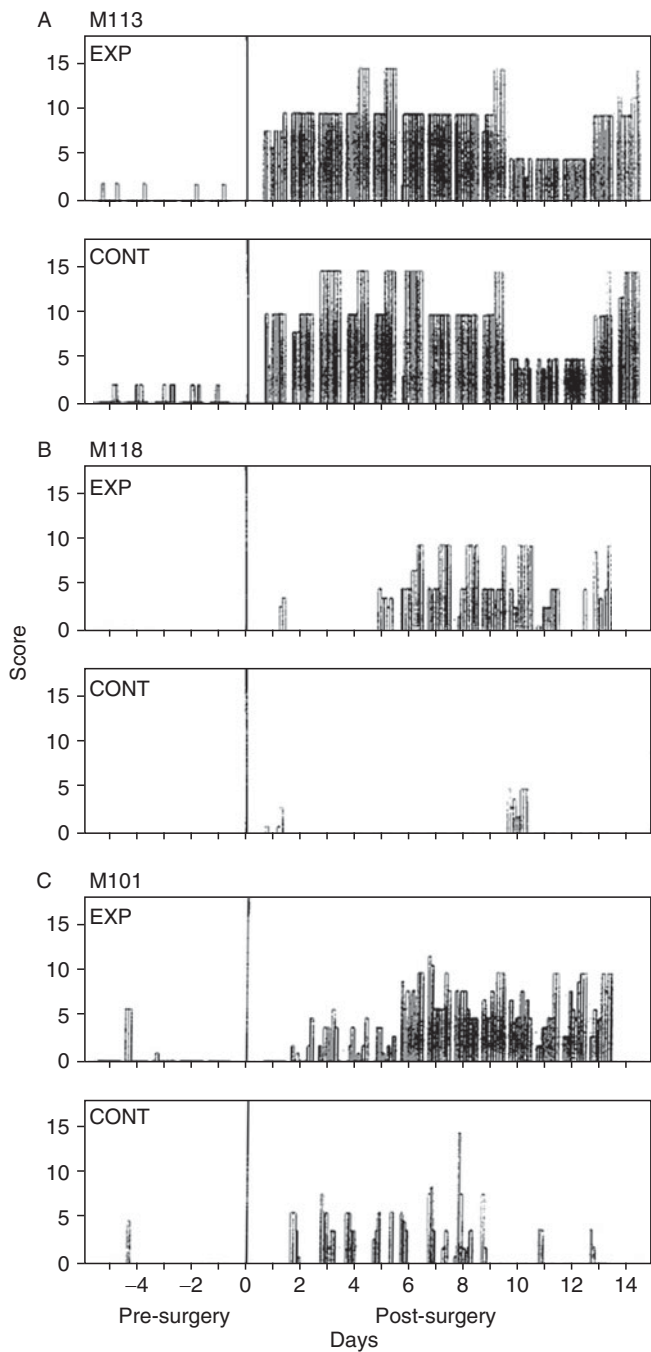


Fig. 7.1. Scores of the withdrawal responses 5 days pre-surgery and 13–14 days post-surgery for the feet ipsilateral (EXP) and contralateral (CONT) to the nerve injury in three animals as shown in panels (A), (B) and (C). The eight columns

Chung model of painful neuropathy in monkeys ($n=3$) has been reported following tight ligation of the L7 spinal nerve (Carlton *et al.*, 1994) congruent with the rat model (Kim and Chung, 1992). Sensory abnormalities were studied on the plantar surface of the foot which includes the L7 dermatome. All three monkeys developed hypersensitivity to mechanical stimulation with von Frey hairs and a camel-hair brush, consistent with mechanical allodynia. Contralateral mechanical hypersensitivity was studied by the application of von Frey filaments to the hindlimb on the lesioned or the control side before and up to 2 weeks after surgery (Fig. 7.1). By 24–48 h after surgery, the response rate increased progressively on both sides, although the responses were more vigorous on the side of the spinal nerve ligation.

The ipsilateral response to cooling stimuli, such as acetone (three animals) and cold water baths (one animal), were consistent with cold allodynia. Two of the three monkeys also developed increased sensitivity to mechanical stimulation on the contralateral foot which is contrary to clinical studies of peripheral neuropathic pain. Heat hyperalgesia developed in all three, as demonstrated by the withdrawal thresholds in response to a heat stimulus. These behavioral phenomena, particularly mechanical and cold allodynia, are similar to those observed in patients with peripheral neuropathic pain.

The human analog of the Chung model was studied after C7 root section in five patients undergoing contralateral brachial plexus reconstruction (Ali *et al.*, 1999a). A transient but significant neuropathic pain developed in the denervated dermatome in one of these five. Two months after surgery this patient had dysesthesia and hyperalgesia to both mechanical and cold stimuli, but not to heat in the denervated dermatome. The spontaneous pain and hypersensitivity persisted during a sympathetic block induced by phentolamine infusion. Only mild parasthesia persisted at a 1-year follow-up.

In the human C7 model the side contralateral to the C7 section was subject to a brachial plexus injury years earlier, and so was not studied. Clearly, the monkey and human Chung model are better validated than the models described above. In the monkey Chung model the presence of hypersensitivity

Caption for Fig. 7.1. (cont.)

associated with each day represent the eight different von Frey hair strengths, weakest to strongest moving from left to right, so that each of the eight columns represents a response to a hair and stimulus periods are not shown. Compared with pre-surgery scores, all animals demonstrated a significant increase in withdrawal response scores to various von Frey hair strengths during the post-surgery survival period for the EXP, and in the case of the monkeys shown in (A) and (C), for the CONT foot (Friedman test, $P < 0.05$). From Carlton *et al.* (1994).

bilaterally suggests that this model is not entirely congruent with clinical peripheral neuropathic pain syndromes.

The monkey studies suggest that nerve injuries which allow recovery (e.g. nerve crush) do not develop the mechanoreceptor hypersensitivity to innocuous stimulation which is often a feature of neuropathic pain. The ipsilateral behavioral phenomena observed in the Chung model may be related to the responses of ipsilateral STT cells recorded in monkeys with the same model (Palecek *et al.*, 1992) and responses of peripheral nerve axons in an L6 tight ligation model (Ali *et al.*, 1999b). In this model recordings were made from uninjured cutaneous C-fiber nociceptors in the peroneal nerve after partial denervation of the skin by the prior ligation (Ali *et al.*, 1999b). Uninjured C-fiber nociceptors were recorded from an in vitro skin-nerve preparation at 2–3 weeks after ligation and compared with those from 29 C-fiber nociceptors in control animals. Selective alpha1-adrenergic and selective alpha2-adrenergic agonists, were applied to the receptive field in increasing concentrations. Nociceptors from in vitro control experiments were not significantly different from nociceptors recorded previously during in vivo experiments. In comparison with controls the afferents found after ligation had a higher incidence of spontaneous activity and of a response to both the alpha1 agonist (phenylephrine) and a selective alpha2 agonist (UK14304 Pfizer, UK) (Ali *et al.*, 1999). In animals with L6 ligation, the peak response to the alpha1-adrenergic agonist was significantly greater than that to the alpha2-adrenergic agonist. Among fibers sensitive to alpha1-adrenergic blockers the mechanical threshold was significantly lower than for fibers that were insensitive. Histology revealed a major (55%) reduction in the number of unmyelinated terminal axons in the epidermis of the lesioned versus the contralateral limb. Thus, C-fiber nociceptors that innervate partially denervated skin show increased spontaneous activity and increased alpha-adrenergic sensitivity.

Changes in the activity of spinothalamic tract (STT) neurons have been described in the monkey Chung model induced by C7 nerve ligation. An attempt to induce neuropathic pain in monkeys using a variant of the constriction injury model of Bennett and Xie (1988) was unsuccessful, apparently due to the size of the sciatic nerve or the thickness of its connective tissue sheath. In the Chung model, enhancement of behavioral responses and of the activity of STT cells were judged in reference to responses observed on the contralateral side following sham surgery and in control animals (Palecek *et al.*, 1992). The behavioral abnormalities were found bilaterally while abnormalities of fibers and neurons were found ipsilateral to the injury.

Extracellular recordings were made from STT neurons in the dorsal horn on the lesioned (Fig. 7.2, three left columns) and on the control side (right column). The STT neurons on the ligated side were subdivided into two groups, depending

were more responsive to mechanical stimuli than were cells in the other groups, and they had substantial responses to tactile stimulation using a camel-hair brush. Similarly, the responses of the STT neurons in the EPN R group to hot or cold stimuli were greater than were those of the EPN C and control cells (right column). The background discharge rates of STT cells in the EPN R group were also higher than those of EPN C and control cells. It was suggested that activation of primary afferent fibers by the ligation, as well as the development of ectopic activity in dorsal root ganglion cells or in fibers at the ligation site, may have been responsible for inducing central sensitization of dorsal horn neurons, including STT cells. This central sensitivity may be secondary to the release of excitatory amino acids and peptides from primary afferent terminals (Palecek *et al.*, 1992).

Consistent with this proposal, it was found that NMDA receptor antagonists, such as dextrorphan (Carlton *et al.*, 1997) and memantine (Carlton *et al.*, 1998), attenuated the responses of STT neurons in monkeys made neuropathic following spinal nerve ligation. Furthermore, an antagonist of kainate GluR5 receptors (LY382884) had a similar effect, suggesting that both non-NMDA and NMDA receptors were involved in the enhanced responses of the STT neurons (Palecek *et al.*, 2004). Recently, it was observed that the phosphorylation of type II calcium/calmodulin kinase (CaMKII) is increased in STT neurons of monkeys following spinal nerve ligation (Zou *et al.*, 2005). CaMKII is known to participate in central plastic changes, such as those seen in long-term potentiation in the hippocampal formation (O'Dell *et al.*, 1991).

There is scant evidence of primate forebrain activity related to peripheral neuropathic pain. An interesting SPECT study in patients with a type of chronic peripheral neuropathic pain (complex regional pain syndrome) demonstrated hyperperfusion of the thalamus contralateral with the painful limb compared with the ipsilateral thalamus in patients with symptoms for only 3–7 months, but hypoperfusion of the contralateral compared with the ipsilateral thalamus in patients with long-term symptoms (24–36 months) (Fukumoto *et al.*, 1999). In contrast, symmetric perfusion of bilateral thalami was found in controls. No differences were seen between controls and patients who had had symptoms of the disease for 10–13 months. Decreases in thalamic perfusion have been found in patients with peripheral neuropathic pain, where the thalamus contralateral to the affected body region exhibited substantially lower CBF than the ipsilateral thalamus (DiPiero *et al.*, 1991; Hsieh *et al.*, 1995; Iadarola *et al.*, 1995).

Central pain in primates

Lesions of the central nervous system (CNS) produce the syndromes and models which have most commonly been used to investigate primate

neuropathic pain syndromes. Chronic pain syndromes associated with CNS injury in humans were first described by Dejerine and Roussy. They found that stroke-induced pain resulted from thalamic lesions, and coined the term “thalamic pain syndrome” (Dejerine and Roussy, 1906). This term was disputed by Biemond (1956). Modern imaging has confirmed that central pain can arise from multiple different types of lesions in the spinal cord, brainstem, subcortical white matter and cerebral cortex, as well as thalamus (Beric *et al.*, 1988; Hirai and Jones, 1989; Leijon *et al.*, 1989; Vestergaard *et al.*, 1995; Bowsher *et al.*, 1998). When caused by strokes these conditions are known as central post-stroke pain (CPSP) syndromes.

The majority of studies of mechanisms of central pain in primates have been carried out in humans. In both CPSP and spinal cord injury (SCI) central pain it is remarkable that loss of pain and thermal sensation is always a feature (Beric *et al.*, 1988; Boivie *et al.*, 1989; Vestergaard *et al.*, 1995; Bowsher, 1996; Greenspan *et al.*, 2004). This pattern of sensory loss is associated with transection of the spinal cord resulting in chronic pain localized below the level of the transaction (in SCI central pain), or a stroke, resulting in central pain on the side of the body opposite the stroke in CPSP. In both cases the diagnosis of central pain is based on evidence of a CNS injury, evidence of pain and temperature loss and the exclusion of other mechanisms of pain.

Other features that CPSP shares with SCI central pain include the evidence for interaction between innocuous and nociceptive sensory channels leading to allodynia but not hyperalgesia. These syndromes also share the phenomena of pain referred within the area of sensory loss. The degree of sensory loss has also been correlated with the degree of pain in patients with CPSP. The clinical features and sensory testing in patients with central pain have advanced our understanding of the mechanism of this syndrome.

Clinical features of SCI central pain

Clinicians have distinguished between pain at or above and those below the level of the lesion. Pain at or above the lesion level is thought often to be related, at least in part, to nociceptive input from somatic injuries associated with a traumatic spinal injury. Below-lesion pain, however, is more likely attributable specifically to the neurological consequences of spinal cord damage; it represents either the supraspinal consequences of denervation or a focus of hyperexcitability in the spinal cord and is therefore a type of central pain syndrome (Donovan *et al.*, 1982; Davidoff and Roth, 1991). The clinical features and types of pain have been reported in 127 patients with SCI central pain (Tasker *et al.*, 1992). The spontaneous pain has been characterized as: steady (95% of patients), intermittent (often shooting, 31%) and evoked (allodynia,

hyperpathia or hyperesthesia, 45%). Steady pain was described as thermal (burning, 75% and cold, 4%) or dysesthetic (tingling, 28%), and mechanical (aching, 13%; pressure, 18%; and rhythmic, 9%). These results are generally consistent with a smaller detailed study of 19 patients in which the following sensations were evoked in 30–70%: burning, tight, piercing and radiating (Davidoff and Roth, 1991). A steady, burning, dysesthetic component was the most common in a study of 102 patients who developed SCI central pain (Fenollosa *et al.*, 1993).

Allodynia occurred in 47% of patients in Tasker's series, but only in areas of preserved sensation (Tasker *et al.*, 1992; Tasker, 2002). Taking complete and incomplete lesions together, it occurred in 21% as a band at the upper level of the sensory loss, as a diffuse sensation in 29% and as a patchy sensation in 50%. A Danish study reported loss of pinprick or temperature sensation which was complete in 17 out of 20 patients, and incomplete in three. Allodynia was reported in dermatomes at the lesion level in eight out of 20 patients, below the lesion level in one patient and diffusely, including the face, in another patient (Finnerup *et al.*, 2003a).

Patients with spinal cord injury with pain may also have an elevated heat pain threshold above the lesion level; and this threshold may be returned to normal or near normal following a pain-relieving dorsal root entry zone (DREZ) lesion (Defrin *et al.*, 1999), suggesting that an intact afferent innervation sustains a pain-generating focus in the intact spinal or supraspinal structures. In a related study of SCI patients (with traumatic paraplegia), Defrin and colleagues also found that both the threshold and thermal quality of pain produced by heat or cold depended strongly on the integrity of innocuous thermal sensations, a finding that highlights the interaction between nociceptive and non-nociceptive pathways in the CNS (Defrin *et al.*, 2002).

These findings demonstrate that patients with SCI central pain have a loss of STT mediated thermal sensation or pain sensation or both on quantitative sensory testing (Beric *et al.*, 1988; Finnerup *et al.*, 2003b; see also Eide, 1998). However, this loss does not identify patients with SCI central pain among a population with SCI (Finnerup *et al.*, 2003b). Therefore loss of STT mediated sensations is a necessary but not sufficient condition for the development of SCI central pain.

The sufficient condition for the presence of central pain in SCI patients may be the presence of hypersensitivity to cold or tactile stimuli (Finnerup *et al.*, 2003b). When compared with SCI patients without central pain, SCI patients with central pain more frequently had hypersensitivity to mechanical and cold stimulation in dermatomes corresponding to the lesion level (Fig. 7.3). The intensity of brush-evoked pain at the lesion level was correlated with spontaneous pain below the level of the injury (Finnerup *et al.*, 2003b). The below-injury

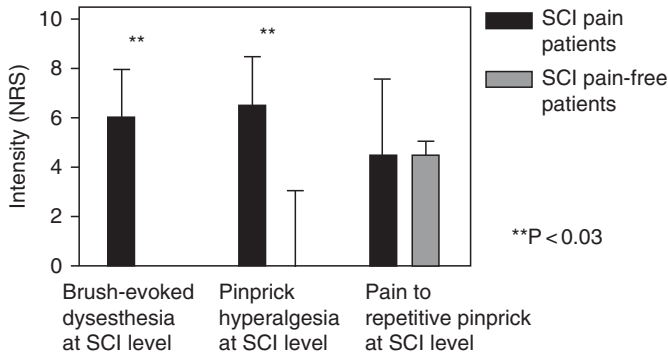


Fig. 7.3. Intensity of evoked sensations in pain patients ($n = 20$) and pain-free ($n = 20$) patients with spinal cord injury (SCI). Error bars are 10th and 90th percentile. From Finnerup *et al.* (2003b), figure 2.

level spontaneous pain cannot arise from the activity of dorsal horn neurons at that level. Therefore these results point to the role of brainstem, thalamic and cortical neurons receiving input in somatic sensory pathways in mechanisms of central pain related to afferent input (see below).

Clinical features of CPSP

Central pain caused by lesions of the brain is known as central post-stroke pain (CPSP), and is as intractable as that arising from lesions of the spinal cord. The CPSP can arise from lesions of any etiology above the spinal-medullary junction, but is most commonly the result of a stroke (Greenspan *et al.*, 2008b). There are many similarities between the clinical features of CPSP and those of SCI central pain. Both types of central pain have sensory loss for thermal or pain modalities, as well as spontaneous and evoked pain. The pain of CPSP is nearly always present during the waking hours although it may vary in intensity depending on environmental conditions and psychological factors. The pain may be increased particularly in cold ambient temperatures even though cold allodynia is absent. Heightened emotional states such as fear, anger and anxiety may increase pain intensity and unpleasantness together or separately. The pain is most often perceived as deep, often aching in quality, although a superficial component is sometimes described. Patients will often identify the temporo-spatial characteristics of the pain as diffuse, rather poorly localized, and usually constant rather than pulsating or vibrating. Burning and aching are frequently offered as qualitative pain descriptors (Riddoch, 1938).

Clinical studies show that loss of thermal or pain sensation or both is necessary for the development of central pain, although there are significant

differences in the sensory abnormalities among patients with CPSP (Bogousslavsky *et al.*, 1988; Bowsher *et al.*, 1998; Leijon *et al.*, 1989; Schmähmann and Leifer, 1992). The distribution of pain is within or adjacent to the area of sensory loss. These studies also demonstrate that the lesions anywhere above the spinomedullary junction can lead to CPSP as long as it impairs STT-related (pain and temperature) function.

A prospective study examined 267 consecutive patients admitted for stroke at one institution over a 1-year post-stroke interval. Among those 87 patients who survived at least 6 months *with sensory abnormalities*, CPSP developed in 16 (18%). The latent period of onset of pain in CPSP following the stroke was less than 1 month in ten patients, and greater than 6 months in three (Andersen *et al.*, 1995).

A descriptive report of 73 patients with CPSP found that the onset of pain was often delayed, consistent with previous studies (Tasker, 2002). Pain in CPSP was commonly characterized as steady (usually burning, 64.4%), dysesthetic (31.6%), intermittent (16.4%), and with allodynia or hyperalgesia (64.9%). The distribution of intermittent pain was similar to that of spontaneous pain overall, and to that of sensory loss. Onset was often delayed between 1 and 4 weeks in 47–63% and greater than 4 weeks in approximately 20% (Boivie and Leijon, 1991; Andersen *et al.*, 1995; Tasker, 2002). Distribution of pain varied and bore no relation to any clinical features. Size, side, location of the lesion, degree of sensory loss, age and sex were all unrelated to the quality or severity of the pain.

There are three series of CPSP patients in which quantitative sensory testing (QST) was carried out and descriptors of pain qualities were determined (Table 7.2). In the recent series, ongoing pain was described by a majority of patients by temperature or mechanical descriptors (usually pressure) (Greenspan *et al.*, 2004). In the two comparable studies of CPSP similar thermal or mechanical descriptors were usually chosen by a majority of patients (Boivie *et al.*, 1989; Vestergaard *et al.*, 1995). Patients had average pain ratings of between 2.5 and 7.5 (visual analog score – VAS). Although these results are similar to those in SCI central pain, tingling sensations are more common in the SCI and pressure sensations are more common in CPSP.

Across the three studies of CPSP, QST was reported in individual patients. These studies documented tactile hypoesthesia in 27–52% of the patients tested (Boivie *et al.*, 1989; Vestergaard *et al.*, 1995; Greenspan *et al.*, 2004; cf. Bowsher, 1996). Tactile allodynia or hyperalgesia was found in 9–59%; the difference in incidence may be the result of differences in the stimuli including brush, rotating von Frey hair (Andersen *et al.*, 1995) or pinprick (Boivie *et al.*, 1989).

These studies reported a large proportion of CPSP patients with cool hypoesthesia (63–85%), though 0–23% showed cold allodynia (Boivie *et al.*, 1989; Vestergaard *et al.*, 1995; Greenspan *et al.*, 2004). All studies reported a large

Table 7.2. Comparison of series of patients with CPSP who were studied clinically and by quantitative sensory testing. The fourth column includes both clinical findings ($n = 16$) (Vestergaard et al., 1995) and quantitative sensory testing ($n = 11$) (Andersen et al., 1995). Similarly, the third column includes both clinical (Leijon et al., 1989) and sensory testing results (both $N = 27$) (Boivie et al., 1989). Reprinted from Greenspan J.D., Ohara S., Sarlani E., Lenz F. A., Allodynia in patients with post-stroke central pain (CPSP) studied by statistical quantitative sensory testing within individuals. Pain 109: 359–366. Copyright 2004, with permission from Elsevier.

Reference	(Greenspan et al., 2004)	(Boivie et al., 1989; Leijon et al., 1989)	(Andersen et al., 1995; Vestergaard et al., 1995)
<i>Descriptors</i>			
Burning cold/cold pain	53% overall; 38% burning and cold; 15%, hot and cold	59%, 16/27	38%, 6/16 (freezing 3/16)
Mechanical pain	70% overall; 33% sharp/stab; 23% pressure heavy; tight/ squeezing 7% each	Aching 30%, pricking 30%, lacerating 26%	86%, 23/27
Pain rating	7.1 mean, 2.0 SD	2.5–7.9 mean by stroke location	3.3 median (0–7)
Touch method	Von Frey for threshold: brushes for allodynia	Von Frey for threshold, pinprick for hyperalgesia	Von Frey hair, von Frey rotating for hyperalgesia
Normal threshold	50%, 5/10	48%, 13/27	54%, 6/11
Hypoesthesia	50%, 5/10	52%, 14/27	27%, 3/11
Allodynia/Hyperalgesia	54%, 7/13	16/27, 59% – hyperalgesia	1/11 – hyperalgesia
Cool method	Peltier Medoc	Peltier Somedic, warm minus cool threshold	Peltier Somedic
Normal threshold	15%, 2/13	0/27	9%, 1/11
	85%, 11/13, 3 with equal bilateral hypoesthesia	Difference in cool–warm thresholds 17/27; larger change in cool 2/27	91%, 10/11
Cold pain method	As above		
Normal threshold	31%, 4/13	7% normal difference between cold and heat pain threshold	18%, 2/11 – unaffected side lower

Table 7.2. (*cont.*)

Hypoalgesia	46%, 6/13 (2 indeterminate)	93% abnormal difference between cold and heat pain threshold	45%, 5/11 (4/11 – bilateral hypoalgesia)
Allodynia	23%, 3/13	No abnormally sensitive thresholds, but 5/22 (23%) reported discomfort to metal at room temperature	0/11
<i>Warm method</i>	As above	–	–
Normal threshold	15%, 2/13	Difference in cool–warm thresholds, 17/27; larger change in warm threshold 8/27	11/11
Hypoesthesia	85%, 11/13		
<i>Heat pain method</i>	As above		
Normal	93%, 12/13	7% normal difference between cold and heat pain threshold	9%, 1/11
Hypoalgesia	7%, 1/13 (2 indeterminate)	93% abnormal difference between cold and heat pain threshold	91%, 10/11
Allodynia	0/13 (2 borderline)	No abnormally sensitive thresholds	0/11

proportion of patients with warm hypoesthesia (85–100%), but no clearly abnormal cases of heat allodynia (0% to borderline in 7%). A study correlating sensory loss with hypersensitivity found that tactile and cold hypoesthesia were significantly correlated with preservation in tactile and cold modalities, respectively (Greenspan *et al.*, 2004). As in the case of SCI central pain, cold and tactile hypoesthesia and allodynia were common in CPSP. Hypersensitivity was most common in the presence of preserved sensation, whether in terms of modality (CPSP) or of location of hypersensitivity, at the level of the injury (SCI central pain).

Anatomy of lesions resulting in CPSP

Pain following spinal cord infarction is similar to that previously described above for SCI pain except that these patients do not have pain at the lesion level that can be attributed to nociceptive input from a traumatic injury. Post-mortem analysis of spinal cord infarction is rare, but the available evidence indicates that the spinothalamic tract must be damaged, an observation consistent with the incidence of central pain following anterolateral cordotomy (Nathan, 1963; Nathan and Smith, 1979; Bowsher, 1988; Tasker *et al.*, 1992; Nagaro *et al.*, 1993, 2001; Lahuerta *et al.*, 1994; Villanueva and Nathan, 2000).

The brainstem infarction most commonly associated with CPSP is within the distribution of the posterior inferior cerebellar artery (PICA or Wallenberg's syndrome), involving the spinothalamic tract in its passage through the lateral medulla (MacGowan *et al.*, 1997; Peyron *et al.*, 1998; Kim and Choi-Kwon, 1999; Fitzek *et al.*, 2001). Lenticulo-capsular hemorrhage may also cause CPSP (Kim, 2003).

Lateral and posterior thalamus and parasyllvian cortex are most clearly linked to the sensory-discriminative aspect of pain (Chapters 1 and 2). Thalamic lesions most frequently associated with CPSP occur following infarctions within the territory of the inferolateral branches of the posterior cerebral artery (Bogousslavsky *et al.*, 1988; Schmahmann, 2003). Injections of lidocaine into monkey VP, corresponding to human Vc, are associated with a decreased ability to detect small changes in temperature in both the innocuous and noxious range (Duncan *et al.*, 1993). A large lesion of posterior thalamus involving regions posterior to Vc resulted in documented deficits of touch, warm, cool, sharp and mechanically evoked pain but not heat or cold pain (Greenspan and Winfield, 1992). These results are consistent with studies of patients with sensory loss and CPSP.

A study in patients with pure somatic sensory stroke ($n = 21$) identified eleven thalamic strokes, nine lacunes and two hemorrhagic strokes. The lacunes were

confined to posterior lateral thalamus probably involving Vc. Five involved both tactile and thermal/pain sensations and six involved either tactile or thermal/pain sensations, nine of which were located in the ventral posterior lateral thalamus corresponding to Vc (Schaltenbrand and Walker, 1982; Hirai and Jones, 1989; Kim, 1992). Six of these were associated with loss of some and sparing of other somatic sensory modalities. Therefore lesions of the pain and temperature somatic sensory pathway in the posterior thalamus are associated with central pain.

In another study, QST was carried out in four patients with CPSP or small lesions in the region of thalamic nucleus Vc (see Fig. 4.11). All four patients had alterations of cold pain sensation, while three patients had altered cool sensation. The patient with the least involvement of Vc had normal cool detection thresholds, suggesting that a lesion involving a critical volume of Vc is required to impair this modality. Perception of warmth was impaired only in lesions involving nuclei posterior to Vc, consistent with the effect of injection of local anesthetic into monkey ventral posterior thalamus (corresponding to human Vc) (Hirai and Jones, 1989; Duncan *et al.*, 1993). Heat pain perception was not impaired in any of these lesions, but was impaired with a larger lesion of Vc (Montes *et al.*, 2005). Tactile perception was always impaired on the involved side. Therefore, there are modality-specific elements in the human posterior thalamus, but lesions of Vc not involving regions posterior to Vc, including VMpo, are sufficient to impair cold sensibility and to produce CPSP. Similar techniques have been used in studies of sensory function following cortical lesions (see Chapter 4).

The recent version of the disinhibition hypothesis proposes that central pain results from a lesion involving a cold-signaling pathway which projects to the insula through posterior thalamic nucleus VMpo (Craig *et al.*, 1996) (see below as well as Chapters 2 and 3). In patients with CPSP, it is proposed that a lesion of this pathway disinhibits a medial STT pain-signaling pathway projecting to anterior cingulate cortex (ACC) via the medial dorsal nucleus (MD) (Craig *et al.*, 1996; Craig, 2000). According to this hypothesis, lesions of VMpo lead to cold hypoesthesia, and to the disinhibition of the ACC which results in the burning pain of CPSP. Therefore, the location of thalamic and cortical strokes in CPSP provides a critical test of this hypothesis.

Lesions of the thalamus and cortex have also been studied by imaging techniques in patients with CPSP. Previous studies have used CT to localize lesions in the thalamus in patients with central pain ($n = 12$). In four cases the lesions involved the thalamus, but all cases involved other structures in addition to the thalamus (Andersen *et al.*, 1995). In a similar study of 27 patients with CPSP, nine out of 27 had thalamic lesions of which two were limited to the thalamus and

the rest could not be further specified (Leijon *et al.*, 1989). In a study of MRI scans in patients with central pain most patients (49/70) had lesions that included the “ventral posterior nucleus” (corresponding to Vc) (Bowsher *et al.*, 1998). Finally, MRI- and atlas-based methods have been used to demonstrate that thalamic lacunes leading to CPSP were located in Vc and do not involve VMpo (Montes *et al.*, 2005; Kim *et al.*, 2007), contrary to the disinhibition hypothesis.

Lesions of cortical elements of the STT-thalamocortical system in patients with central pain involve somatic sensory areas. Cortical lesions associated with CPSP occur within the posterior parietal cortex and are most likely to involve the insular and adjacent opercular cortex (Kim, 2007). Infarctions in this territory will result in variable degrees of sensory loss, which may be sufficiently dense to present clinically as thalamic infarction, hence the term “pseudothalamic syndrome” (Bassetti *et al.*, 1993). Several other pain-related syndromes, such as asymbolia for pain (Schilder and Stengel, 1931; Biemond, 1956), are associated with insular-opercular strokes, but their presence appears unrelated to the CPSP that may follow these lesions. Finally, several studies have provided evidence that CP may follow thermosensory deficits associated with lesions in the parietal cortex (Schmahmann and Leifer, 1992; Fukuhara *et al.*, 1999; Peyron *et al.*, 2000). Imaging analysis of patients with CPSP have identified lesions in the parietal lobe in 4/5 patients with cortical lesions leading to central pain (Vestergaard *et al.*, 1995); precise anatomy of capsular lesions (two patients) could not be further specified. In another study, patients with central pain had parietal lesions in all extrathalamic cases (Leijon *et al.*, 1989). A prior study of MRI scans in patients with CPSP had cortical lesions localized to insular or parietal cortex (Bowsher *et al.*, 1998). In sum, these studies suggest the forebrain structures involved in central pain.

Other clinical conditions with central pain

Approximately 20% of patients with multiple sclerosis (MS) will develop central pain, usually as a result of a spinal cord plaque; brainstem, thalamic and cortical (subcortical white matter) lesions have been implicated also in the central pain of MS (Osterberg *et al.*, 2005). Central pain is also a frequent complication of syringomyelia. There is little information about the incidence or prevalence of pain in syringomyelia of all causes; it is the most common early symptom in most patients with post-traumatic syringomyelia (PTS) (Schurch *et al.*, 1996) although much of the pain in PTS is reported to be at or above the spinal cord lesion level. In a recent study of 46 patients with syringomyelia, 31 had central neuropathic pain and a congenital cause (Chiari type 1 malformation) was established for 27 (Ducreux *et al.*, 2006).

Patients with Parkinson's disease (PD) may complain of regional, poorly localized, aching pain that appears unrelated to the degree of rigidity or tremor (Schott, 1985). The lack of a clinically evident peripheral cause of this pain has led to the assumption that it is of central origin in most instances (Starkstein *et al.*, 1991; Schestatsky *et al.*, 2007). However, because of the widely distributed pathology of PD, a focal lesion cannot be identified in these patients. Given the importance of dopamine as a mediator of pain and nociceptive modulation (see Chapter 6), it is possible that the pain of PD may be due to an impairment of this endogenous modulatory mechanism. Finally, recent imaging studies (see Chapter 8) have provided evidence that the generalized pain of fibromyalgia may be due to an impairment of endogenous pain modulatory mechanisms although an anatomically identifiable central lesion has not been found (Gracely *et al.*, 2002, 2004; Geisser *et al.*, 2003; Staud *et al.*, 2003; Cook *et al.*, 2004; Williams and Gracely, 2006; Harris *et al.*, 2007a; Sundgren *et al.*, 2007).

Mechanism of ongoing pain in patients with central pain

There is no a priori reason to suspect that there is only one cause or mechanism of CP. Indeed, the multiple pathological conditions and lesion locations associated with CP suggest that several different mechanisms may be involved in different clinical conditions. One salient finding among most studies is that the degree of sensory loss, especially of thermal senses, both warm and cold, correlates with the intensity of the neuropathic pain (Bowsher, 1996; Ducreux *et al.*, 2006). This observation is in accord with experimental and clinical evidence for an interaction among thermosensory mechanisms and the central processing of nociceptive information. The experimental evidence shows that both warm and cold innocuous stimuli modulate the perceptions of heat and cold pain (Casey *et al.*, 1993; Craig and Bushnell, 1994; Craig *et al.*, 1996); and the clinical evidence is that the integrity of pathways mediating innocuous thermal sensations is necessary for the perception of heat and cold pain (Defrin *et al.*, 2002; Ofek and Defrin, 2007). Impairment of tactile sensations and their pathways, however, is not associated with CP. The amplitude of cerebral potentials evoked by noxious infra-red laser stimulation (LEPs) of the affected side is reduced in the great majority of CPSP patients with thermosensory loss although tactile sensations and short-latency somatosensory-evoked potentials are intact (Casey *et al.*, 1996a; Garcia-Larrea *et al.*, 2002); LEP abnormalities do not, however, correlate with hyperalgesic or allodynic abnormalities in these patients. Relevant to these findings, a magnetoencephalographic (MEG) study of a patient with a brainstem spinothalamic infarction revealed abnormal cingulate cortex responses to innocuous electrical stimulation, suggesting a loss of spinothalamic

modulation of access to cortical limbic structures (Lorenz *et al.*, 1998). Thus, an impairment of thermosensory, but not tactile discriminative, function appears to be a necessary but insufficient condition for CP (Boivie *et al.*, 1989; Boivie and Leijon, 1991; Boivie, 2006); this is most likely to occur clinically following lesions that directly involve the spinothalamic tract or its ventral posterior thalamic terminations. However, as noted above, thermosensory deficits and CP may follow lesions in the opercular-insular or parietal cortex. The interruption of normal thermosensory mechanisms mediated through the spinothalamic tract may disinhibit normal controls over central nociceptive processing; this effect, however, does not appear to be limited to pathways or mechanisms mediating the sense of cold (Casey *et al.*, 1993; Craig and Bushnell, 1994; Craig, 1998, 2003, 2008).

Functional imaging studies have reported both hypo- and hyperactivity of the thalamus in central pain patients. Two positron emission tomography (PET) case studies reported decreased cerebral blood flow (CBF) in the ipsilesional thalamus in central pain patients during rest (Hirato *et al.*, 1993; Canavero and Bonicalzi, 1998; Peyron *et al.*, 2000; Cahana *et al.*, 2004). Due to poor spatial resolution of these PET studies, the specific thalamic nuclei could not be determined. This relative thalamic hypoactivity could be reversed by motor cortex stimulation (Peyron *et al.*, 1995) or analgesia produced by repeated cycles of daily IV lidocaine infusion (Cahana *et al.*, 2004). During PET acquisition of motor cortex stimulation and lidocaine treatment, pain was reduced compared with the rest state.

In the specific case of patients with baseline (resting) hypoperfusion of the VP thalamus, it is possible that CPSP is due to the loss of GABAergic inhibitory mechanisms that normally control the excitability of VP thalamocortical neurons (Casey, 2007). The inhibitory synaptic control of VP projection neurons derives from a combination of inputs from the thalamic reticular nucleus and the substantial population of GABAergic neurons within the VP complex of primates (Chapter 4) (Ohara *et al.*, 1989; Jones, 2002). Functional imaging studies (PET, SPECT) suggest that a clinically significant fraction of patients with neuropathic pain, including CPSP, may have hypoperfusion of VP at rest or a hyperactive thalamic response to somatic stimulation of the affected body area (Cesaro *et al.*, 1991; Hirato *et al.*, 1991, 1994; Pagni and Canavero, 1995). The loss of GABA synaptic activity within VP would cause focal thalamic hypoperfusion because of the reduced metabolic demand for neurotransmitter recycling (Shulman and Rothman, 1998; Magistretti *et al.*, 1999; Raichle *et al.*, 2001). Following lesions of the lemniscal or STT pathways to the VP, there is a marked reduction of GABA receptor immunoreactivity (Rausell *et al.*, 1992) and GABA synaptic contacts on VP neurons are markedly reduced (Ralston *et al.*, 1996). In addition, trauma, including ischemia, changes the response of VP neurons to GABA_A receptor

activation (exogenous and endogenous) from inhibitory to excitatory and causes endogenous GABA to increase the intracellular Ca^{++} of VP neurons and the spontaneous “spiking” of these neurons (van den Pol *et al.*, 1996); this observation is clinically significant because patients with CP may have spontaneous bursting (at rest) of VP neurons consistent with the generation of low-threshold Ca^{++} spikes and the effect of GABA on intracellular Ca^{++} (see Chapter 7) (Lenz *et al.*, 1987, 1989, 1994b; Hirayama *et al.*, 1989; Hua *et al.*, 2000).

Hyperactivity of the thalamus has also been described. A SPECT study reported bilateral regional metabolic increases in the thalamus in a case of SCI central pain during the experience of spontaneous, high intensity, paroxysmal central pain. However, reduced thalamic blood flow was observed when the spontaneously occurring pain was at a low intensity compared with resting values in healthy subjects (Ness *et al.*, 1998). Other SPECT and PET studies of CPSP patients demonstrated hyperactivity in the thalamus after stimulating the allodynic side compared with stimulating the non-allodynic side and/or to patients without allodynia (Cesaro *et al.*, 1991; Peyron *et al.*, 1998, 2000; Ducreux *et al.*, 2006).

Mechanisms of tactile allodynia in central pain

Tactile hypoesthesia and tactile allodynia, as measured by von Frey hairs and moving brushes, are common clinical features of central pain (Table 7.2). A recent study of quantitative sensory testing in CPSP described above has also demonstrated that tactile allodynia is more often associated with normal tactile sensibility than tactile hypoesthesia (Greenspan *et al.*, 2004). Tactile sensibility measured by von Frey hairs and a moving brush are mediated through the dorsal column pathway (Mountcastle, 1984; Lenz *et al.*, 1988; Lee *et al.*, 1999), more than the STT pathway (Willis, 1985; Willis and Coggeshall, 1991; Lenz *et al.*, 1994a; Lee *et al.*, 1999). Sensory testing in patients with lesions of the dorsal columns revealed mild deficits in tactile sensation, while lesions of the STT (sparing the dorsal columns) were associated with no deficit in tactile sensation (Nathan *et al.*, 1986). Therefore, the reduced tactile thresholds in the recent study are likely due to decreased transmission of stimuli through the dorsal column-thalamic-cortical pathway (Greenspan *et al.*, 2004). In these patients with CPSP, brush allodynia occurred in the presence of normal tactile thresholds, suggesting that there is no lesion of the ascending dorsal column pathway (Nathan *et al.*, 1986).

These results support a model in which brush-evoked allodynia involves input to the forebrain through an intact pathway that includes dorsal column-thalamic Vc – postcentral gyrus and parietal operculum (Van Buren and Borke, 1972; Jones, 1985; Lenz *et al.*, 1988). In fact, the activation of afferents known to project through the dorsal columns evoked unpleasant dysesthesias only in

stroke patients with post-stroke dysesthesias, a subset of patients with central pain (Triggs and Beric, 1994). The thalamocortical structures likely to be involved in producing allodynic sensations to tactile stimulation are the thalamic nucleus Vc, and projections to the postcentral gyrus and parietal operculum (Lenz *et al.*, 1988; Ohara *et al.*, 2004) (see [Chapters 2 and 4](#)).

The involvement of the dorsal column pathway in central pain is also supported by electrophysiological studies of the forebrain. Microstimulation in Vc evokes painful sensations more commonly in patients with CPSP than in controls operated for treatment of either movement disorders or non-CPSP pain syndromes (Davis *et al.*, 1996; Lenz *et al.*, 1998a). In patients with CPSP and hyperalgesia, microstimulation in Vc evoked pain more frequently than in patients without hyperalgesia (Lenz *et al.*, 1998a). Stimulation in Vc evoked pain more frequently in the representation of the part of the body where the patient experienced hyperalgesia than did stimulation in the representation of other parts of the body (Lenz *et al.*, 1998a). The pain-related function of Vc is demonstrated by the presence of STT terminals (Mehler, 1966), sites where stimulation evokes pain (Ohara and Lenz, 2003), and recording studies which demonstrate that some cells in Vc respond differentially or selectively to painful stimuli (Lee *et al.*, 1999). In combination with the present results these studies are strong evidence of a role for the dorsal column-thalamic Vc-somatic sensory cortical pathway (SI) in tactile allodynia of CP.

Few imaging studies have examined cortical activation-related tactile-evoked allodynia of any etiology. The only imaging study of tactile allodynia in central pain demonstrated that tactile allodynia produced a pattern of brain activation distinct from that of cold allodynia in patients with spinal lesions involving the STT (Ducreux *et al.*, 2006). Tactile stimuli consisted of repetitive stroking with a soft brush applied in the allodynic area of patients with and without central pain and normal controls. The pattern of activation for tactile allodynia was very similar to that obtained by non-painful brushing in normal volunteers and patients without pain. In all groups, activation was observed in the contralateral SI, contralateral SII, inferior and superior parietal areas. Activation specific to allodynia was elicited in the contralateral thalamus, bilateral middle frontal gyrus, caudate nucleus and supplementary motor areas. Interestingly, tactile allodynia was not associated with activation in the insula or ACC. Similar blood flow activation, including powerful activation of SI, was observed with allodynia provoked by a stimulus including elements of both cold and tactile modalities (Peyron *et al.*, 1998; Kim *et al.*, 2007).

A PET study using the capsaicin experimental pain model reported similar activation patterns during non-painful light brush stimulation and capsaicin-induced experimental tactile allodynia mainly in the following regions: contralateral

SI, bilateral parietal lobule/SII, ACC, ipsilateral insula and ipsilateral putamen (Iadarola *et al.*, 1998). Activation specific to allodynia was mainly observed in bilateral superior frontal gyrus, ipsilateral posterior insula and ipsilateral inferior parietal lobule/SII. In an fMRI study using this same capsaicin model (Kilgard and Merzenich, 1998; Baron *et al.*, 1999a), contralateral SI and bilateral SII activation were found during non-painful mechanical stimulation using von Frey filaments. When stimulation provoked secondary mechanical hyperalgesia, significant activation was found in the contralateral prefrontal cortex and parts of the superior and inferior frontal gyrus. No activation in the ACC was found.

Neurochemical studies

The most basic study of neurochemistry in central pain reported changes in MR spectroscopic signals consistent with different classes of thalamic cells. An MR spectroscopy study found that metabolite concentrations of the neuronal marker *N*-acetyl-aspartate (NA) and the glial cell marker *myo*-inositol (Ins) in the thalamus differed between patients with or without central pain after spinal cord injury (Pattany *et al.*, 2002). Mean NA concentrations and the NA/Ins ratio were significantly lower for pain patients compared with pain-free patients. Mean Ins concentrations were higher for pain patients versus pain-free patients and this difference approached significance. Further, NA concentrations were negatively correlated with pain intensity, and Ins concentrations were positively correlated with pain intensity in the pain group. No significant differences were found between the right and left thalamus, but it is unclear if pain was localized unilaterally. These results reflect dysfunction or loss of neurons in the thalamus in patients with central pain secondary to spinal cord injury.

It has been suggested that up- or down-regulation of receptors may be involved in the development of central pain, which could also explain the delayed time course of the development of central pain (Bowsher *et al.*, 1998). Recent PET studies reported on opioid receptor binding in both healthy subjects and central pain patients. A recent study in Old World monkeys (Baumgartner *et al.*, 2006) demonstrated that many areas traditionally thought to be involved in pain processing have a high binding potential for opioids in healthy male subjects. Highest binding potentials were found in the thalamus (specific nuclei were not identified), basal ganglia (putamen and caudate), amygdala, ACC and operculo-insular region. The SI and M1 have significantly less binding potential. No hemispheric differences were found.

Recent PET receptor binding studies demonstrated reduced opioid receptor binding of a non-selective ligand in many of these areas in CPSP patients versus

healthy controls (Willoch *et al.*, 1999, 2004; Jones *et al.*, 2004). Significantly reduced regional binding was found independent of lesion site, mainly involving the thalamus, SII, insula, prefrontal cortex, ACC and inferior parietal cortex (Brodmann area 40). Reduced radio-labeled opioid binding may reflect competition of the exogenous ligand with increased occupation of endogenous opioid peptides; however, the observation that two patients who received naloxone infusions did not demonstrate increased pain contradicts this explanation (Jones *et al.*, 2004). Possible other explanations are loss of receptors due to the lesion, transneuronal degeneration or receptor alterations such as receptor internalization or down-regulation (Willoch *et al.*, 2004). These observations of reduced opioid receptor binding in central pain patients may explain the poor response of many of these patients to opioid treatment (Rowbotham *et al.*, 2003; Katz and Benoit, 2005).

Up-regulation of receptors is also possible following lesion-induced denervation. For example, GABA_A receptors were up-regulated in monkeys at long survival times following an extensive cervical dorsal rhizotomy (Rausell *et al.*, 1992). A recent study demonstrated that the expression of the metabotropic glutamate receptor subtype 1 was up-regulated in laminae IV and V STT cells in rats after spinal cord injury compared with uninjured animals (Mills *et al.*, 2002). Spinal cord injury can also dysregulate sodium channel expression, specifically in the dorsal horn of the spinal cord and in thalamic neurons (Waxman and Hains, 2006). An imbalance of central excitatory and inhibitory mechanisms has been proposed to contribute to central pain. Pharmacological studies support the importance of neuronal hyperexcitability as a mechanism of central pain. Agents that inhibit hyperexcitability such as lidocaine (by blocking voltage-sensitive sodium channels), ketamine (by blocking NMDA receptors and thereby glutamatergic excitation) and lamotrigine (blocking both sodium channels and glutamate receptors) have been shown to be effective in relieving central pain (Cohen and Abdi, 2002; Nicholson, 2004). Also increasing GABAergic inhibition with either baclofen or propofol has been shown to be effective (Cohen and Abdi, 2002; Nicholson, 2004). However, it is not possible to identify the site of action of the agents in these clinical studies.

Motor cortex and central pain

Motor cortex stimulation has been used with some success (50–75%) for the treatment of central pain (Nguyen *et al.*, 2000; Rasche *et al.*, 2006). Motor cortex stimulation has been shown to modulate dorsal horn spinal cord activity. Electrical stimulation of the motor cortex inhibited responses to noxious pressure and pinch stimuli in a graded fashion (higher voltage of electrical

stimulation reduced neuronal activity more), but not to innocuous brush as recorded from wide dynamic range neurons in lumbar spinal dorsal horn in rats (Senapati *et al.*, 2005). However, mixed results from motor cortex stimulation have been reported in monkeys so that motor cortex stimulation resulted in excitation or excitation followed by inhibition of STT cells (Yeziarski *et al.*, 1983).

A recent PET study shed light on the possible underlying mechanism of motor cortex stimulation in relieving central pain. It demonstrated that motor cortex stimulation in chronic neuropathic pain patients induced activation, partly during the stimulation period but mainly in the poststimulation period in many areas: in the posterior MCC, pregenual ACC, orbitofrontal cortex, putamen, thalamus and brainstem (PAG and pons) (Peyron *et al.*, 2007). Regional CBF changes during this poststimulation period correlated with pain relief. A functional connectivity analysis showed that these areas are all connected and provide a network that is influenced by motor cortex activation. Lack of efficacy of motor cortex stimulation in a subset of patients may be due to damaged corticospinal tracts or intra-cortical connections.

The combination of DTI and fMRI allows for assessment of anatomo-functional correlations (Seghier *et al.*, 2005). Combined diffusion tensor imaging (DTI) and fMRI were performed in a CPSP patient with a lesion confined to the right thalamic ventroposterolateral (VPL) nucleus and the adjacent posterior arm of the internal capsule. Fiber tract imaging with DTI showed selectively reduced right lateral sensory thalamocortical fibers, while functional imaging with fMRI showed pain-specific increased signal changes in anterior cingulate, ipsilateral left putamen and ipsilateral left associative parietal regions (Brodmann's areas 5/7) to cold stimulation of the left hand. Diffusion tensor imaging studies on fiber tracts and perfusion studies on relative blood flow to regions are necessary to investigate this hypothesis and may potentially be a method to screen patients who may be more responsive to motor cortex stimulation.

Current flow in the brain can also be produced by a transient magnetic field resulting from a current pulse conducted through a coil over the scalp (transcranial magnetic stimulation or TMS). This is a relatively new technology that offers the possibility of transiently stimulating or perturbing neuronal activity in the brain non-invasively. Since the outcome of motor cortex stimulation varies between patients and this procedure is invasive, TMS of the motor cortex may be of potential value to screen patients that may be responders for the electrical motor cortex stimulation. A recent study showed that repeated sessions of repetitive transcranial magnetic stimulation (rTMS at 20 Hz for 10 minutes each day for 5 successive days) over the motor cortex reduced pain by about 40% compared with baseline and sham rTMS in patients with post-stroke central pain for at least 2 weeks after the end of the treatment (Khedr *et al.*, 2005).

Involvement of the STT in the mechanism of central pain

Many studies suggest that impairments of temperature and pain sensation are associated with the development of central pain (Boivie, 1994). Stimulation of the STT produces thermal and pain sensations (Tasker *et al.*, 1982) and lesioning of the STT by cordotomy causes thermal and pain sensory loss (Nathan and Smith, 1996). In addition, neurons in a major thalamic terminus of the STT (nucleus Vc) and the region posterior and inferior to this nucleus (Mehler, 1966; Blomqvist *et al.*, 2000) respond to thermal or painful stimuli (Lenz *et al.*, 1993a; Davis *et al.*, 1999). Stimulation of this region evokes warm or cold sensations (Lenz *et al.*, 1993b; Davis *et al.*, 1999) and lesions impair pain/thermal sensations and sometimes lead to central pain (Kim *et al.*, 2007). Therefore, temperature and pain sensations are signaled by the STT and surgical lesions leading to central pain often involve STT and its thalamo-cortical connections (Cassinari and Pagni, 1969). Therefore, it is reasonable to suppose that lesions of pain- and temperature-signaling pathways are common to all central pain syndromes, and such lesions may exert their effects at the supraspinal termini of the spinothalamic tract.

Figure 7.5 shows an example of recordings and responses to stimulation in the thalamus of a patient with a T8 spinal cord transaction (Lenz *et al.*, 1994b). In the

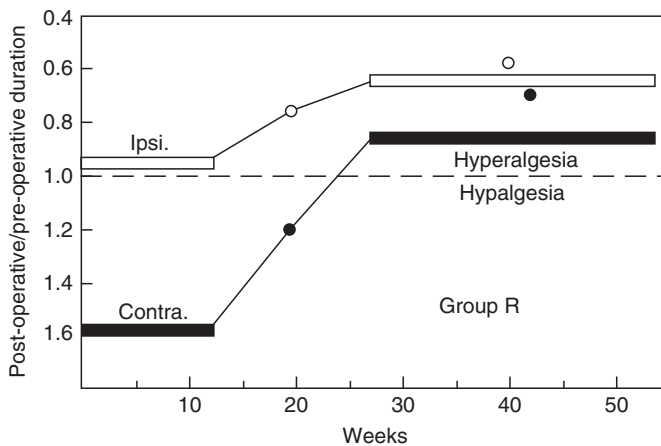


Fig. 7.4. Mean ratios of the post-operative/pre-operative trial durations for group R are shown for the early and late post-operative periods. Group R is the group of animals whose responsivity to contralateral stimulation returned to normal. The average lengths of the early and late periods are depicted by the horizontal extent of the bars. The connected points give the mean ratios for all sessions intervening between the early and late period. The unconnected dot depicts the average timing and value of the biweekly period with the smallest ratio, i.e. the point of maximum recovery. From Vierck *et al.* (1990), figure 4.

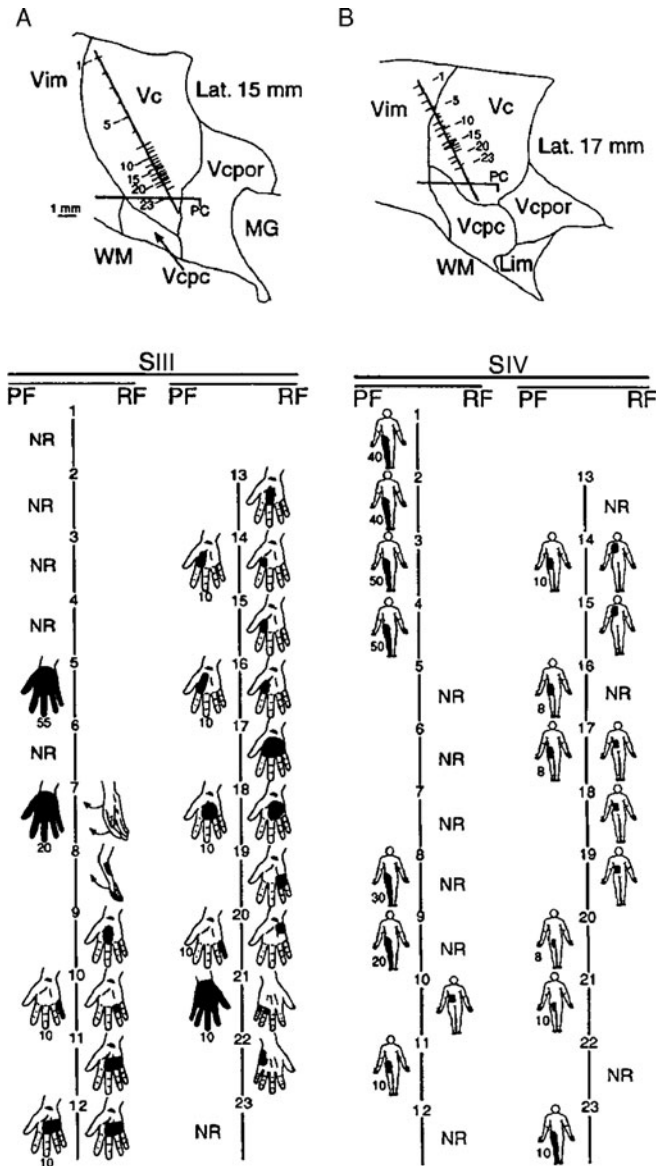


Fig. 7.5. Map of receptive fields (RFs) and projected fields (PFs) for trajectories in the region of the principal sensory nucleus of the thalamus (Vc) in a patient with spinal cord transaction at T8. (A) Trajectory in the 15 mm lateral plane through the region of Vc that represents the arm. (B) Trajectory 2 mm lateral to the first (lateral 17 mm). Top panels in (A) and (B) show the position of the trajectory relative to nuclear boundaries as estimated radiologically. The anterior commissure-posterior commissure line is the horizontal line (AC-PC line), and the trajectories are the oblique lines. Ticks at the right of the trajectories are the locations of cells. Long ticks: cells with RFs. Short ticks: cells without RFs. Microstimulation sites are shown to the left of the trajectory. Long ticks:

15 mm lateral plane (Fig. 7.5) the receptive fields (RFs) and projected fields were all referred to the hand, a part of the representational homunculus which is above the level of the transaction. The next trajectory (Fig. 7.5) was in the 17 mm lateral plane, where the representation of the leg is usually found, relative to the hand representation (Lenz *et al.*, 1988). Along this trajectory many cells did not have RFs, and those that did had RFs on the chest wall. This is a larger representation of the chest wall than normal where it usually forms a sliver above the large representation of the extremities. The neurons with chest wall RFs were located at sites where microstimulation evoked sensations located in the lower extremities, which were anesthetic. Therefore activity at the border-zone of the sensory loss may be referred to a lower extremity, consistent with clinical and QST studies of SCI central pain (Finnerup *et al.*, 2003b).

These lesions also lead to sensitization of the STT-thalamo-cortical pathway in patients with CPSP, as shown in Fig. 7.6. In such patients, electrical stimulation at microampere current levels (microstimulation) in Vc and in the region inferior and posterior to Vc evokes pain sensations more commonly and non-painful cold less commonly than in patients without central pain (Lenz and Byl, 1999; Radhakrishnan *et al.*, 1999). Stimulation of this region evoked pain more commonly in patients with hyperalgesia in the setting of central pain than in those without hyperalgesia (Lenz *et al.*, 1993b; Davis *et al.*, 1999; Blomqvist *et al.*, 2000). Therefore sensitization of this pathway may lead to the ongoing pain and hyperalgesia of central pain syndromes.

There is also evidence of sensitization of medial and intralaminar nuclei which receive nociceptive input, including the medial dorsal nucleus. The most detailed description of the pain evoked by stimulating these nuclei reported two types of sensation (Sano, 1977, 1979). The first type was a diffuse, burning pain, which was similar to the patient's ongoing pain and was referred to the contralateral half of the body. The other type of sensation was a generalized "unpleasant" sensation, not localized to a particular body part. Rinaldi and co-workers have also produced sensations by microstimulation in the medial

Caption for Fig. 7.5. (cont.)

somatosensory response to stimulation. Short ticks: no response to stimulation. Region of Vc includes sites 7–23 in (A), and 9–23 in (B). Scales as indicated. The positions of nuclei are inferred from the position of the AC–PC line, which is only an estimate of nuclear location. Bottom panels in (A) and (B): paired figurines for sites as numbered in the middle panel. Figurine at right: RF; NR, neuron without RF. Figurine at left: PF for threshold microstimulation (TMS) at that site. Number below the figurine: threshold in microamperes. From Lenz *et al.* (1994b), figure 1.

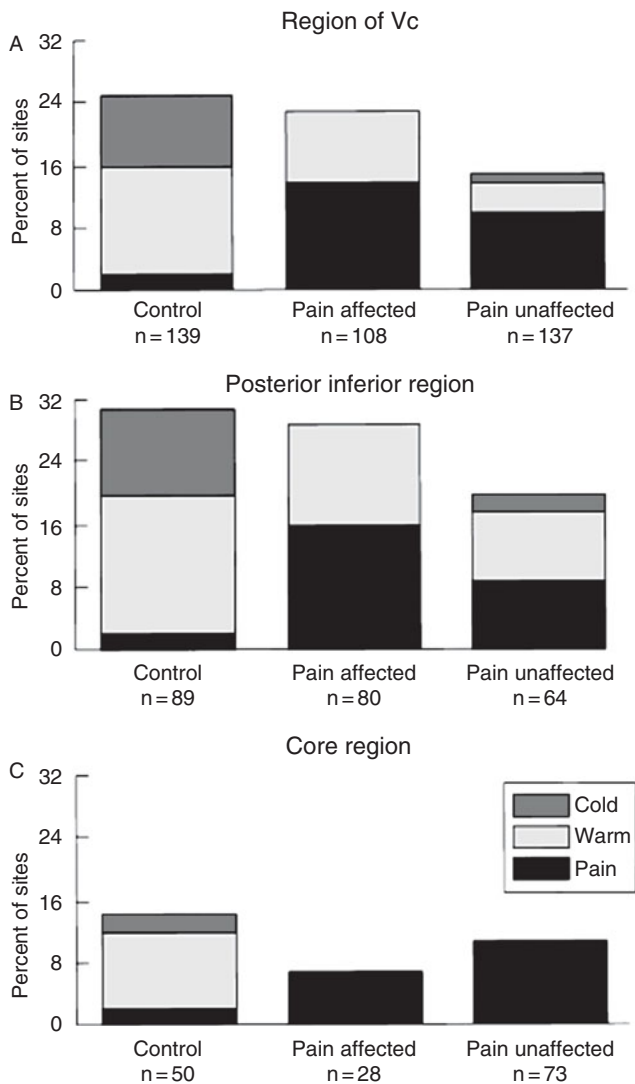


Fig. 7.6. Percentages of pain, cold and warm sensations evoked by stimulation in the core of Vc (C) and in posterior-inferior areas separately (B) and combined (A). Percentages are shown for movement disorder patients and for areas of the thalamus representing the part of the body where the patient does (pain affected) or does not (pain unaffected) experience pain. From Lenz *et al.* (1998a), figure 5.

thalamus, but these were not considered painful (Rinaldi *et al.*, 1991). Instead a sensation of “pulling” was produced by stimulation in the parafascicular nucleus while throbbing was produced by stimulation in the central medial nucleus (Hecaen *et al.*, 1949; Urabe and Tsubokawa, 1965; Tasker *et al.*, 1982).

In subjects with peripheral and neuropathic central pain, burning and pain were evoked more commonly by stimulation in the medial and intralaminar thalamus than at other sites in the thalamus (Tasker *et al.*, 1982). Stimulation at currents in the milliamperage range (macrostimulation) evoked burning that was nearly always on the contralateral side of the body. Burning was evoked much less commonly in patients with movement disorders than in patients operated upon for chronic pain, of whom more than half had CPSP (Tasker *et al.*, 1982). In the patients with chronic pain, the pain sites were usually clustered, and burning was induced contralaterally without somatotopic organization. Stimulation-evoked burning and non-burning pain were each more common in patients with neuropathic pain than in patients with “cancer pain.” These findings clearly raise the possibility that medial and intralaminar nuclei participate in the mechanism of central pain.

Animal models

One primate model of SCI lesions leading to central pain is the hypersensitivity of Old World monkeys with lesions of the anterolateral quadrant of the spinal cord (Vierck, Jr. and Luck, 1979; Vierck *et al.*, 1990). In an operant-conditioning paradigm, monkeys pulled a bar to terminate cutaneous electrical stimuli of different intensities delivered to the leg contralateral or ipsilateral to a thoracic anterolateral cordotomy. The maximum duration of stimulation (trial duration) was 5 seconds. Anterolateral tractotomy increased the trial duration for contralateral noxious stimulation in all monkeys, but the duration of this effect was variable among animals. In the earlier study (Vierck, Jr. and Luck, 1979), animals with lesions that included the ventral pathways, especially bilaterally, had the most lasting hyperalgesia. In the later investigation (Vierck *et al.*, 1990), the most lasting hyperalgesia (up to 20 months’ observation) included monkeys with more superficial unilateral lesions; recovery was seen among animals with more extensive, usually bilateral lesions that encroached on spinal gray matter. The finding of most relevance to central pain, however, was the presence of a delayed *bilateral* hyperalgesia among the monkeys that recovered.

Figure 7.6 shows the ratio of post-operative/pre-operative trial durations; a ratio of less than one indicates hyperalgesia and greater than one indicates hypoalgesia. The animals that recovered included those with lesions extending bilaterally into the ventral white matter and medially into the gray matter of the spinal cord; this observation suggests that the lesions affected central mechanisms that normally attenuate the behavioral responses to noxious stimuli. The reflexive response to electrocutaneous stimuli was initially reduced contralaterally, but to some extent ipsilaterally, although the relevance of this

response to SCI central pain is unclear. The recovery tended to be bilateral, with a greater reflexive response ipsilaterally. This pattern distinguished itself from the purposive/escape behavior, in which the changes tended to be contralateral (Vierck *et al.*, 1990; Boivie, 1999).

Anatomic studies of the thalamus have been carried out in monkeys with thoracic spinal cord lesions combining lesions of both the ipsilateral anterolateral quadrant of the spinal cord, and the contralateral dorsal column. Compared with controls these lesioned animals show decreased GABA immunoreactive elements in the thalamic ventrobasal complex (see Chapter 2 and Ralston *et al.*, 2000). Electron microscopic analysis demonstrates the presence of two types of GABAergic elements, including F elements which are mostly axonal terminals of the neurons in the thalamic reticular nucleus. The second type of terminal is a presynaptic dendrite of local interneurons (PSD). Results in three monkeys demonstrated significant decreases in both types of GABA immunoreactive elements in the ventrobasal complex.

Thalamic recordings in the hindlimb representation of the ventrobasal complex were carried out in these animals and demonstrated absent responses to thermal and mechanical somatic sensory stimuli, graded into the painful range. In the forelimb representation evoked responses were increased for thalamic multireceptive cells (MR) which respond to both cutaneous brushing and compressive stimuli with activity that is not graded into the noxious range. In the forelimb representation low threshold spike bursts (LTS – see Fig. 7.8 later in this chapter) were increased during spontaneous activity. In the hindlimb representation there were no responses to somatic stimulation. Burst rates were increased, and firing rates between bursts were decreased, consistent with studies in humans (Lenz *et al.*, 1994b).

Thalamic recordings were also carried out in monkeys with thoracic anterolateral cordotomies (Weng *et al.*, 2000). As reviewed above, some of these animals showed increased responsiveness to electrocutaneous stimuli and thus may represent a model of SCI central pain (Vierck, 1991). In comparison with normal controls, MR cells in the monkeys with anterolateral cordotomies showed significant increases in the number of bursts occurring spontaneously or in response to brushing or compressive stimuli. The changes in bursting behavior were widespread, occurring in the thalamic representation of upper and lower extremities, both ipsilateral and contralateral to the cordotomy.

The location of this bursting activity in the forelimb representation ipsilateral to the spinal injury suggests that bursting is not sufficient for the SCI central pain, which is contralateral to the anterolateral cordotomy (Tasker *et al.*, 1991). However, such bursting could cause pain if the bursting cell was in an area where there was hypersensitivity to thalamic microstimulation. In these areas

the sensation of pain was evoked more frequently by a grouped/bursting pattern of pulses in patients with central pain than in patients without central pain (Davis *et al.*, 1996; Lenz *et al.*, 1998a, 2004).

Old World monkeys with anterolateral cordotomies are said to develop autotomous behavior, such as self-inflicted destruction of denervated parts of the body in some studies (Levitt, 1989), but not others (Vierck, Jr. and Luck, 1979; Vierck *et al.*, 1990). This behavior is often interpreted to indicate the presence of dysesthesias, and perhaps central pain (Levitt and Levitt, 1981; Levitt, 1983). The presence of autotomy in patients with congenital analgesia, and without the sensation of pain, has been taken to indicate that autotomy is not necessarily an indicator of chronic pain (Sweet, 1981).

Autotomy reactions, sometimes described as excessive grooming behavior, have been studied following lesions of rodent spinal cord pathways (Albe-Fessard and Rampin, 1991; Ovelmen-Levitt, 1991; Ovelmen-Levitt *et al.*, 1991). Autotomy never followed posterior column sections either alone or in combination with simultaneous section of ipsilateral, lateral or anterolateral quadrants. The conclusion of these studies is that autotomy occurs in cases where section of the anterolateral quadrant or one half of the spinal cord allows for sensory transmission through ipsilateral nociceptive pathways.

A number of rodent models of SCI have been used to study the mechanism of SCI central pain, including excitotoxic lesions and spinal cord contusions. Behavioral evidence of hyperalgesia and abnormal hypersensitivity of dorsal horn neurons to thermal and mechanical stimuli has been reported in rats after cavitary lesions of the spinal cord central gray. These cavitary lesions were created by injection into the gray matter of the spinal cord of quisqualic acid, an excitotoxin acting at non-NMDA glutamate receptors (Yeziarski and Park, 1993; Yeziarski *et al.*, 1993). This excitotoxic SCI injury leads to a cascade of chemical and inflammatory events resulting in increased extracellular excitatory amino acid (EAA) concentrations, which may be important mediators of the delayed injury which occurs in this model.

Studies by Hulsebosch and colleagues have highlighted the role of the metabotropic EAA receptor (mGluR) class in the release of EAA (Mills *et al.*, 2002). Among the mGluR receptors group I, comprising mGluR1 and mGluR5, seem to activate several intracellular pathways that lead to increased extracellular EAA concentrations. The results demonstrate that this pathway can initiate a number of intracellular cascades and perhaps glial activation, which lead to increased extracellular EAA concentrations, possible mediators of the delayed injury and central neuropathic pain behaviors observed in this excitotoxic model.

A role for sodium channels in SCI central pain is suggested by studies carried out in rats with spinal cord contusion injuries (Hains *et al.*, 2006; Waxman

and Hains, 2006). In these animals the expression of non-tetrodotoxin (TTX) dependent sodium channels in dorsal horn and thalamic neurons may correlate with the presence of thalamic bursting behavior similar to that found in humans with SCI central pain. These animals also displayed spontaneous behaviors and responses to sensory stimulation congruent with those observed in central pain. Administration of anti-sense mRNA in these animals reversed thalamic bursting and the behaviors which are related to pain (Hains *et al.*, 2006). These studies suggest that the presence of non-TTX dependent sodium channels of this type may be the factor which leads to central pain, in response to, or in addition to STT-mediated sensory attenuation, or both. It is unclear how these studies in rodents relate to the clinical features and treatment of human SCI central pain after complete or partial SCI.

Cold allodynia and the disinhibition hypothesis of central pain

The sensory abnormalities in patients with central pain speak to the hypothesis that central pain/dysesthesia syndromes are associated with lesions of a cool-signaling STT pathway which disinhibits a nociceptive STT pathway (Craig *et al.*, 1996; Dostrovsky and Craig, 1996). This hypothesis proposes that there is a cool-signaling STT pathway passing from spinal lamina I through a lateral thalamic nucleus (ventral medial posterior, VMpo) to the insula. The hypothesis further proposes that this pathway normally inhibits a heat-pinch-cold nociceptive (HPC) STT pathway passing from spinal lamina I through a medial thalamic nucleus (medial dorsal) to the anterior cingulate cortex (ACC) (Craig and Bushnell, 1994; Craig *et al.*, 1996). In patients with central pain, it is proposed that a lesion of the lateral cool pathway disinhibits the medial pain pathway and ACC, so that cold allodynia and the burning ongoing pain of CPSP result from impairment of cold sensibility (Craig and Bushnell, 1994).

A number of lines of evidence help to evaluate this hypothesis. A study of small thalamic lesions leading to CPSP uniformly involved the human principal sensory nucleus (ventral caudal nucleus – Vc) but did not involve the VMpo (Montes *et al.*, 2005; Kim *et al.*, 2007). Approximately 50% of patients with CPSP do not have pain described by temperature and less than 30% have cold allodynia (Greenspan *et al.*, 2004) (Table 7.2). The results suggest that cool hypoesthesia is associated with burning, cold, ongoing pain of CPSP. However, cold allodynia was not associated with impaired cold sensibility but was associated with preserved cold sensibility (Greenspan *et al.*, 2004), although cool hypoesthesia was frequently present. One subject first detected the cold thermode stimulus as cold pain at a temperature of 30.2 °C, and had the most extreme cold allodynia, to the point that she could not tolerate placing her hand in a 30 °C waterbath.

In the cases of CPSP with cold allodynia the disinhibition hypothesis suggests that ACC should be activated in response to cold stimuli. There are a number of imaging studies which do not support this suggestion. In a subject with cold allodynia a single subject protocol PET study (Fig. 7.7) measured the responses to immersion of either hand in a 20 °C waterbath. The scan during stimulation of the affected hand was characterized by intense activation of contralateral sensorimotor cortex. The largest PET study of CPSP-induced allodynia involved patients with a lateral medullary stroke (Wallenberg syndrome) (Peyron *et al.*, 1998). The allodynic test stimulus was a cold/mechanical stimulus described as “a cold non-noxious stimulus (ice in a flat plastic container) . . . moved slowly” over the skin. When this stimulus was used on the affected side, it produced activation of structures very similar to those activated in response to the 20 °C waterbath stimulation described above (Peyron *et al.*, 1998; see also Cesaro *et al.*, 1991; Hirato *et al.*, 1994). The evidence of imaging studies demonstrates that cold allodynia is associated with activation of sensorimotor cortex and not ACC.

Patients with SCI central pain uniformly had loss of pain or temperature sensation or both (Beric *et al.*, 1988; Eide, 1998; Finnerup *et al.*, 2003b). However, the degree of sensory loss for thermal or pain sensations is not a predictor of central pain in the population of patients with SCI (Eide, 1998; Finnerup *et al.*, 2003b). Therefore, loss of STT function is a necessary but not sufficient condition for the development of central pain in patients with SCI. Abnormal hypersensitivity to tactile and thermal stimuli is more common in SCI patients with central pain than in those without. The intensity of tactile allodynia at the border of sensory loss is a significant predictor of the intensity of spontaneous pain in the levels below the lesion. Spinal cord injury central pain patients show normalization of some changes in sensibility following successful dorsal root entry zone (DREZ) lesions, which suggests that intact afferent innervation sustains a pain-generating activity above the level of injury or in supraspinal structures (Defrin *et al.*, 1999). In addition both the threshold and the quality of thermal pain were strongly dependent upon the integrity of innocuous thermal sensations (Defrin *et al.*, 2002), as in the study of CPSP described above (Greenspan *et al.*, 2004).

These results suggest that SCI central pain is associated with hyperactivity in neurons higher along the somatic sensory pathways including structures receiving input from the dorsal columns. This is consistent with a range of anatomical and physiological studies of CPSP as reviewed below.

Thalamic low-threshold spike (LTS) bursting activity in central pain

The occurrence of thalamic LTS bursting in patients with central pain occurs at rates above those found in patients with movement disorders

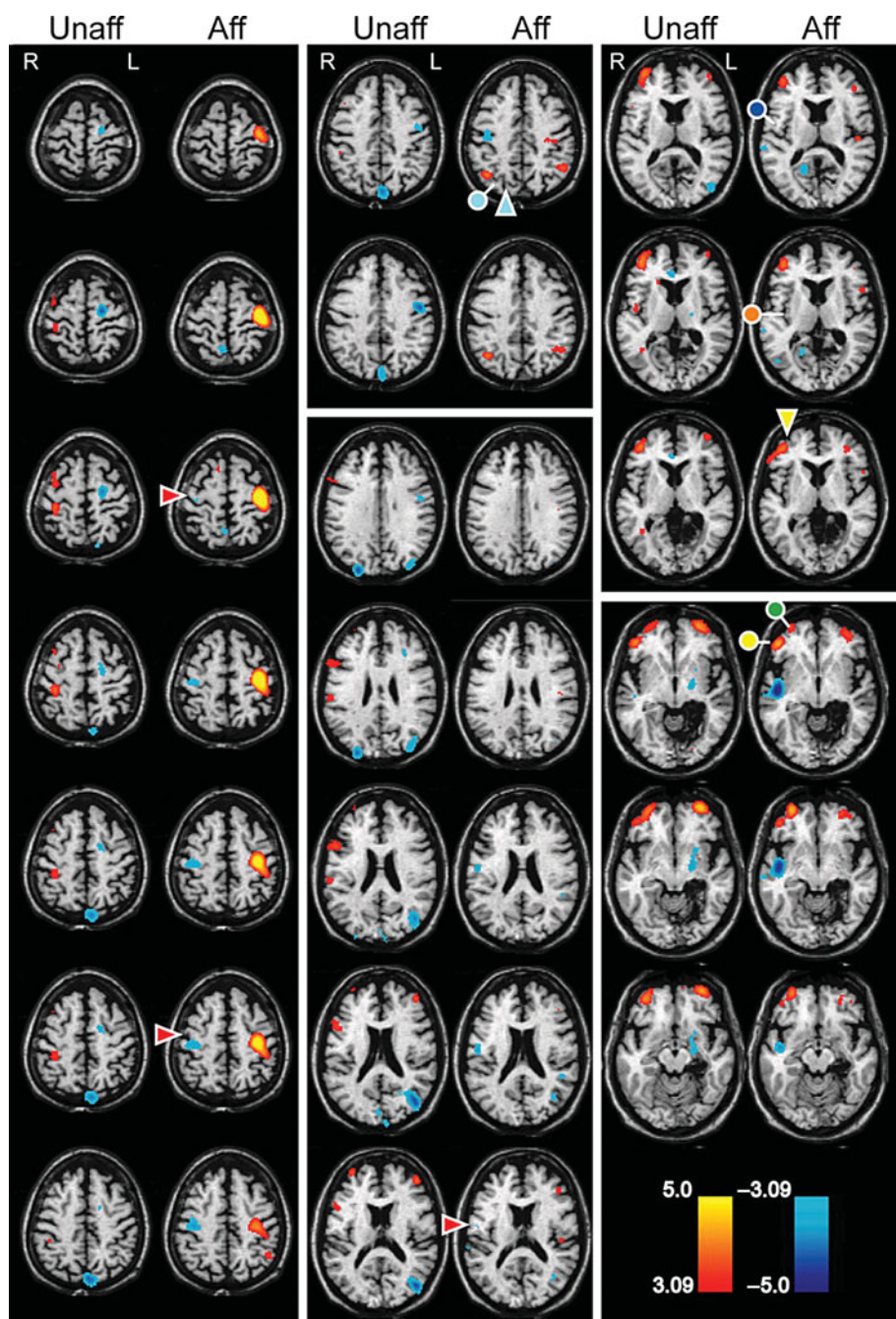


Fig. 7.7. Blood flow consequences of 20 °C waterbath stimulation of the left (clinically affected, Aff) and right unaffected, Unaff) hands in a patient with CPSP after a right thalamic infarction. PET blood flow data are displayed in color on the structural magnetic resonance images as appropriate (see labels). The color bars indicate t scores,

(Lenz *et al.*, 1994b). These bursts are triggered by low-threshold calcium spikes deinactivated by an inhibition of approximately 100 ms (Jahnsen and Llinas, 1984a, 1984b). These bursts are preceded by prolonged inhibition followed by short, ≤ 5 ms, ISI followed by progressively longer ISI (see Fig. 7.8). In patients with a spinal transection, the highest rate of bursting occurs in cells that do not have peripheral receptive fields and that are located in the representation of the anesthetic part of the body. These cells also have the lowest firing rates in the interval between bursts (principal event rate) (Lenz *et al.*, 1994b).

The LTS bursts and low firing rates between bursts of these cells suggest that they have decreased tonic excitatory drive and are hyperpolarized, perhaps due to loss of excitatory input from the STT (Eaton and Salt, 1990; Ericson *et al.*, 1993; Blomqvist *et al.*, 1996; Dougherty *et al.*, 1996). Therefore the available evidence suggests that affected thalamic cells in patients with spinal transection were dominated by spike bursts consistent with membrane hyperpolarization (Steriade and Deschenes, 1984; Steriade and Llinas, 1988; Steriade *et al.*, 1990; Davis *et al.*, 1998a; Lenz *et al.*, 1998a).

Spike bursting activity is maximal in the region posterior and inferior to the core nucleus of Vc (table 4 in Lenz *et al.*, 1994b). Stimulation in this area evokes the sensation of pain more frequently than does stimulation in the core of Vc (Hassler and Reichert, 1959; Hassler, 1970; Halliday and Logue, 1972; Dostrovsky *et al.*, 1991; Lenz *et al.*, 1993b). Thus, increased spike burst activity may be correlated with some aspects of the abnormal sensations (e.g. dysesthesia or pain) that these patients experience. However, in patients with spinal transection, the painful area and the area of sensory loss overlap (Lenz *et al.*, 1994b). Thus, the bursting activity might be related to sensory loss, rather than to pain.

These findings about spike burst activity in spinal cord injury patients have been called into question by a recent study in patients with chronic pain (Radhakrishnan *et al.*, 1999). It has been reported that the number of bursting cells per trajectory in patients with movement disorders (controls) is not different from that in patients with chronic pain. However, there are significant differences between the earlier study (Lenz *et al.*, 1994b) versus the later (Radhakrishnan *et al.*, 1999) in terms of patient population (spinal cord injury vs. mixed chronic pain), location of cells studied (Vc vs. anterior and posterior to Vc) and analysis methods (incidence of bursting cells vs. bursting parameters).

Caption for Fig. 7.7. (cont.)

red–yellow for increases and blue for decreases in blood flow with respect to the resting conditions. Colored symbols indicate named sulci (arrowhead) and gyri (circles) as identified in the text. The patient's left (L) is shown on the reader's right (R), as indicated by the L in the figure. From Kim *et al.* (2007), figure 1.

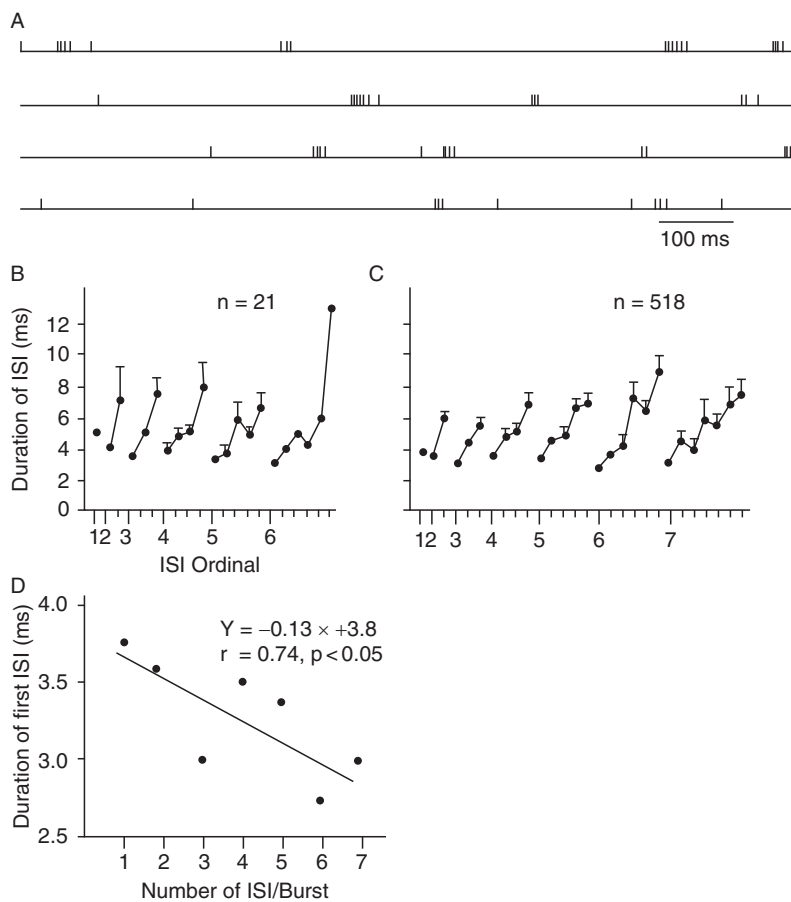


Fig. 7.8. Interspike interval (ISI) characteristics of bursts recorded in patients with SCI central pain. (A) shows the digitized spike train of a cell recorded in one of these patients. Time scale as indicated. (B) plots the average ISI duration (mean and SEM) as a function of the position of the ISI within a burst for bursts recorded in that cell. For example, the three points joined by lines above and to the right of the number 3 show results for bursts composed of four action potentials or three ISI. The three points represent, from left to right, the duration of the first, second and third ISIs in bursts of three ISIs. (C) demonstrates the same data for 22 cells recorded in two patients with spinal cord transection. (D) plots the mean duration of the first ISI in a burst as a function of the number of ISIs in a burst, for the data displayed in (C). From Lenz *et al.* (1989), figure 1.

Nor is it clear how a bursting cell was defined in the later study although no post-operative analysis was applied in all cells. Therefore, the increase in bursting activity demonstrated in the earlier study is more applicable to the region of the principal somatic sensory nucleus of patients with central pain from spinal transection (Lenz *et al.*, 1994b).

Further support for increased spike bursts occurring in spinal cord transected patients is found in thalamic recordings from monkeys with thoracic anterolateral cordotomies (Weng *et al.*, 2000), some of which showed increased responsiveness to electrocutaneous stimuli and thus may represent a model of central pain (see above section on models) (Vierck, 1991). The most pronounced changes in firing pattern were found in thalamic multireceptive cells which respond to both cutaneous brushing and compressive stimuli with activity that is not graded into the noxious range. In comparison with normal controls, multireceptive cells in the monkeys with cordotomies showed significant increases in the number of bursts occurring spontaneously or in response to brushing or compressive stimuli. The changes in bursting behavior were widespread, occurring in the thalamic representation of upper and lower extremities, both ipsilateral and contralateral to the cordotomy.

Although there is an increase in spike burst activity in chronic pain states, there does not appear to be a direct relationship between spike burst firing and pain. Spike bursts are also found in the thalamic representation of the monkey upper extremity and of the representation of the arm and leg ipsilateral to the cordotomy. Pain is not typically experienced in these parts of the body in patients with thoracic spinal cord transection or cordotomy (Beric *et al.*, 1988). Spike bursts are increased in frequency during slow wave sleep in all mammals studied (Steriade *et al.*, 1990) including man (Zirh *et al.*, 1997). However, such bursting could cause pain if stimulation in the vicinity of the bursting cell produced the sensation of pain. This finding has been reported in two studies of sensations evoked by microstimulation of the region of Vc in patients with chronic pain secondary to neural injury (Davis *et al.*, 1996; Lenz *et al.*, 1998a).

Evidence for ipsilateral mechanisms of stroke pain

Pain was identical in our patients with absent RFs from proximal tract interruption to that seen in the presence of intact PFs and RFs; the former retained intact PFs, showing that trans-synaptic degeneration does not occur in the thalamus, and that thalamic neurons and thalamo-cortical connections can be left intact and apparently isolated after a stroke yet still capable of generating conscious effects and presumably capable of activation by alternate somatosensory input, possibly to generate pain.

A patient was studied who had a massive right-sided thrombotic stroke causing left homonymous hemianopsia, spastic hemiplegia, and multimodality hemisensory loss with allodynia and hyperpathia. Stereotactic exploration with microelectrodes to treat him with DBS was carried out (Tasker, 2002). An extensive exploration of the region of Vc thalamus revealed no neuronal activity.

In addition, a hemispherectomized patient has been reported who complained of touch-evoked pricking and burning pain in her paretic hand, especially when the hand was cold (Olausson *et al.*, 2001). Quantitative sensory testing demonstrated that on the paretic side she confused cool and warm temperatures, and confirmed that she had a robust allodynia to brush stroking that was enhanced at a cold ambient temperature. Functional magnetic resonance imaging showed that during brush-evoked allodynia, brain structures implicated in normal pain processing (viz. posterior part of the anterior cingulate cortex, secondary somatosensory cortex and prefrontal cortices) were activated. The fMRI findings thus indicate that the central pain in this patient was subserved by pain structures implicated in normal pain processing.

Hyperalgesia in response to thermal stimuli has been associated with activation of the ipsilateral opercular and insular cortex after cingulotomy, but not on the contralateral side pre-operatively. This pattern would be unusual in a population study protocol of healthy controls (Apkarian *et al.*, 2005), although ipsilateral activations occurred commonly in an fMRI study of healthy single subjects (Davis *et al.*, 1998b). Ipsilateral parasyllian activation has also been observed during the increased (allodynic) responses to thermal stimuli, in patients with central pain related to lesions of the brain or spinal cord (Peyron *et al.*, 2000, 2004; Ducreux *et al.*, 2006). Experimental tactile allodynia following cutaneous injection of capsaicin led to activation of the superior frontal gyrus (Brodmann area 10) bilaterally, insula bilaterally, portions of the inferior frontal gyrus (Brodmann area 47) contralaterally, putamen/globus pallidus ipsilaterally, SII/inferior parietal lobule (Brodmann area 40) bilaterally, middle frontal gyrus (Brodmann areas 6, 8 and 10), and cingulate gyrus (Brodmann area 24) midline/ipsilaterally; and contralateral SI (slices 136 to 152) (Iadarola *et al.*, 1998). These results and the present post-operative results suggest that ipsilateral activations are a common factor in increased ratings of pain following brain lesions, whether clinically significant (allodynic) or not.

The mechanism of the increased activation of ipsilateral parasyllian structures post-operatively may be disinhibition of pain-related inputs to these structures by the cingulotomy (Van Hoesen *et al.*, 1993; Lenz *et al.*, 1998b; Vogt, 2005). This disinhibition could lead to pain-related increased synaptic activity and blood flow. In addition, post-operative pain-related activation of the right (ipsilateral) parietal and insular cortex after cingulotomy (figure 1 in Greenspan *et al.*, 2008a) might be consistent with reports of activation of right inferior parietal cortex following stimulation of either side (Coghill *et al.*, 2001). In that study pain intensity-dependent activation was not lateralized but was localized to contralateral regions of the primary somatosensory cortex, secondary somatosensory cortex, insular cortex and bilateral regions of the cerebellum, putamen,

thalamus, anterior cingulate cortex and frontal operculum. In contrast, right-sided activations were found in the thalamus, inferior parietal cortex (Brodmann area 40), dorsolateral prefrontal cortex (Brodmann areas 9/46) and dorsal frontal cortex (Brodmann area 6) in response to painful (and non-painful) stimulation, regardless of the side of stimulation.

These observations implicate ipsilateral pathways in the generation of the steady pain, allodynia and hyperpathia that plague such patients. Whatever the ipsilateral paths responsible for the pain, they must be somatotopographically organized to preserve the somatotopographic features of the pain and capable of inducing steady pain and allodynia, incriminating the ipsilateral STT. Therefore, the central and peripheral pain syndromes are characterized by ongoing pain and hypersensitivity to mechanical and thermal stimuli. Activity in the spinal cord of models of peripheral neuropathic pain and the thalamus of patients with SCI central pain and primate models is characterized by increased ongoing activity and increased responses to somatic stimuli. These neuronal activities may correspond to the ongoing pain and hypersensitivity of the central and peripheral neuropathic pain syndromes and their models.

Mechanisms of pain and sensitization following peripheral injury

Damage to the skin in humans can lead to several abnormal sensory manifestations, including pain that is localized to the site of damage, as well as primary and secondary allodynia and hyperalgesia (Hardy *et al.*, 1967). It is assumed that comparable sensory changes also occur under similar conditions in animals. The immediate pain depends on the activation of peripheral nociceptive afferent fibers that supply the damaged area, the transmission of nerve impulses by the nociceptors to the spinal cord, and the activation of neurons that project in ascending nociceptive pathways, such as the spinothalamic tract (see Chapter 3). The nociceptive signals are then processed in the thalamus and cerebral cortex, as well as in other structures of the brain, such as the amygdala, leading to the sensation of pain and other pain reactions (Hardy *et al.*, 1967). The latter include motivational-affective, autonomic and hormonal changes. In addition, the damaged area may become tender, so that previously non-painful stimuli may now elicit pain, a phenomenon called “allodynia.” Furthermore, stimuli that are normally painful may become more painful, a condition called “hyperalgesia” (Merskey, 1986).

The allodynia and hyperalgesia due directly to tissue damage are limited to the area of damage; this region is termed the area of “primary allodynia and hyperalgesia.” The allodynia and hyperalgesia can often be elicited by mechanical or thermal stimuli. For instance, a normal sensation of warmth in response

to an innocuous warm stimulus (such as a warm shower) can become heat pain in an area of primary thermal allodynia. Primary allodynia and hyperalgesia are believed to result from the sensitization of primary afferent nociceptors directly affected by the initial noxious stimulus (Lamotte *et al.*, 1982, 1983). Peripheral sensitization of primary afferent nociceptors will be discussed in a later section.

Several methods have been used to produce localized damage that causes pain, followed by the development of secondary allodynia and hyperalgesia (Hardy *et al.*, 1967). The intradermal injection of capsaicin, the active ingredient found in chili peppers, is a strong noxious stimulus that produces these effects, with a limited duration (LaMotte *et al.*, 1991). The pain only lasts for about 15 minutes (depending on the dose of capsaicin). The allodynia and hyperalgesia spread from near the primary area into a secondary area that includes a progressively larger region concentrically surrounding the primary area (Fig. 7.9). After a high dose of capsaicin (100 µg), these changes can last as long as 2 hours. The primary afferent nociceptors that innervate the tissue in the secondary area are not sensitized by the capsaicin, since their terminals are remote from the injected chemical irritant (Baumann *et al.*, 1991; Lamotte *et al.*, 1992). For this reason, the increased central nervous system response that leads to pain sensation in secondary allodynia and the enhanced pain of secondary hyperalgesia is attributed to the sensitization of central nociceptive neurons through neural circuits that are activated by primary afferent nociceptors that synapse in the dorsal horn (Fig. 7.9).

Torebjörk *et al.* (1992) have provided strong evidence from experiments on human subjects that pain evoked by stimulation in an area of secondary allodynia results from plastic changes that occur within the central nervous system, a process generally called central sensitization (LaMotte *et al.*, 1992). Figure 7.10 gives an example of their findings. An intraneural microelectrode was used to stimulate large primary afferent nerve fibers in the superficial peroneal nerve. The drawing in Fig. 7.10A shows the location above the ankle at which the tip of the microelectrode was inserted into the nerve. Electrical pulses were applied (Stim.) at a position in the nerve that allowed the excitation of one or only a few tactile afferents. This resulted in the projection by the brain of a tactile sensation to the area indicated in black. Capsaicin was then injected 10 mm distal to the area of the projected tactile sensation (at the location of the open circle in Fig. 7.10B). Fourteen minutes after the injection, intraneural stimulation of the tactile afferents now produced a projected painful sensation, in addition to the tactile one. This pain spread so that it became distributed in an area that overlapped the area of the projected tactile sensation. This “secondary tactile allodynia” was transient. The area it occupied retracted and by 39 minutes after the capsaicin injection, it no longer overlapped with the area of projection of the tactile sensation (Fig. 7.10C). It is important to emphasize that the stimulus that evoked the touch

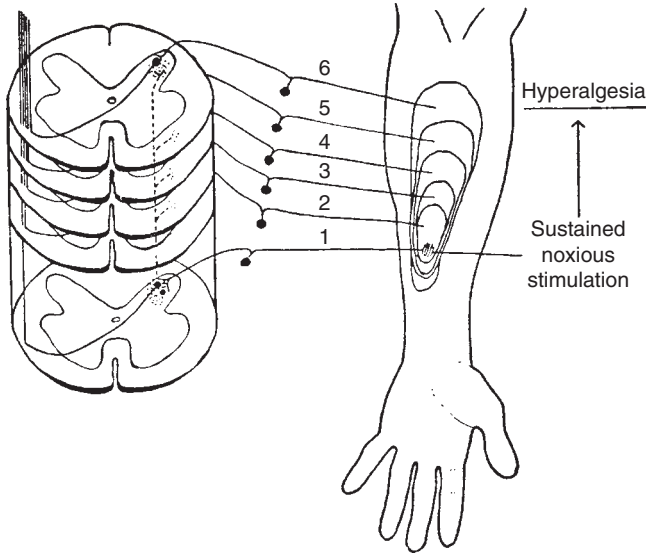


Fig. 7.9. Nociceptive afferent fibers that supply a small area of skin (labeled 1) are shown to enter the spinal cord through a dorsal root and to terminate in the dorsal horn of that segment. Activation of spinothalamic tract cells that respond directly to the noxious stimulus would trigger ascending activity, leading to a sensation of pain projected to the site of stimulation. In addition, activity in the neural circuit that interconnects dorsal horn neurons at different levels of the spinal cord results in a progressively developing central sensitization of these neurons. As the thresholds of the dorsal horn neurons are lowered, their responses to stimulation of the skin conveyed in afferents entering the spinal cord over dorsal roots 2–6 become enhanced, leading to secondary allodynia and hyperalgesia when the skin supplied by these afferents is stimulated. From Hardy *et al.* (1967).

sensation was applied within the nerve at a position considerably proximal to the capsaicin injection site and that the tactile sensation was evoked whenever the nerve was stimulated throughout the experiment. The allodynia could not have resulted from peripheral sensitization of nociceptive afferent fibers in the nerve, since the capsaicin would not have affected the electrical threshold of these fibers at the rather distant point of stimulation. Therefore, it can be concluded that the tactile allodynia resulted from plastic changes that had occurred in the central nervous system that had resulted in central sensitization.

Peripheral sensitization

As already mentioned, primary allodynia and hyperalgesia are attributed to peripheral sensitization of primary afferent nociceptors. In Fig. 7.11A,

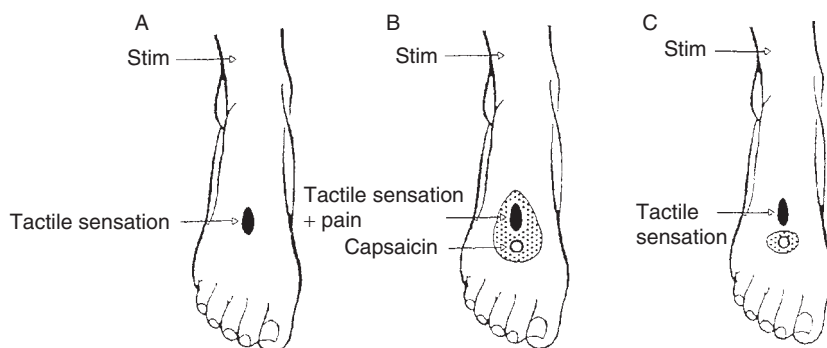


Fig. 7.10. Change in the projected sensation produced by intraneural microstimulation following a noxious chemical stimulus, i.e. intradermal injection of capsaicin. In (A) stimulation (stim) was applied at a site in the nerve that evoked a purely tactile sensation. In (B) capsaicin was injected at a point 10 mm distal to the area of projected touch sensation. By 14 minutes after the injection, stimulation in the nerve evoked a combination of touch and pain sensations projected to the secondary area, which overlapped the previous area of projected tactile sensation but extended beyond this. In (C) after 39 minutes the secondary area retracted and no longer overlapped the area of projected tactile sensation. Stimulation in the nerve no longer evoked pain. From Torebjörk *et al.* (1992).

a series of heat stimuli were applied to an area of skin in a human subject. The subject's pain rating of stimuli of different intensities before a mild burn of the stimulated area are shown in the lower panel of Fig. 7.11A, and the pain ratings after the mild burn was placed in the stimulated area are shown in the upper panel of Fig. 7.11A. The increase in the pain ratings for the heat stimuli applied after the burn demonstrated the development of heat hyperalgesia. Figure 7.11B provides an example of the sensitization of a monkey cutaneous C-fiber nociceptor that resulted from a similar mild burn (Lamotte *et al.*, 1983). The responses of the C-nociceptor to graded intensities of heat stimuli were recorded from the peripheral nerve of a monkey, before (lower panel) and after (upper panel) the burn (Fig. 7.11B). The burn was placed at the same location as the heat stimuli. The threshold for activation of the C fiber was reduced and the responses increased following the burn. The changes in C fiber responses in the monkey and the pain ratings in the human were well correlated, consistent with the suggestion that the sensitization of nociceptors by a burn underlies the development of primary heat hyperalgesia.

The sensitization of nociceptors can result from their exposure to irritant chemicals (such as capsaicin, formalin or mustard oil), low pH or inflammatory mediators. Important inflammatory mediators include bradykinin,

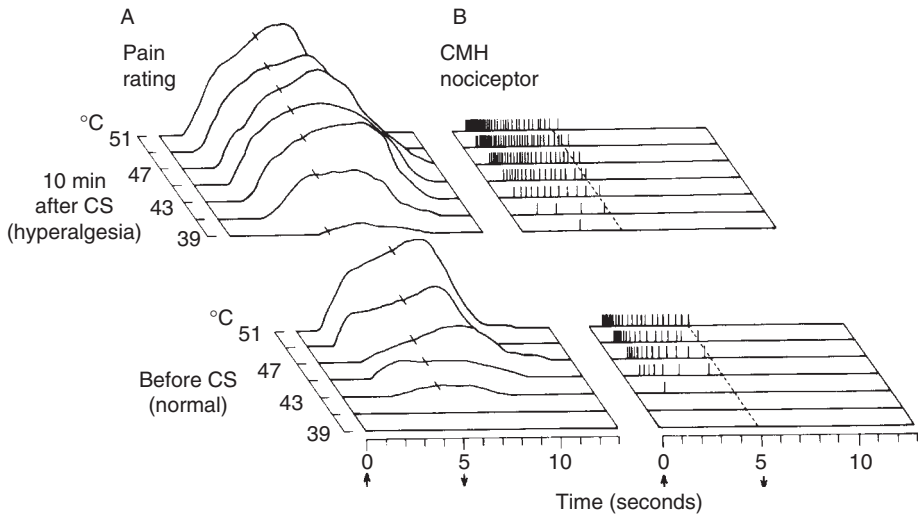


Fig. 7.11. A mild burn (conditioning stimulus, CS) was applied to the skin in a human subject and in a monkey to produce heat hyperalgesia and sensitization of a nociceptor under similar conditions. In (A), the human subject was asked to rate the magnitude of pain experience during each of a series of heat stimuli of different magnitudes. The pain ratings were made before and after the mild burn of the skin under a thermode. The ratings increased after the burn. In (B), single unit recordings were made from a (C) polymodal nociceptor (CMH) recorded from a nerve in the arm of a monkey. The same series of heat stimuli were applied to the monkey's arm before and after a comparable mild burn. From LaMotte *et al.* (1983).

prostaglandins and other products of arachidonic acid metabolism, serotonin, catecholamines, ATP, adenosine and histamine (see review by Willis and Coggeshall, 2004). Nerve growth factor can also contribute to the peripheral sensitization of nociceptors (Koltzenburg *et al.*, 1999). A key event in peripheral sensitization is an increase in the intracellular concentration of Ca^{++} , which activates second messenger cascades (Guenther *et al.*, 1999; Kress and Guenther, 1999). Protein kinases, such as PKC, PKA and PKG, can then phosphorylate ion channels (Dray *et al.*, 1988; Taiwo *et al.*, 1990; Willis and Coggeshall, 2004) or membrane receptors, such as TRPV1 (capsaicin) receptors (Lopshire and Nicol, 1998; Guenther *et al.*, 1999), and the altered channels lead to increased transmembrane currents and a greater excitability of the nociceptive afferents.

Of particular interest are what have been called “silent” (or “sleeping”) nociceptors, which are normally insensitive to mechanical stimuli. These were first observed in nerves that supply joints (Coggeshall *et al.*, 1983; Schaible and Schmidt, 1985, 1988), but similar nociceptors have since been described in cutaneous and visceral nerves (see Willis and Coggeshall, 2004). When exposed

to inflammatory mediators, such as bradykinin or prostaglandin, they become sensitized (“awaken”) and respond vigorously even to weak mechanical stimuli (Schaible and Schmidt, 1988). A similar event undoubtedly occurs in human arthritis. This kind of change is undoubtedly a common occurrence in disease states characterized by peripheral sensitization, which is responsible for the development of primary allodynia and hyperalgesia.

Responses of monkey STT cells during central sensitization

Cutaneous burn damage

When the skin is damaged by a mild burn, heat stimuli evoke larger responses in monkey STT cells and their threshold to heat stimuli is reduced (Kenshalo, Jr. *et al.*, 1979; Ferrington *et al.*, 1986). These changes reflect the development of primary heat hyperalgesia and are likely to reflect peripheral sensitization of primary afferent nociceptors (see the previous section). However, the responses of monkey STT neurons to innocuous mechanical stimuli are also increased following a mild burn. Since mechanoreceptors do not sensitize, this suggests that the mild burn may also produce secondary mechanical allodynia. This idea was confirmed by Kenshalo *et al.* (1982), who found that, after a mild burn, the responses of monkey STT cells to innocuous mechanical stimuli were increased not only when the mechanical stimuli were applied to the burned area but also when they were applied to undamaged skin. This result is illustrated in Fig. 7.12. The curves represent mean stimulus-response functions of monkey STT neurons to graded displacements of the skin by a mechanical stimulator before and after peripheral sensitization was produced by application of a series of noxious heat stimuli that lasted 30 s (Fig. 7.12A,B) or 120 s (Fig. 7.12C,D). The mechanical stimuli were applied either within the area of skin that received the heat stimuli (labeled “INSIDE”) or 10 mm away (“OUTSIDE”). The control responses in Fig. 7.12E were recorded before and after a sham thermal stimulus (for the sham thermal stimulus, the thermal stimulator was placed in contact with the skin, but no thermal stimuli were given). No change was observed. Note that the 30 s noxious heat stimuli failed to alter the responses to mechanical stimuli applied in the stimulated area (Fig. 7.12A), although the responses to the same mechanical stimuli were increased when they were applied outside the area exposed to noxious heat. By contrast, the responses to the mechanical stimuli were increased following 120 s noxious heat stimuli, whether the mechanical stimuli were applied inside or outside the heated area. Presumably, the 30 s heat stimuli did not result in peripheral sensitization of nociceptors supplying the heated area, whereas the 120 s heat stimuli did. However, both durations of heat stimuli

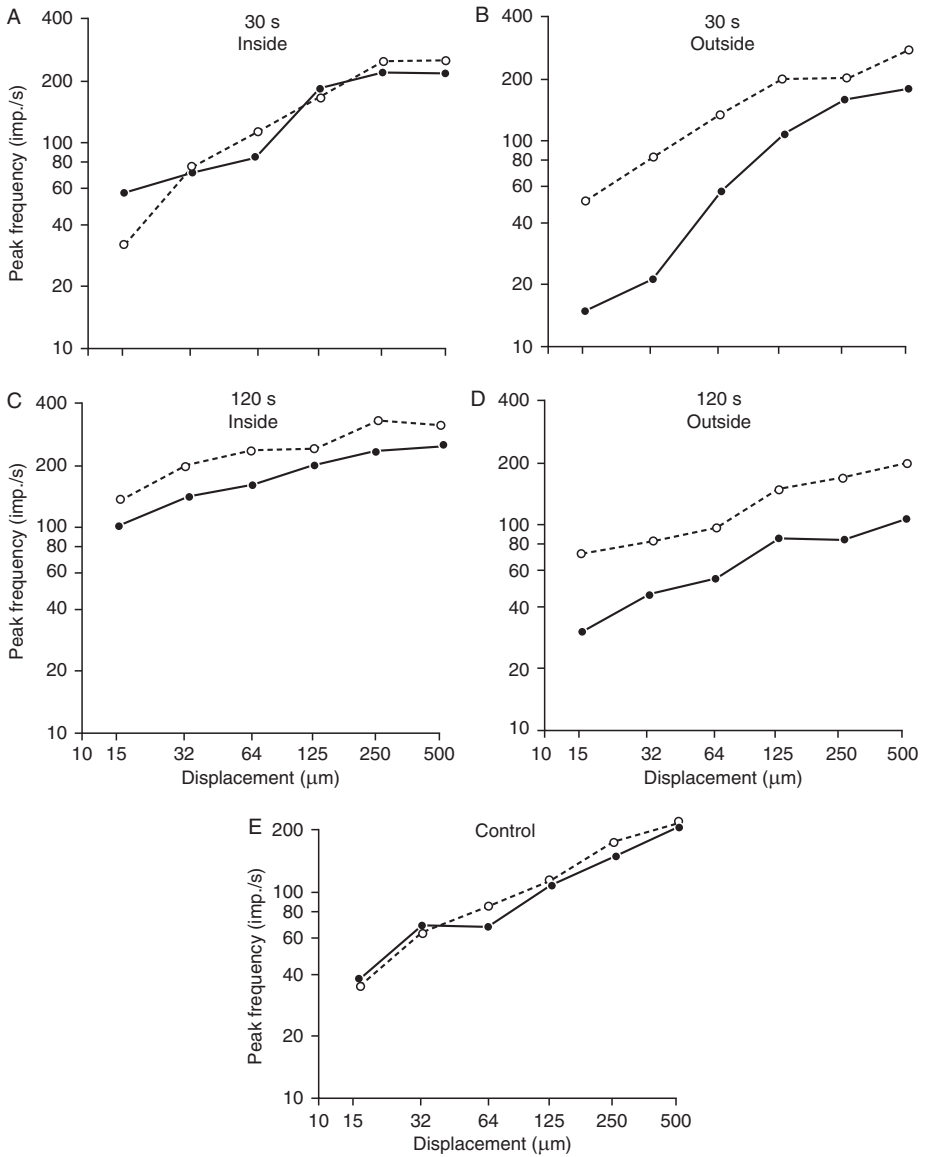


Fig. 7.12. Stimulus-response curves are shown for average activity evoked in a monkey STT cell by graded displacements of the skin (15 to 500 μm , 2 s duration, 10 repetitions) by a mechanical stimulator before and after a series of noxious heat pulses (to 43, 45, 47 and 50 $^{\circ}\text{C}$). The duration of each heat pulse was either 30 s or 120 s. The mechanical stimuli were applied either inside the area that received the heat pulses or outside that area. From Kenshalo *et al.* (1982).

must have caused central sensitization of the STT neuron, accounting for the increased responses of the cell when mechanical stimuli were applied outside of the heated area.

Intradermal injection of capsaicin

A convenient experimental model for the production of primary and secondary allodynia and hyperalgesia is the intradermal injection of capsaicin into the skin in human subjects and in monkeys (Baumann *et al.*, 1991; Lamotte *et al.*, 1991; Simone *et al.*, 1991; Dougherty and Willis, 1992), as well as in cats and rats (Sun *et al.*, 2003a, 2003b, 2004). Figure 7.13(I) shows the changes in the responses of a monkey STT cell that resulted from an intradermal injection of capsaicin. The ongoing activity of the neuron increased dramatically immediately after the injection (compare A with B). Furthermore, the responses to brushing the hairy skin (Brush; C vs. D), compressing the skin with a weak arterial clip (Press; E vs. F) and pinching a fold of skin with a strong arterial clip (Pinch; G vs. H) all increased at 15 minutes or more following the capsaicin injection. The drawing of the hindlimb at the bottom of Fig. 7.13(I) shows the receptive field before (hatched area) and after (solid line around open area) the injection, which was made at the site indicated by the arrowhead. The numbers along the border of the receptive field correspond to those in C (above the horizontal lines which represent the time of stimulation at the different sites). The histograms in Fig. 7.13(II) show the responses of an STT cell to the release of several excitatory amino acid receptor agonists by microiontophoresis from a multibarreled micropipette (GLUT, glutamate; ASP, aspartate; NMDA, N-methyl-D-aspartate; QUIS, quisqualic acid) before (Control) and at least 15 minutes after capsaicin injection. The released excitatory amino acids activated the neuron at lower current doses and the effects of a given current dose were larger following the capsaicin injection.

The observation in the experiment of Fig. 7.13 that stimulation of cutaneous receptors far from the site of a capsaicin injection produced larger responses of the STT cell by 15 minutes after capsaicin is consistent with the hypothesis that the capsaicin has enhanced the excitability of the STT cell by the process of central sensitization, since the primary afferent fibers that were stimulated and that evoked increased responses after capsaicin were unlikely to have undergone peripheral sensitization by the injection. Further evidence for central sensitization of the STT cell is the finding that its responses to iontophoretically administered excitatory amino acids were increased. It could be argued that the excitatory amino acids acted indirectly by exciting interneurons which secondarily excited the STT cell; however, if this were the case, the results of the experiment would still represent the development of central sensitization, but in interneurons.

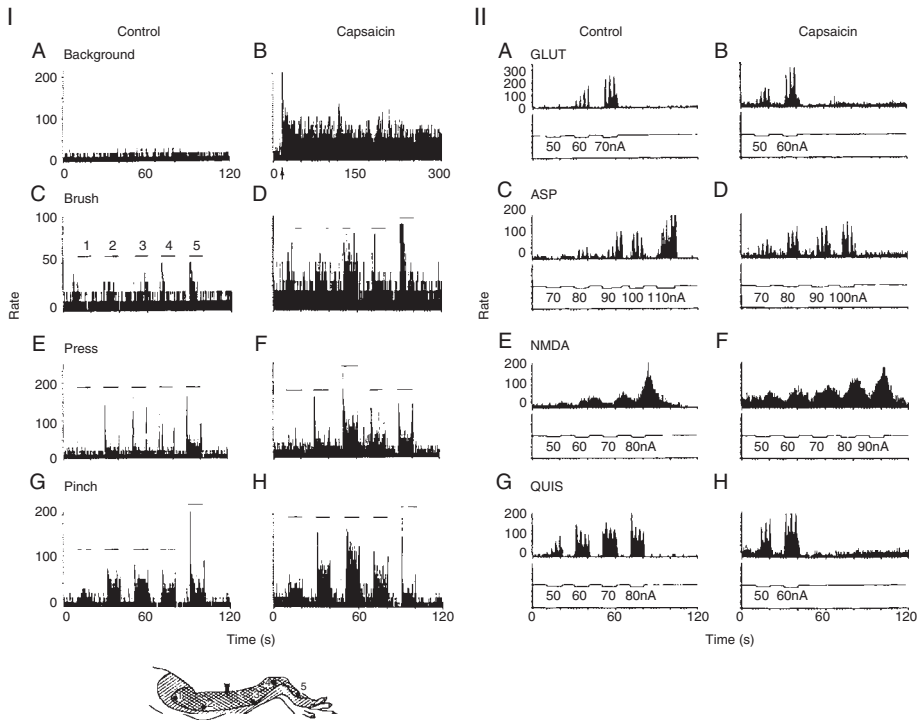


Fig. 7.13. (I) shows the increased activity of a monkey STT cell following capsaicin injection into the receptive field. The left column includes: (A) the background discharge; (C) responses to innocuous brushing of the receptive field at points 1–5, as seen on the drawing of the hindlimb and the receptive field at the bottom; (E) responses to press stimuli at the same points in the receptive field; and (G) responses to noxious pinch at the same sites. (B, D, F and H) are the responses to the same stimuli beginning 15 minutes after injection of capsaicin at the location indicated in the drawing by the arrowhead. II shows the responses of the cell to the iontophoretic release of graded current doses of excitatory amino acid agonists before (A, C, E and G) and more than 15 minutes after (B, D, F and H) the capsaicin injection. From Dougherty and Willis (1992).

Another factor that presumably contributes importantly to an increased excitability of monkey STT cells during central sensitization is that the inhibitory actions of glycine and GABA are reduced following an intradermal injection of capsaicin (Lin *et al.*, 1996a, 1996b). In Fig. 7.14, the activity of a monkey STT neuron was enhanced by maintained pinching of the receptive field. The inhibitory amino acids, glycine and GABA were released in the vicinity of the STT cell by microiontophoresis, using graded current doses. The inhibitory amino acids produced a strong inhibition of the cellular activity. However, by 15 minutes after the first dose of capsaicin, the inhibitory actions were suppressed. The

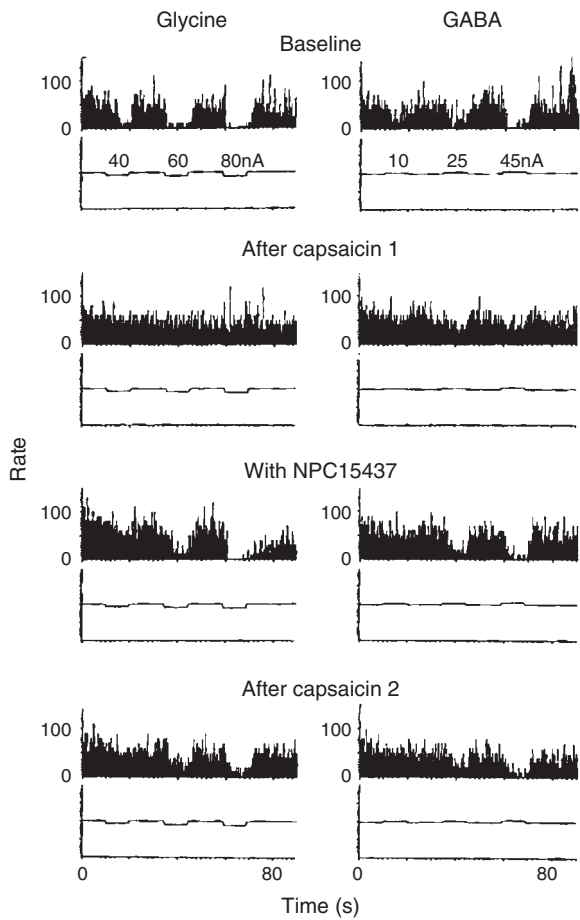


Fig. 7.14. The activity of a monkey STT neuron was increased during the rate histograms by maintaining pinching of the skin in the receptive field. During the times indicated by the current monitor, graded current doses of glycine or of GABA were released by microiontophoresis into the extracellular space in the vicinity of the STT cell. The control records in the top row show the inhibitory actions produced by the amino acids. An intradermal injection of capsaicin was then made, and the second row of records was made about 15 minutes after the injection. The inhibitory actions of the amino acids were suppressed. After these responses had recovered, the PKC inhibitor, NPC15437, was then infused into the spinal cord for an hour and the effects of the amino acids retested (third row). A second dose of capsaicin was then injected. Fifteen minutes after this injection, the inhibitory action of the amino acids was not substantially altered (lowest row). From Lin *et al.* (1996a).

effects of the inhibitory amino acids recovered after about 1.5 hours, when the PKC inhibitor, NPC15437, was administrated into the spinal cord by microdialysis. A second intradermal injection of capsaicin now failed to affect the inhibitory responses at 15 minutes following the second injection.

The reduction in the inhibition of monkey STT neurons by local application of glycine or GABA following an intradermal injection of capsaicin was subsequently shown to depend on the generation of nitric oxide by nitric oxide synthase and activation of the NO-cGMP cascade (Lin *et al.*, 1999c). Furthermore, the nitric oxide-cGMP cascade was found to contribute to the central sensitization of monkey STT cells (Lin *et al.*, 1999a, 1999b, 1999c).

Neurogenic central sensitization following intradermal injection of capsaicin

Neurotransmitters released by nociceptive terminals in the spinal cord

The neurotransmitters that are thought to be released in the spinal cord dorsal horn at synapses formed by the terminals of nociceptors on second-order neurons include glutamate, substance P, neurokinin A and calcitonin gene-related peptide (CGRP) (Duggan *et al.*, 1988, 1990; Schaible *et al.*, 1990, 1994). Several studies have measured neuropeptide release by means of antibody microprobes, a technique with sufficient resolution to localize peptide transmitter release to particular spinal cord laminae. Immunohistochemical staining of identified STT cells at an ultrastructural level has revealed the presence of numerous glutamate-containing synaptic terminals on the somas of monkey STT cells, as well as substance P- or CGRP-containing terminals on their dendrites (Carlton *et al.*, 1988; Westlund *et al.*, 1992; Willis, 2002).

Furthermore, iontophoretic release of neuropeptides, such as substance P or neurokinin A, increases the excitability of monkey STT neurons (Dougherty *et al.*, 1992, 1995). The combined release of both substance P and NMDA (or of any of several other excitatory amino acids) can result in a prolonged (hours) enhancement of the responses of these neurons to peripheral stimulation and the later iontophoretic release of the excitatory amino acid (Fig 7.15; Dougherty and Willis, 1991; Dougherty *et al.*, 1993). These plastic changes produced by the combined action of an excitatory amino acid and substance P were suggested to reflect the development of central sensitization of the affected monkey STT neuron.

More recent experiments in rats have shown that CGRP also plays an important role in the development of mechanical allodynia and hyperalgesia and the central sensitization of nociceptive dorsal horn neurons in rats following intradermal injection of capsaicin (Sun *et al.*, 2003, 2003a, 2003b, 2004, 2004a, 2004b, 2007).

Neurotransmitter receptors that trigger central sensitization

The central sensitization of monkey STT cells following intradermal injection of capsaicin depends on the activation of NMDA receptors and also of NK1 receptors (Dougherty *et al.*, 1994). Figure 7.16 illustrates evidence for this. The left column of records shows the sensitization of the mean responses

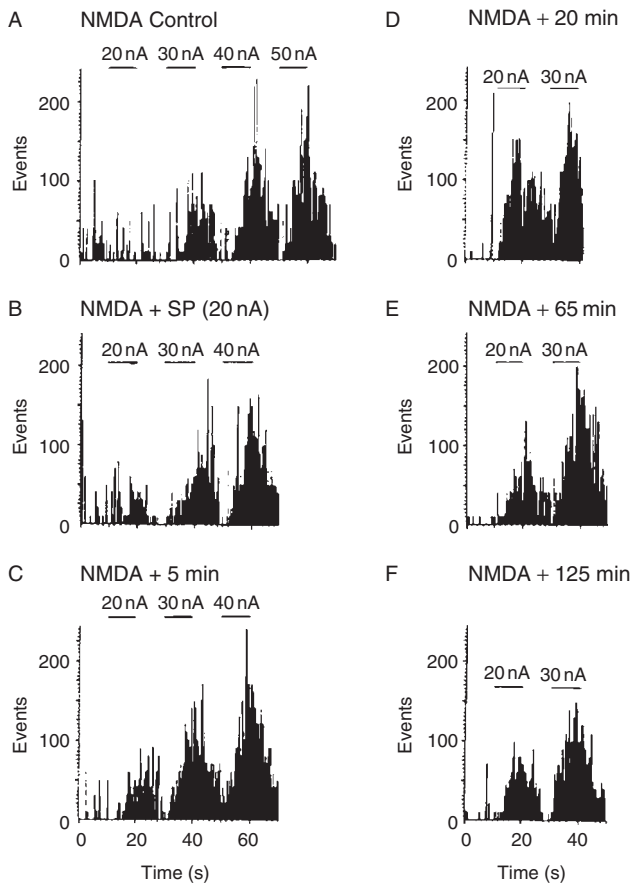


Fig. 7.15. Rate histograms show the responses of a monkey STT cell to graded current doses of NMDA released in the vicinity of the neuron by microiontophoresis. The control responses to the release of NMDA by currents of 20–50 nA are shown in (A). When there was a combined release of NMDA and substance P (SP, 20 nA), the responses increased. The current that released SP was then turned off, and the responses of graded current doses of NMDA were tested periodically and enhanced responses were observed for several hours. Repeated control responses to NMDA did not result in potentiation of later NMDA responses; instead the later responses to NMDA were usually reduced.

of a sample of monkey STT neurons to brush stimuli, and the right column shows the sensitization to press stimuli. Capsaicin was injected twice (1st and 2nd) at an interval of an hour, which was generally sufficiently long to allow recovery from the 1st injection. In Fig. 7.16A, the non-NMDA receptor antagonist, CNQX, or the NMDA receptor antagonist, AP7, was infused into the spinal cord by microdialysis during the time between the two capsaicin

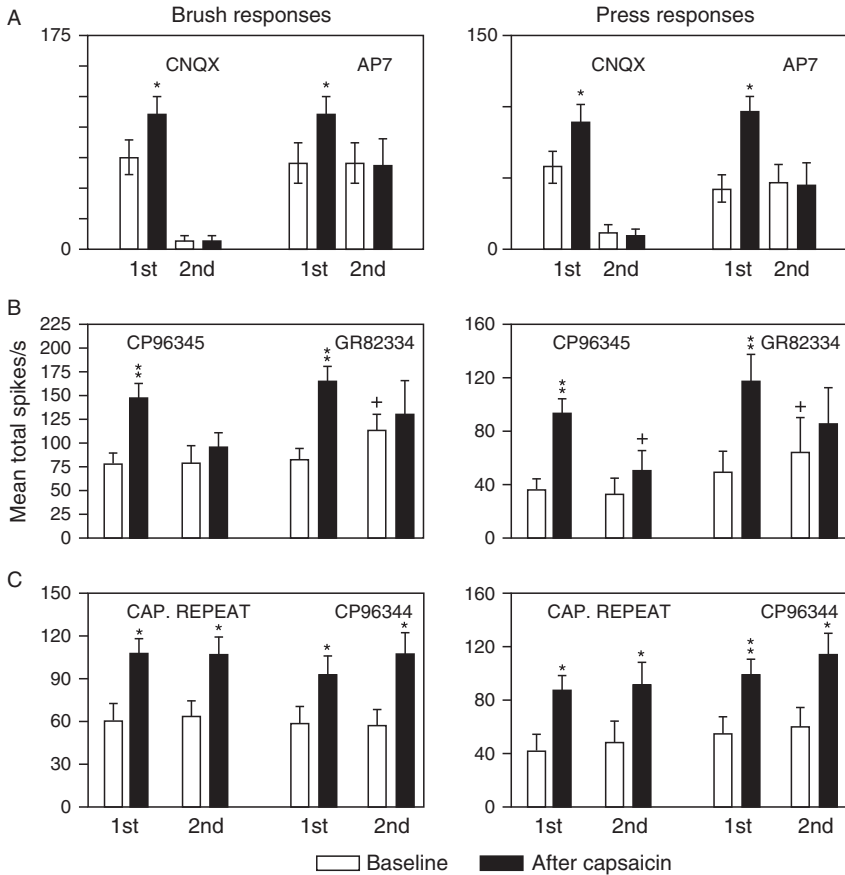


Fig. 7.16. The bar graphs show the mean responses of a population of monkey STT cells to brush or press stimuli before and after each of two intradermal injections of capsaicin. Between each pair of capsaicin injections, a drug was infused into the spinal cord dorsal horn by microdialysis. In (A), the drugs used included the non-NMDA glutamate receptor antagonist, CNQX, and the NMDA receptor antagonist, AP7. The CNQX essentially eliminated the responses to the mechanical stimuli (this action also prevented sensitization); the AP7 did not affect the control responses but blocked sensitization. In (B), the drugs were two different NK1 receptor antagonists, CP96345 and GR82334. Both prevented sensitization of the responses. In (C), sensitization by each of the two capsaicin injections is shown at the left and the failure of the inactive analog of one of the NK1 receptor antagonists is shown to have no effect on sensitization. From Willis (2002).

injections. CNQX nearly eliminated the responses to brush and press, and it prevented sensitization. By contrast, AP7 did not affect the control responses to mechanical stimulation, but it prevented sensitization of these by the capsaicin injection. In Fig. 7.16B, neither of two different NK1 receptor antagonists,

CP96345 and GR82334, affected the control responses to the mechanical stimuli, but both antagonists prevented sensitization. In Fig. 7.16C, two capsaicin injections produced equivalent levels of sensitization in the absence of drug administration or during administration of CP96344, an inactive analog of the NK1 receptor antagonist, CP96345. Metabotropic glutamate receptors, in particular subtype mGluR1, have also been found to affect central sensitization of monkey STT cells (Neugebauer *et al.*, 1999, 2000).

It is well recognized that the activation of NMDA receptors leads to an influx of Ca^{2+} through the postsynaptic membrane into the affected neuron (see Collingridge and Watkins, 1994) and that the activation of such G-protein coupled receptors as NK1 and CGRP receptors would result in the release of Ca^{2+} from intracellular stores (see Nicholls *et al.*, 1992). In addition, excitation of a neuron can result in the activation of voltage-gated calcium channels and calcium influx into the cytoplasm of the neuron (see North, 1995). The increase in intracellular concentration of Ca^{2+} would be expected to enhance the activity of several intracellular signal transduction pathways (Fig. 7.17), leading to the phosphorylation and a changed functional state of numerous membrane-associated and intracellular proteins.

Effects of agents that facilitate or block intracellular signaling pathways

Several series of experiments have demonstrated that a number of different protein kinases play a role in the central sensitization of monkey STT cells. In one experimental design, central sensitization was evoked by an intradermal injection of capsaicin in a control group, and then in experimental groups; the possibility that central sensitization could be prevented by administration of particular protein kinase inhibitors was tested. The goal in such experiments was to identify a protein kinase activated by the capsaicin injection indirectly by the action of the inhibitor of the protein kinase. An alternative experimental design was to determine if central sensitization could be produced by administration of an activator of a particular protein kinase. In both experimental designs, agents were administered into the spinal cord dorsal horn through a microdialysis fiber to ensure that the actions were within the spinal cord and not at some remote site.

An example of central sensitization of a monkey STT cell that resulted from the activation of protein kinase C following intradermal injection of capsaicin is seen in Fig. 7.18(I) (Palecek *et al.*, 1994; Lin *et al.*, 1996b; Sluka *et al.*, 1997). The responses of a monkey STT neuron to brush and press stimuli, but not to pinch stimuli, were increased following the first injection of capsaicin into the

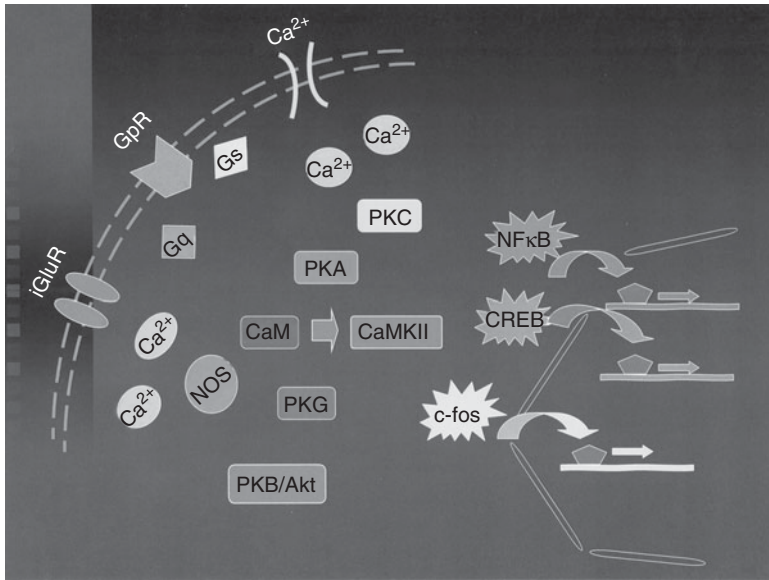
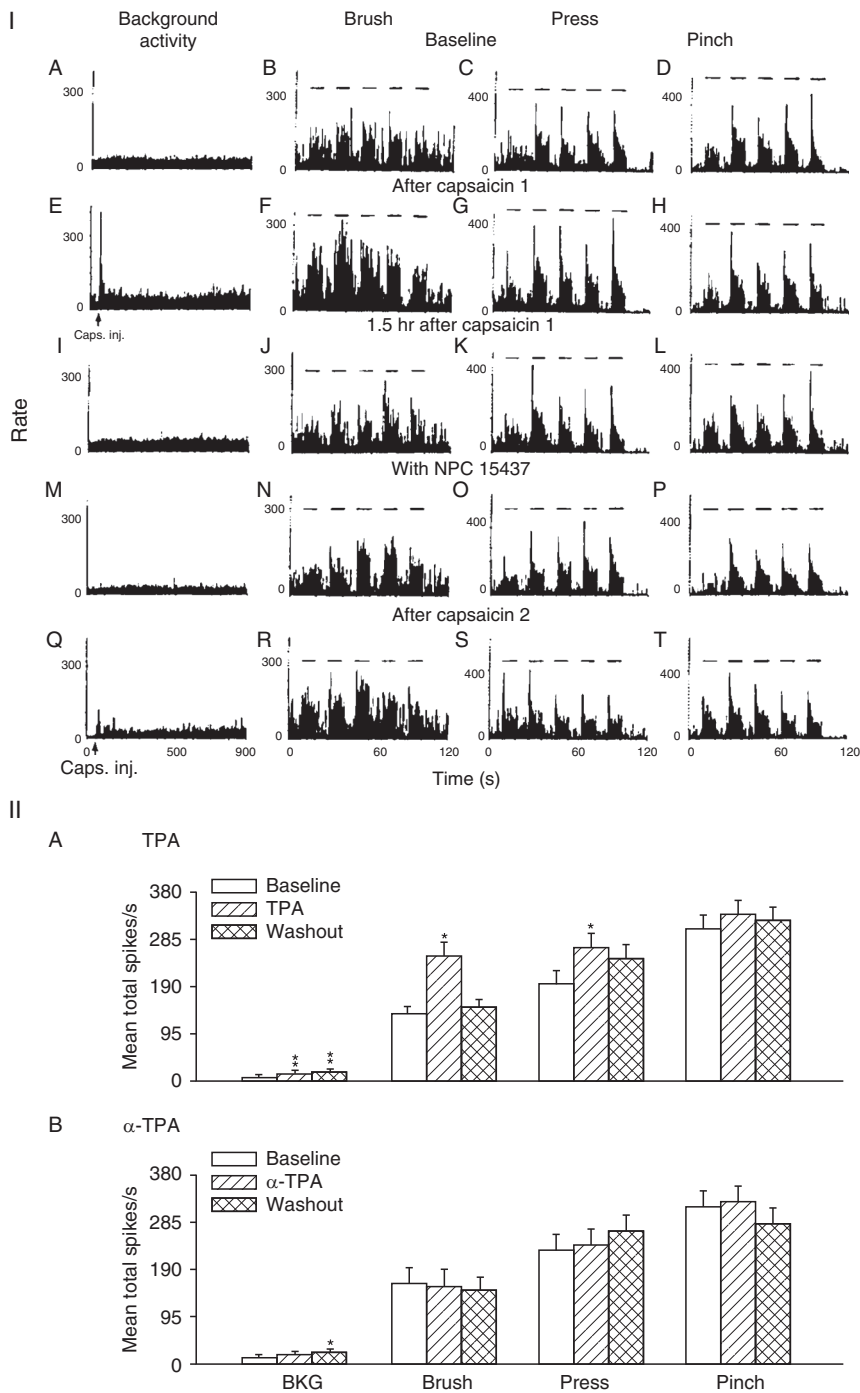


Fig. 7.17. Schematic illustration of the intracellular signal transduction system in a neuron. The surface membrane of the cell is indicated by the double dashed line at the left. The membrane contains ionotropic glutamate receptors (iGluR), such as NMDA receptors, G-protein coupled receptors (GpR), such as NK1 and CGRP receptors, and voltage gated calcium channels (Ca^{2+}). Activation of NMDA receptors or of voltage-gated calcium channels results in an influx of Ca^{2+} ions into the cytoplasm of the neuron. Activation of G-protein coupled receptors can stimulate the release of Ca^{2+} from intracellular stores. The calcium can bind to calmodulin (CaM), activating calcium/calmodulin kinase II (CaMKII). Other protein kinases (such as PKC, PKA, PKG, PKB/akt) can be activated, and these activated protein kinases phosphorylate a number of proteins, such as those forming ion channels and membrane receptors. Nitric oxide synthase (NOS) can also be activated, causing the synthesis and release of nitric oxide. Transcription factors are also activated, such as NFκB, CREB and c-fos, and these translocate into the nucleus of the neuron (at the right) and may affect gene expression.

receptive field (compare Fig. 7.18 (I B-D) to Fig. 7.18 (I F-H)). The background activity of the neuron was also enhanced (compare Fig. 7.18 (I A) with (E)). One and a half hours after the first injection of capsaicin, the responses of the neuron had essentially recovered (Fig. 7.18 (I J-L)). Then NPC15437, a selective inhibitor of protein kinase C, was administered into the dorsal horn of the spinal cord by microdialysis. The responses of the STT cell to the mechanical stimuli at this time are shown in Fig. 7.18 (I N-P). A second capsaicin injection in the presence of NPC15437 had little effect on the responses to mechanical stimulation (Fig. 7.18 (I R-T)).



In another series of experiments, PKC was activated by microdialysis administration into the spinal cord of an active phorbol ester (12-O-tetradecanoylphorbol-13-acetate, abbreviated TPA) (Fig. 7.18 (II A)) or of an inactive analog of the phorbol ester (4 α -phorbol 12, 13 didecanoate, abbreviated α -TPA) (Fig. 7.18(II B)). The mean background activity and the mean responses to brush and press stimuli, but not to pinch stimuli, of a sample of nine monkey STT cells were increased by TPA, whereas α -TPA had no significant effect on seven STT cells.

Another protein kinase that was found to contribute to central sensitization of monkey STT cells is protein kinase A (Lin *et al.*, 2002). Forskolin is known to activate PKA. Figure 7.19 (I) illustrates the action of forskolin infused into the dorsal horn by microdialysis on the responses of a monkey STT neuron to brush, press and pinch stimuli. The responses to press and pinch were increased, but not those to brush. Figure 7.19 (II A) confirms this observation for the mean effects of forskolin infusion in recordings from a sample of 23 STT neurons. The inactive analog, D-forskolin, had no effect on a sample of seven STT cells (Fig. 7.19 (II B)). Figure 7.20 shows that infusion of the PKA inhibitor, H89, prevented the changes expected in the responses following the infusion of forskolin.

In similar experiments, several other protein kinases were also found to help trigger central sensitization of monkey STT cells. These protein kinases include calcium/calmodulin kinase II (CaMKII) (Fang *et al.*, 2002) and PKG (Lin *et al.*, 1997, 1999a, 1999b, 1999c; Sluka *et al.*, 1997). The release of nitric oxide through the action of nitric oxide synthase also helps the triggering of central sensitization of monkey STT cells (Lin *et al.*, 1999a, 1999c). Activation of CaMKII, PKC, PKA, PKG and PKB/Akt, as well as of nitric oxide synthase, has also been shown to contribute to central sensitization in rats (Sluka *et al.*, 1997; Sun *et al.*, 2007).

Caption for Fig. 7.18. (cont.)

stimuli were applied to five different sites on the skin of the receptive field. The first injection of capsaicin increased the background activity of the neuron (E) and the responses to the brush and press stimuli (F and G), but not to the pinch stimuli (H). The activity of the cell 1.5 h after the injection is shown in (I–L). Following this, the PKC inhibitor, NPC15437, was infused into the spinal cord dorsal horn through a microdialysis fiber. The activity of the neuron during this infusion is shown in (M–P). A second injection of capsaicin was made, and the activity of the neuron after this is shown in (Q–T). In (II A) is a bar graph showing the mean baseline responses of nine STT cells, the responses of the same neurons to microdialysis infusion of TPA, and finally the responses after washout of the agent. In (II B), the same responses are shown before, during α -TPAS administration and after washout. The asterisks indicate significant changes. From Lin *et al.* (1996b).

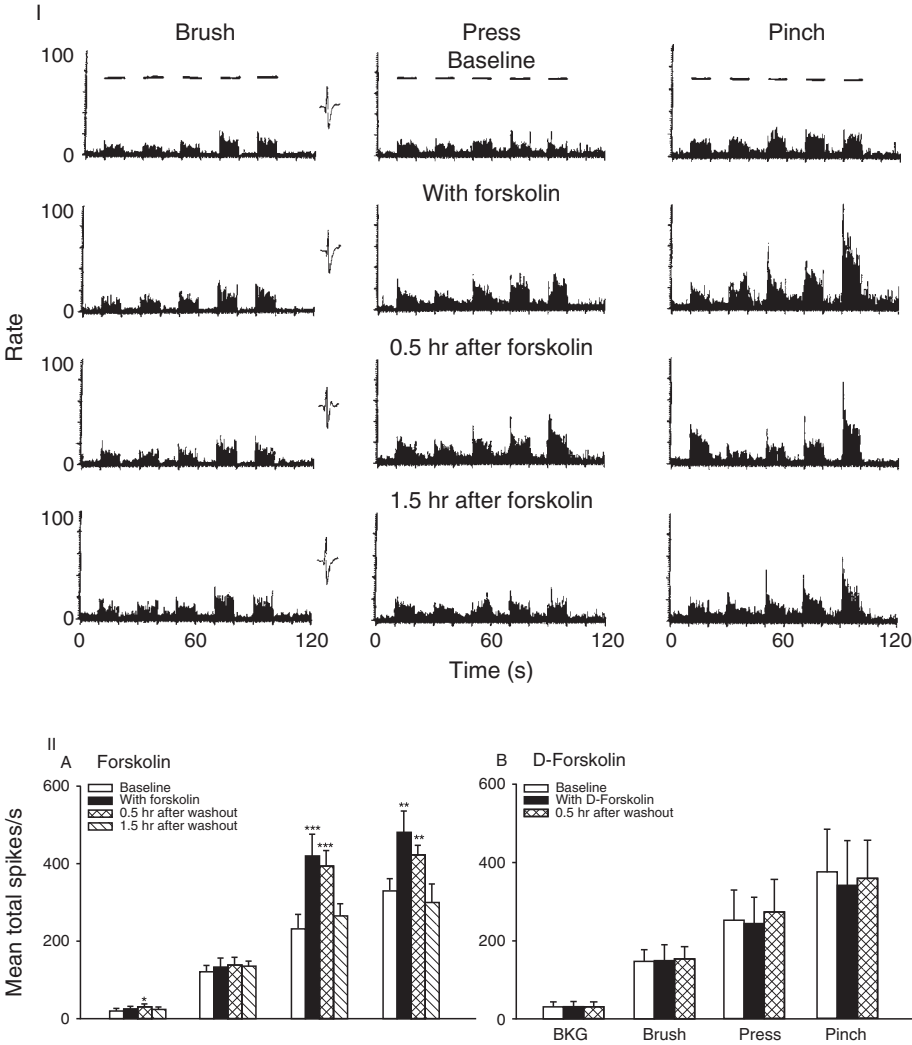


Fig. 7.19. The rate histograms in (I) show the responses of a monkey STT cell to mechanical stimulation at five different sites in the receptive field. Brush, press and pinch stimuli were used. The top row of histograms show the baseline responses, and the other three rows the responses during forskolin infusion and then 0.5 h and 1.5 h after forskolin infusion into the dorsal horn by microdialysis. Insets are the action potential of the STT cell recorded at various times during the experiment that correspond with the histograms. The bar graphs in (II) show the background activity and responses to the mechanical stimuli before and during forskolin infusion and after washout. The asterisks indicate significant changes. From Lin *et al.* (2002).

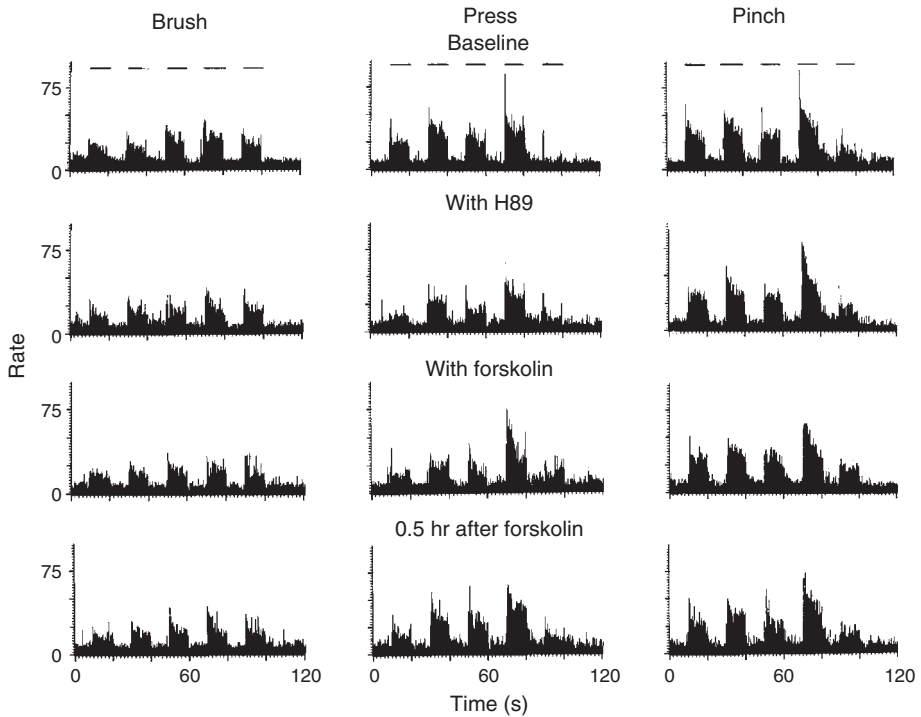


Fig. 7.20. The rate histograms show that forskolin was unable to enhance the responses of a monkey STT cell after microdialysis infusion of the PKA inhibitor, H89. The upper row of histograms are the baseline responses to stimulation at five different sites in the receptive field, using brush, press and pinch stimuli. Infusion of H89 did not produce any notable effects on the responses. After H89 infusion, forskolin also had no effect during its infusion or 0.5 h afterwards.

Phosphorylation of proteins by protein kinases activated during central sensitization

Several proteins have been found to be phosphorylated in monkey or rat spinal cord following the intradermal injection of capsaicin. These include several different subunits of NMDA glutamate receptors (NR1 and NR2B) (Zou *et al.*, 2000; Zhang *et al.*, 2005; Harris *et al.*, 2007b), the GluR1 subunit of AMPA receptors (Fang *et al.*, 2003a, 2003b), as well as CaMKII and CREB (cyclic adenosine monophosphate-responsive element-binding protein) (Wu *et al.*, 2002). The phosphorylation of CREB is regulated by CaMKII (Fang *et al.*, 2005). NR1 subunits are phosphorylated by PKA on serine 890 and 897. It was found that the phosphorylation of NR1 subunits of NMDA receptors in rat spinothalamic tract neurons after capsaicin injection depends on PKA, since it is prevented by

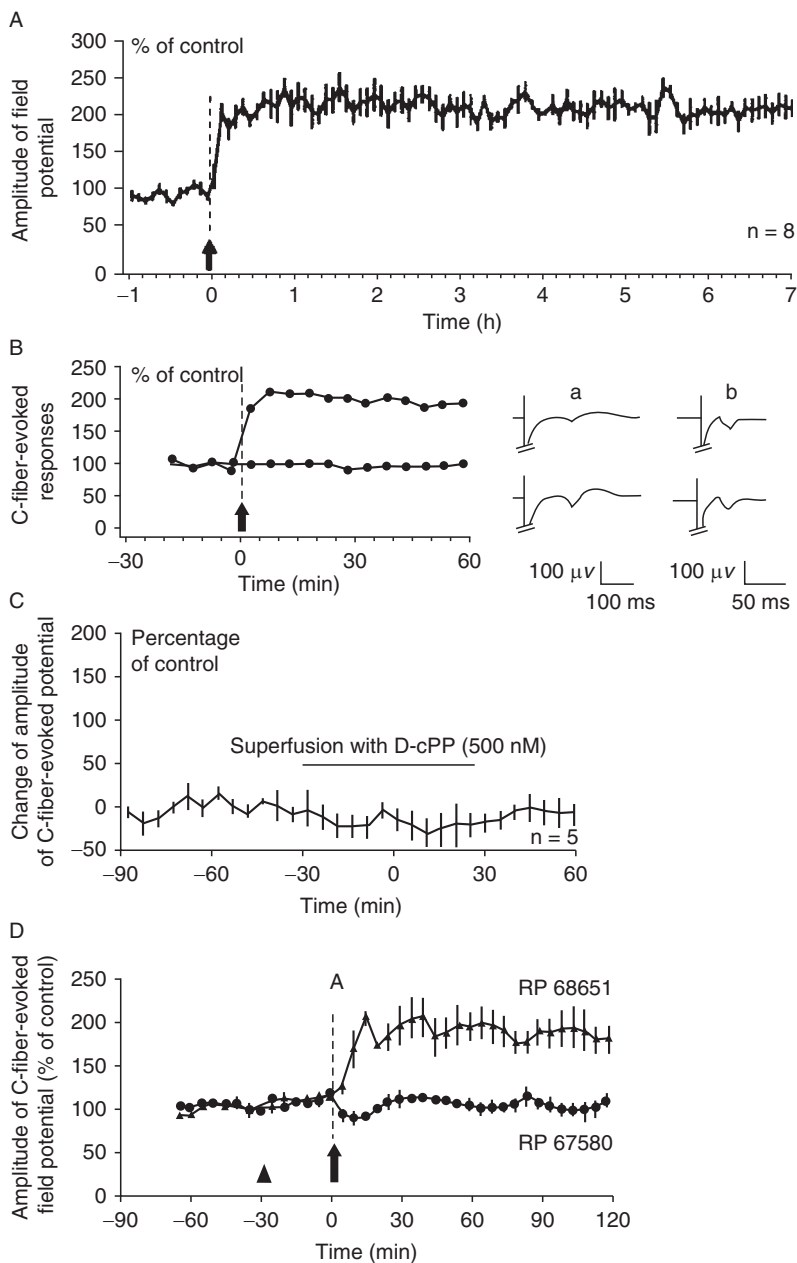


Fig. 7.21. In (A) is plotted the size of the spinal cord field potential that was recorded from the dorsal horn in a rat in response to electrical stimulation of the sciatic nerve with a stimulus strength that activated C fibers. At the time shown by the arrow, the nerve was stimulated repetitively (100 Hz) at C-fiber intensity, and the field potential was increased for more than 7 hours. The graph in (B) shows the increase in the C-fiber-evoked field potential that followed repetitive stimulation of the sciatic

pretreatment with H89 (Zou *et al.*, 2002). The phosphorylation of the GluR1 subunit of AMPA receptors depends on actions of both PKA and PKC (Fang *et al.*, 2003b). It has been shown that phosphorylation of NMDA receptors increases their responses to agonists (Cerne *et al.*, 1993).

Phosphorylation is reversed by the action of protein phosphatases, such as protein phosphatase 2A. This enzyme can be inhibited by okadaic acid and also by a more specific inhibitor, fostriecin (Zhang *et al.*, 2003). Administration of these inhibitors enhanced the duration of secondary mechanical allodynia and hyperalgesia in behavioral tests performed on rats (Zhang *et al.*, 2003) and increased the degree of phosphorylation of NR1 and NR2B subunits of NMDA receptors (Zhang *et al.*, 2005) following intradermal injection of capsaicin in rats.

Possible equivalence of central sensitization and spinal cord long-term potentiation

There are many parallels between central sensitization of neurons in the spinal cord, such as monkey STT cells (Willis, 2002), and long-term potentiation (LTP) in neurons of the brain (Collingridge and Bliss, 1987). Since LTP is often considered in terms of the plastic changes responsible for learning and memory, its demonstration in the neural networks of the hippocampal formation has generally been emphasized ever since its initial recognition in that structure (Collingridge and Bliss, 1987). However, recently, a number of investigations have suggested that LTP can be evoked in the spinal cord, as well as in the brain (Randic *et al.*, 1993; Sandkuhler and Liu, 1998; Svendsen *et al.*, 1999a, 1999b).

Figure 7.21A shows LTP of the field potential produced by electrical stimulation of C fibers in the sciatic nerve and recorded from the spinal cord dorsal horn. Stimulation was applied at the time indicated by the arrow. The graph at

Caption for Fig. 7.21. (cont.)

nerve (upper trace), as well as the lack of change in the size of the C-fiber volley (lower trace). To the right are sample records of the field potential (a) and of the C-fiber volley (b). In (C), an NMDA receptor antagonist was superfused over the spinal cord during the time indicated by the horizontal line. Tetanic stimulation of the nerve failed to result in LTP. In (D), the lower graph (filled circles) shows that intravenous pretreatment of the spinal cord with an NK1 antagonist (RP 67580) blocked LTP that would otherwise have occurred following stimulation at the time of the arrow, whereas an inactive enantiomer, RP 68651, had no effect (filled triangles). A, B, C and D from Liu and Sandkuhler (1995); Sandkuhler and Liu (1998).

the left in Fig. 7.21B shows the increased amplitude of the C-fiber-evoked field potential before and after tetanic stimulation of the peripheral nerve (upper part of the graph) and the absence of any change in the C-fiber volley (lower part of the graph). The LTP lasted for more than 60 minutes. Records of the field potential before and after stimulation are in Fig. 7.21Ba (middle set of records), and the C-fiber volley before and after stimulation are in Fig. 7.21Bb (records at the right). Figure 7.21C shows that superfusion of the spinal cord with an NMDA receptor antagonist prevented LTP, and Fig. 7.21D shows that administration of an NK1 receptor antagonist had a similar effect. Spinal cord LTP thus depends on the activation of both NMDA and NK1 receptors, as does central sensitization (see Fig. 7.16).

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Functional imaging of chronic pain

Introduction

In [Chapter 5](#), we discussed the normal responses to a variety of noxious stimuli and their modulation by peripheral and central neural mechanisms. This review showed that noxious stimuli preferentially and most commonly activate a set of interconnected structures, namely the insula and secondary (SII) somatosensory cortices, anterior cingulate gyrus and thalamus. Several additional structures are also activated during normal acute pain although somewhat less frequently: the primary (SI) somatosensory cortex, components of the striatum, the cerebellum, premotor cortex, dorsolateral and orbitofrontal regions of the prefrontal cortex, and the medial midbrain in the region of the periaqueductal gray matter.

In this chapter we review the evidence that chronically painful conditions, whether of peripheral or central origin, may alter the nociceptive processing that normally follows the application of noxious or innocuous stimuli (see [Chapter 7](#)). In clinical practice and in the interpretation of the results of pain research, the assumption is often made that the perceptual abnormalities sometimes associated with chronic pain states are attributable only to changes occurring at the peripheral or spinal level. Although this assumption may be correct in most instances, functional imaging studies provide evidence to the contrary in some cases. We cannot assume that, in pathological or chronically painful conditions, information ascending through the spinothalamic tract will be processed by the same mechanisms used for acute pain; this has important clinical implications for the management of chronic pain.

The term “chronic pain” is seldom defined. The International Association for the Study of Pain (IASP), however, has suggested the following definition:

Chronic pain has been recognized as that pain which persists past the normal time of healing (Bonica, 1953). In practice this may be less than one month, or more often, more than six months. We have taken three months as the most convenient point of division between acute and chronic pain. (*Classification of Chronic Pain*, p. xi (Merskey and Bogduk, 1994).)

In this chapter, we will be guided, but not completely limited, by this definition.

Chronic pain may be caused by injury to the peripheral or central nervous systems, impairing their normal function; this is neuropathic pain. Some of the functional imaging responses during these neuropathic pain states have been discussed in [Chapter 7](#) and will be reviewed again here.

Most chronic pain occurs because of injuries or abnormalities that originate outside the nervous system, in skin, muscle or internal organs. For simplicity, we will refer to this non-neuropathic condition simply as chronic pain, either somatic or visceral. These injuries, and the associated inflammatory process, may alter the responses of neural receptors to innocuous and noxious stimuli but this is within the range of normal function for these receptors and is not due to an injury of neural tissue. Here we will discuss the changes in CNS function that are revealed by functional imaging studies of patients with chronic pain of both neuropathic and extra-neuronal origin.

There are some cases of chronic pain in which the evidence for injury to either neural or non-neural tissue is not detectable by clinical methods, including physical examination and radiological or laboratory studies. In some of these cases, there is functional imaging evidence for an abnormality of nociceptive processing, usually at the forebrain level. Often, it is not clear whether these abnormalities are responsible for the chronic pain or are the consequence of chronic nociceptive input from unidentified sources. We will summarize the data and discuss the evidence but will not attempt to resolve these issues.

Neuropathic pain

Moisset and Bouhassira (2007) have critically reviewed functional imaging studies of neuropathic pain and concluded that "... there is no unique network for neuropathic pain ..." (p. S86), an observation largely in accord with the following discussion and attributable to several variables that are considered below in more detail (Moisset and Bouhassira, 2007). We note, however, as these authors suggest also, that there may be some common features of the cerebral activity during neuropathic pain that distinguish it from pain that arises from the activation of functionally and anatomically normal nociceptive processing

mechanisms. We will emphasize these common features where appropriate and possible.

SPECT studies of resting and evoked neuropathic pain

Cesaro and colleagues were the first to use functional imaging technology (single photon emission computerized tomography or SPECT with [^{123}I]N-isopropyl-iodoamphetamine or IMP) to demonstrate increased thalamic responses to somatic stimulation in patients with central pain syndrome (Cesaro *et al.*, 1991). Four patients with central post-stroke pain (CPSP) were studied after the injection of IMP. During this time, innocuous somatic stimulation was applied so as to evoke allodynia or hyperpathia. Two patients with thalamic or thalamo-cortical lesions and allodynia/hyperpathia showed a contralateral hyperactivity (relative to the non-involved side) in the region of the thalamus; this did not occur during stimulation of the clinically normal side nor in the patients without hyperpathia. In healthy volunteers, SPECT revealed that regional cerebral blood flow (rCBF) in the contralateral primary somatosensory (SI) cortex was decreased while the hand was immersed in a noxious hot water bath for 3 minutes but increased during vibration and a sensorimotor task (Apkarian *et al.*, 1992). The authors suggested that inhibition of the SI cortex may be causally related to persistent pain. This cortical inhibition hypothesis received some support from the results of another technetium-99 hexamethylpropyleneamineoxime (HMPAO) SPECT study which demonstrated decreased parietal rCBF in two patients, one with CPSP and one with post-rhizotomy facial anesthesia dolorosa; the rCBF was further reduced during innocuous stimulation (Canavero *et al.*, 1993). A patient with central pain, tactile and cold allodynia, and a spinal intramedullary cyst, showed thalamic hypoperfusion contralateral to the affected limb; following surgical evacuation of the cyst, thalamic rCBF increased and pain relief persisted during the 9-month follow-up (Pagni and Canavero, 1995). Several metabolic PET studies (primarily FDG) had established that focal subcortical lesions, usually lacunar infarctions within the thalamo-cortical projection system, frequently resulted in ipsilateral cortical hypometabolism in patients without central or other neuropathic pain (Baron *et al.*, 1986; Pappata *et al.*, 1990; Chabriat *et al.*, 1992). The SPECT studies cited above suggest that some forms of neuropathic pain, including pain of central origin, are associated with major changes in the resting activity and in the excitability of thalamic and cortical structures participating in nociceptive processing.

Imaging studies of resting neuropathic pain

Position emission tomography studies of resting, rather than evoked, cerebral activities also suggest that ongoing neuropathic pain is associated

with changes in the ongoing baseline activity of brain structures responding to noxious stimuli. In one of the first PET studies of chronic pain, five patients with cancer were noted to have hypoperfusion of the thalamus contralateral to their pain; the thalamic perfusion increased following successful ventrolateral cervical cordotomy (Di Piero *et al.*, 1991). Resting glucose hypometabolism, relative to the uninvolved side, was observed in the posterolateral thalamus and postcentral cortex of 13 patients with central pain following unilateral thalamic infarction (Hirato *et al.*, 1994). Resting contralateral thalamic hypoactivity ($H_2^{15}O$ PET) was noted also in four patients with chronic post-traumatic painful peripheral neuropathy (Iadarola *et al.*, 1995). Hsieh *et al.* (1995) used local anesthesia to modulate the ongoing pain in eight patients with a unilateral mononeuropathy. In comparing the rCBF during ongoing pain with that observed following pain-relieving regional anesthesia, they noted that activity was reduced in the contralateral posterior thalamus during ongoing pain; in contrast, the bilateral anterior insulae, posterior parietal, lateral inferior prefrontal, posterior cingulate and right anterior cingulate cortices were active. These findings suggest that reduced resting thalamic activity may be a critical pathophysiological feature of ongoing neuropathic pain in some patients, consistent with a thalamic disinhibition hypothesis (Casey, 2007).

Szelies and colleagues used FDG PET to demonstrate the widespread functional effects of focal thalamic lesions (Szelies *et al.*, 1991). Single localized thalamic infarctions were associated with significantly lower glucose metabolism (CMRGlucose) at rest in the hemisphere ipsilateral to the infarction; bilateral infarctions were associated with even lower hemispheric metabolism. Emphasizing the distributed and even remote effects of focal lesions, an ^{11}C -diprenorphine receptor binding PET study by Willoch *et al.* (2004) revealed that five patients with CPSP following single focal cerebral lesions had widespread reduced opioid binding at rest and spatially remote from the lesions in the contralateral thalamus, parietal, secondary somatosensory, insular, anterior and posterior cingulate, and lateral prefrontal cortices and midbrain gray matter (Fig. 8.1). Whether this finding reflects a pain-related release of endogenous opioid or a lesion-induced impairment of receptor occupancy is unclear.

In a similar PET study directly comparing opioid binding potential in eight patients with CPSP and seven patients with peripheral neuropathic pain (PNP), the reduced binding (posterior midbrain, medial thalamus, insula, and temporal and prefrontal cortices) was found to be significantly distributed toward the hemisphere contralateral to the pain in CPSP patients and more symmetrically distributed between the hemispheres in PNP patients (Fig. 8.2) (Maarrawi *et al.*, 2007a). This result suggests that, at least in CPSP patients, the lateralized reduced binding potential may reflect a lesion-induced loss of receptor function rather

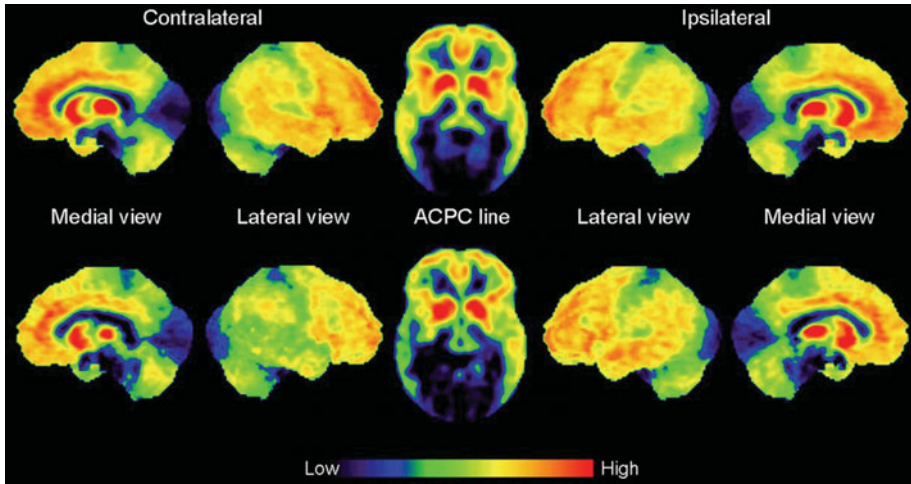


Fig. 8.1. Group mean images of opioid (^{11}C -diprenorphine) receptor binding in age-matched healthy subjects (top row) and five patients (bottom row) with CPSP following single cerebral infarctions (brainstem, thalamus, parietal cortex). Degree of binding is shown by the color bar below the images. Reduced binding in the patient group is seen in the thalamus and parietal and frontal cortices contralateral to the hemibody pain (contralateral images) and in the anterior cingulate cortex bilaterally. Adapted from Willoch *et al.* (2004).

than a pain-related reactive global release of endogenous opioid. In any event, the loss of normal opioidergic nociceptive modulatory mechanisms, as shown by these baseline resting PET scans, may be an important factor in the development of CPSP and perhaps other forms of neuropathic pain.

Of special relevance to pain-related changes in the resting brain is the finding that a group of patients with chronic back pain (2 to 35 years duration, including participants with neuropathic pain in a previous study by the same group Apkarian *et al.*, 2004b), show a disruption of the normal intercorrelated default (resting brain) network discussed in Chapter 5 (Fox *et al.*, 2005; Baliki *et al.*, 2008). During scanning (fMRI), patients and healthy participants performed a visuo-motor target tracking task equally well, but the patients showed a loss of the correlated activations and deactivations that occur normally during task performance (Fig. 8.3). In accord with the previous results of Fox *et al.* (2005), the investigators chose, as “seed” regions for voxelwise correlation of the BOLD response, three that were activated during the task (task positive; intraparietal sulcus, frontal eye fields and middle temporal gyrus) and three that are normally inactivated during a task (task negative; medial prefrontal cortex, posterior cingulate cortex and the lateral parietal cortex). As shown in the example at the top of Fig. 8.3, BOLD activity in the left intraparietal sulcus (LIPS) of both patients and control subjects increases during task performance; in the chronic

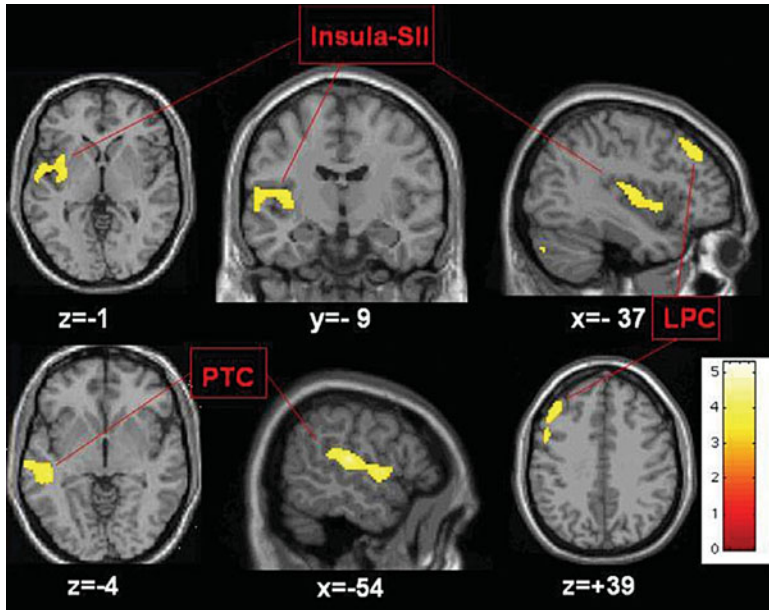


Fig. 8.2. Between-group comparison of reduced ^{11}C -diprenorphine binding potential in patients with central pain (CPSP) and patients with peripheral neuropathic pain (PNP). Color bar indicates t-score values of reduced binding potential differences, which are shown contralateral to the painful side in CPSP patients compared with PNP patients. Adapted from Maarawi *et al.* (2007a).

pain group, however, the anti-correlated BOLD activity in the medial prefrontal cortex (mPFC) of normal individuals is absent in the chronic back pain (CBP) patients. A summary conjunction analysis, which included only voxels correlated or anti-correlated with five of the six selected “seed” regions, shows that the normal correlated network of activated and deactivated regions is greatly reduced in CBP patients compared with healthy individuals (bottom panel, Fig. 8.3). Additionally, in the main effects analysis, the extent of medial prefrontal deactivation shows a trend of correlation with the duration of chronic pain. These results suggest that the brains of at least some patients with chronic pain have undergone a fundamental change in how the default network in the resting brain responds during a task that is unrelated to pain. The authors suggest that this alteration may be related to some of the cognitive or affective abnormalities detected in some patients with chronic pain (Apkarian *et al.*, 2004a). Subsequent functional imaging studies have used PET, but primarily fMRI, to investigate responses to stimulation in patients with allodynia. Consequently, because fMRI does not provide a stable measure of regional baseline perfusion, there is little additional information about resting cerebral activity in neuropathic pain states.

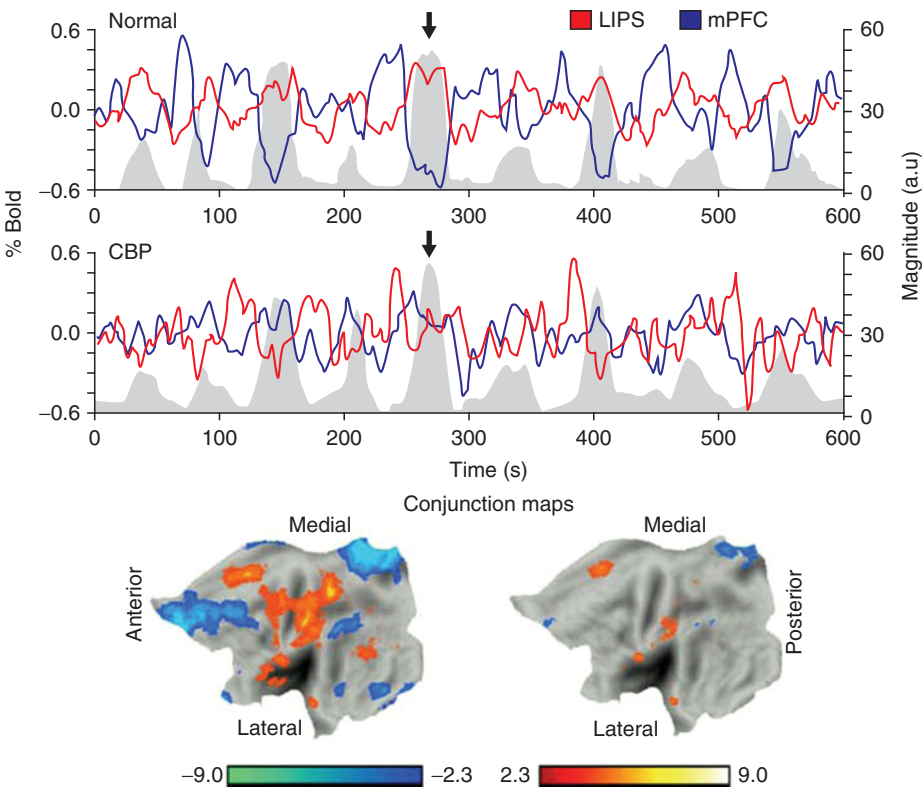


Fig. 8.3. Patients with chronic back pain lose the task-related activations and deactivations of the correlated default network in the normal resting brain. Top panel shows the normalized BOLD responses in the left intraparietal sulcus (LIPS, red line) and the medial prefrontal cortex (mPFC, blue line) of healthy subjects during the performance of a visual tracking task (gray patches along time line). Normally, these activations and deactivations are anti-correlated during the task (example shown at arrow). The middle panel shows the same information obtained from chronic back pain (CBP) patients but there is a loss of the anti-correlated BOLD responses. The lower panel displays the results of a conjunction analysis of the correlated networks, which includes only voxels correlated or anti-correlated with five of the six selected “seed” regions (see text). Correlations of task-related activations (red) and default network deactivations (blue) in healthy subjects (left) and CBP patients (right) are shown on a standardized flattened cortical map. There is an obvious loss of task-related correlated networks in the patient group. See text for additional discussion of these results. Adapted from Baliki *et al.* (2008).

Structural changes in chronically painful conditions

The changes in the resting brain noted above raise the question as to whether chronic pain is associated, either causally or consequentially, with long-term plastic changes in brain function and structure. In [Chapter 7](#), we discussed

the functional and anatomical changes that are associated with the various causes of neuropathic pain. There, we noted the physiological and histological consequences of the denervation that follows peripheral or central injury or of the abnormal spontaneous discharge of nociceptive afferents that may accompany inflammation or neuronal damage. The relationship of the structural changes to chronic pain was based on evidence obtained from controlled animal experiments or on clinical observations that included laboratory evidence about the location and pathological characteristics of the proximate causative lesion.

Within the past decade, the imaging technique of voxel-based morphometry (VBM) has been used to detect decreases, and in some cases increases, in the volume and/or density of gray matter tissue in the brains of patients with chronic pain when compared with healthy control subjects. The VBM method has been presented and critically reviewed in some detail (Ashburner and Friston, 2000, 2001; Bookstein, 2001; Ashburner *et al.*, 2003) and its use in clinical neurology and in studies of chronic pain has been critically reviewed recently (May and Gaser, 2006; May, 2008). The method of VBM uses an automated algorithm to identify the differential physical characteristics of brain tissue and isolate, at the voxel level, samples of cortical or subcortical brain tissue and compare the volume and other radiological characteristics of this sample between or among groups of individuals. The accuracy of the method depends heavily on the accuracy and reproducibility of the anatomical registration and eventual standardization of the images but, in general, there has been some consistency of the results of VBM studies in a variety of neurological and psychiatric conditions. May and Gaser, for example, list 20 different clinical conditions (e.g. schizophrenia, depression, Huntington's disease, post-traumatic stress disorder, chronic fatigue syndrome, etc.) in which VBM measurements have revealed abnormalities (May and Gaser, 2006). A problem with VBM is the interpretation of the results in terms of histology. Changes in the amount of radiologically identified gray matter are not specific at the cellular or subcellular level and may, for example, reflect some combination of anatomical alterations in glia, neurons or neuronal components such as dendrites and synapses. Because of the smoothing process involved, changes in interstitial space could also make some contribution to the results of VBM analysis.

Despite these caveats, it is important to recognize that the structural changes revealed by VBM and related computational methods are likely to be pathophysiologically significant. Several studies of both neuropathic and non-neuropathic pain have provided evidence that chronic pain is associated with structural changes in the resting brain, many of which involve the prefrontal and cingulate cortices (for review, see May, 2008). Apkarian and colleagues showed that, compared with normal subjects, patients with chronic low back pain, including

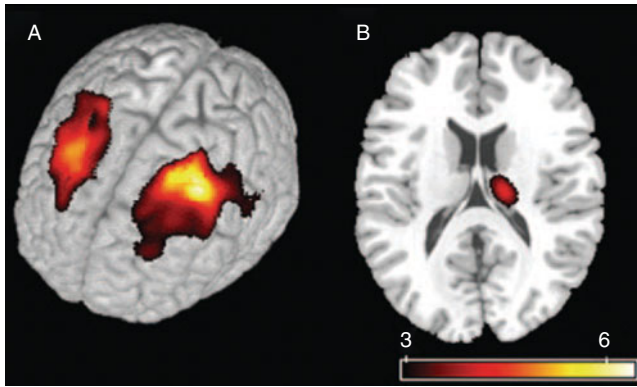


Fig. 8.4. Voxel-based morphometric (VBM) non-parametric analysis reveals reduced cortical (A, bilateral dorsolateral prefrontal cortex) and right thalamic gray matter (B) in the resting brain of chronic back pain (CBP) patients compared with healthy control subjects (contrast image of controls – CBP patients). Color bar indicates pseudo-t values. Adapted from Apkarian *et al.* (2004b).

those with clinical findings consistent with neuropathic pain, had gray matter volume loss in the prefrontal (more specifically, bilaterally in the DLPFC) cortex and thalamus (Fig. 8.4) and that the degree of volume loss correlated with the duration and, in the case of the DLPFC, psychological aspects of the chronic neuropathic pain (Apkarian *et al.*, 2004b). The authors favor the interpretation that the regional volume loss reflects a cellular degenerative process because an earlier *in vivo* MR spectroscopy study of back pain patients revealed reduced *n*-acetyl aspartate and glucose in the DLPFC of these patients compared with healthy individuals (Grachev *et al.*, 2000). Davis *et al.* (2008) have used a specialized analysis to detect thinning of the right anterior cingulate and bilateral insular cortices in patients with irritable bowel syndrome; a VBM analysis also revealed a loss of medial and anterior thalamic gray matter in these patients. And in a follow-up of their study of pain habituation in healthy subjects receiving repetitive noxious heat stimulation during 8 days (see Chapter 5), Teutsch *et al.* (2008) detected an increase of gray matter in the medial prefrontal, inferior parietal, medial temporal and postcentral cortices; these increases had receded when imaging was repeated a year later. It is notable that this increase in gray matter was accompanied, as in their earlier study, by a significant increase in the heat pain threshold, which persisted 3 weeks later but had returned to pre-experimental values when examined a year later. The authors comment on the difference between their results and those observed in chronic pain patients who show instead a reduction of gray matter in some of these same areas, notably the prefrontal cortex and anterior cingulate gyrus.

Imaging allodynia and hyperalgesia

As discussed in [Chapter 7](#), allodynia and hyperalgesia are common symptoms in patients with neuropathic pain of peripheral or central origin. In several imaging studies, allodynia is associated with cerebral activity changes that are not found during normal innocuous or noxious stimulation; these changes often involve the prefrontal cortex. In a PET (H_2^{15}O) study of intradermal capsaicin-induced tactile allodynia in healthy individuals, brush-evoked allodynia, in comparison with the pain of capsaicin, was associated with greater activation bilaterally of the inferior prefrontal cortex (Iadarola *et al.*, 1998). Similarly, capsaicin-induced heat allodynia, compared with contact heat pain of equal intensity, is associated with a unique pattern of activation involving the medial thalamus and orbitofrontal cortex (Lorenz *et al.*, 2002; Casey *et al.*, 2003; Lorenz *et al.*, 2003). In another PET study of capsaicin-induced tactile (brush-evoked) allodynia in healthy individuals, the orbitofrontal and ipsilateral anterior insular cortices were active during allodynic stimulation when compared with the rest (no stimulus) condition although only the contralateral sensory association cortex (Brodmann areas 5 and 7) was active in comparison with the ongoing pain of capsaicin (Witting *et al.*, 2001). In a follow-up study of nine patients with brush allodynia following nerve injury, these investigators found that, compared directly with innocuous brushing of the clinically normal side, allodynic brushing of the affected side was associated with significantly stronger PET activations in the orbitofrontal cortex and ipsilateral insula; in addition, normal, but not allodynic, brushing failed to activate the primary (SI) somatosensory cortex ([Fig. 8.5](#)) (Witting *et al.*, 2006). (The lack of response in the SI cortex could be related to a subsequent finding that tactile discrimination and the SI BOLD response to innocuous electrical stimulation is reduced in patients with complex regional pain syndrome (CRPS), correlating with the level of sustained clinical pain (Pleger *et al.*, 2006).) Lorenz and colleagues showed that, during experimental heat allodynia, activity in the dorsolateral prefrontal cortex may modulate the affective component of pain by changing the functional connectivity between the midbrain and thalamus ([Fig. 8.6](#)) (Lorenz *et al.*, 2003). The observations cited above suggest that activity in certain prefrontal, and specifically orbitofrontal, structures is an important, perhaps defining, component in the experience of allodynic pain compared with the normal pain experience.

Different types and causes of allodynia and hyperalgesia may be associated with different patterns of activation. In a VOI-directed H_2^{15}O PET study of five patients with brush allodynia from traumatic mononeuropathy, allodynic stimulation, when contrasted with normal touch, activated the contralateral posterior parietal cortex, periaqueductal gray (PAG) and thalamus bilaterally

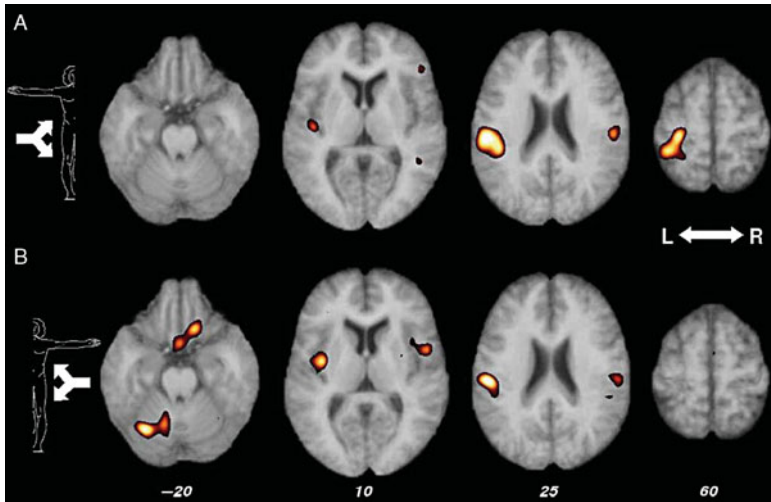


Fig. 8.5. A series of PET activations during brush-evoked allodynia in patients with nerve injury pain. Top row (A): brushing of normal side evokes responses in (left to right) the contralateral insula, bilateral SII, and contralateral SI and sensory association (Brodmann area 5) cortices. Bottom row (B): brush allodynia is associated with activity in (left to right) the cerebellum and orbitofrontal cortex, bilateral insula and bilateral SII cortices. Post-hoc comparisons, using main contrast activations as masks, showed that the orbitofrontal cortex, ipsilateral insula and cerebellum were more active during allodynia and that the SI and sensory association cortex (Brodmann area 5) were more active during normal brushing. Adapted from Witting *et al.* (2006).

(Petrovic *et al.*, 1999). In addition, rCBF in the anterior cingulate and right anterior insular cortices covaried with allodynic intensity. Peyron and colleagues used $H_2^{15}O$ PET in a global search (brainstem and cerebellum excluded) to study the allodynic responses in a parallel comparison study of nine patients with CPSP following lateral medullary infarction (Wallenberg's syndrome) (Peyron *et al.*, 1998). Although these investigators did not report on resting asymmetries, they noted that normally innocuous cold stimulation on the pathological side produced an exaggerated response in the contralateral thalamus (Fig. 8.7) and in the somatosensory (SI, SII), inferior parietal, anterior insular and medial prefrontal cortices; there was also a lack of response and even deactivation in the anterior cingulate gyrus. The abnormal response in the anterior cingulate gyrus is notable, given the role played by this structure in descending pain modulation (Chapter 5). Although activity in the medial prefrontal cortex was present also in this study of cold allodynia, the differences in allodynia-associated activation, compared with the studies cited above, may be affected also by distinct pathophysiological characteristics of Wallenberg's syndrome and by the type of

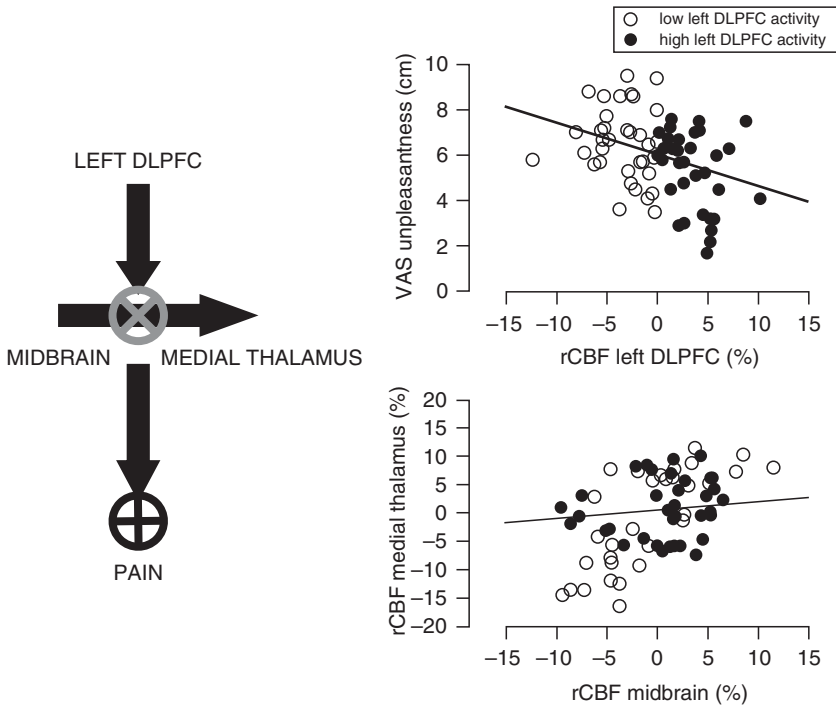


Fig. 8.6. In the human capsaicin model of heat allodynia, the visual analog scale (VAS) rating of unpleasantness is reduced when activity (rCBF) in the left dorsolateral prefrontal cortex (DLPFC) is above the median level (right upper panel). During this higher level of DLPFC activity, the correlation between activity in the midbrain and medial thalamus, a measure of functional connectivity, is reduced (right lower panel). The proposed effect of left DLPFC activity in this condition is summarized in the diagram at left. The DLPFC activity may reduce the affective component of heat allodynia by attenuating the ascending flow of nociceptive information between midbrain structures such as the periaqueductal gray and the medial thalamus. Data from Lorenz *et al.* (2003).

allodynia (cold) tested in this study. The effect of these clinical pathophysiological and stimulation variables is likely to be important in the interpretation of studies of a heterogeneous clinical population and mixed forms of allodynic stimulation. When both cold-mechanical and pure mechanical stimuli were used in a fixed-effects analysis of allodynia in 27 neuropathic pain cases of mixed etiology, a parallel comparison showed that the major effect of allodynic stimulation was an additional activation of the ipsilateral component of structures activated contralaterally by non-allodynic control stimulation plus an ipsilateral activation of posterior parietal and anterior cingulate cortices (Peyron *et al.*, 2004). The significance of ipsilateral activations is suggested also by the results of an unusual case of central pain and contralateral multimodal allodynia

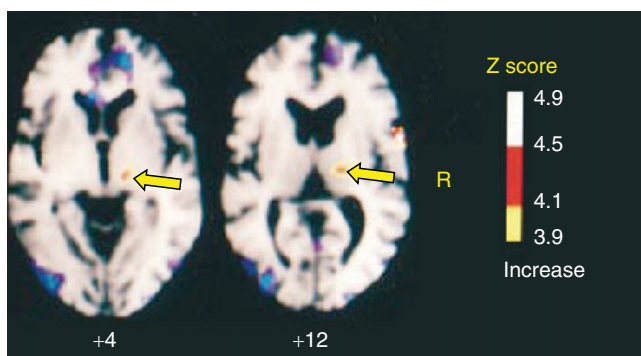


Fig. 8.7. Thalamic response ($H_2^{15}O$ PET; arrows) to normally innocuous cold stimulation in patients with CPSP (lateral medullary infarction) experiencing allodynia. This response was absent during stimulation of the unaffected side. Adapted from Peyron *et al.* (1998).

following embolic infarctions within the right anterior cingulate, SI, SII and insular cortices (Peyron *et al.*, 2000). A combined $H_2^{15}O$ PET and fMRI study showed that cold-rubbing allodynia, but not innocuous cold, was associated with bilateral insular activations in this patient. (Anterior cingulate activation was not detected in either hemisphere but there was generalized resting hypoperfusion of the right frontal lobe.)

The different effects of different types of hyperalgesia were demonstrated in the study of Maihofner and Handwerker (2005), who showed that capsaicin-induced thermal and pinprick hyperalgesia in 12 healthy individuals was associated with different fMRI cerebral activation patterns even though the pain intensities were equal. Although both types of hyperalgesia were associated with activation of the same structures, a direct statistical comparison revealed that, compared with A δ fiber-mediated pinprick secondary hyperalgesia, C fiber-mediated primary thermal hyperalgesia was associated uniquely with increased activation of bilateral anterior insular, medial frontal and cingulate cortices, and the contralateral superior and inferior frontal cortex (Fig. 8.8).

Increased activation of the cingulate, medial frontal and anterior insular cortices was correlated with the perceived unpleasantness of the hyperalgesic stimulation. In accord with the differential frontal responses of the studies cited above, it is notable that both types of hyperalgesia, when compared with the normal noxious mechanical or heat stimuli, were associated with the activation of the inferior frontal cortex. In a subsequent fMRI study of mechanical allodynia in 12 patients with complex regional pain syndrome, including those without (CRPS 1) and those with (CRPS 2) a nerve lesion, this team of investigators found that, compared directly with innocuous stimulation of the normal side, gentle

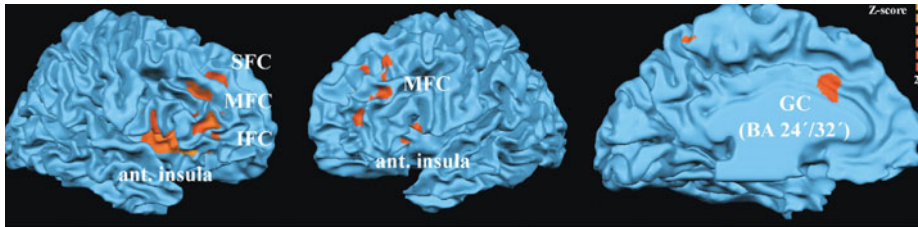


Fig. 8.8. Differences between types of equally intense hyperalgesias. Shown are cerebral activations appearing in the contrast of primary heat hyperalgesia minus secondary pinprick hyperalgesia in capsaicin-induced hyperalgesia in normal humans. The level of activation in the cingulate gyrus (GC), medial prefrontal cortex (MFC) and anterior insula correlated with the level of unpleasantness. SFC and IFC, superior and inferior frontal cortex. Adapted from Maihofner and Handwerker (2005).

brushing of the affected hand evoked additional activity in the motor, parietal association, anterior cingulate and frontal cortices (Maihofner *et al.*, 2006). Activity in the somatosensory, somatosensory association, insular and anterior cingulate cortices remained when the pain ratings were used as analytical predictors, suggesting a role for these structures in the encoding of allodynia.

Differences in fMRI activations related to differences in types of stimulation and clinical condition are evident also in the study of Becerra and colleagues, who examined six patients with right-sided trigeminal neuropathy characterized by chronic, spontaneous and evoked thermal (heat and cold) hyperalgesia and brush-evoked allodynia within the maxillary division (V2) of the trigeminal innervation territory (Becerra *et al.*, 2006). Activation differences between the affected and unaffected V2 divisions were different among the brush, cold, and heat stimuli (Fig. 8.9). In discussion, the authors note that the activations specific to allodynic and hyperalgesic stimuli include both trigeminal sensory pathways and structures putatively involved in the elaboration of the hedonic and cognitive aspects of pain, in particular the inferior and orbital frontal cortices.

Spontaneous ongoing pain

In studying patients, it may be important to consider also the level of both ongoing and evoked pain because activation intensity in the caudal portion of the anterior insula has been shown to vary with the perceived intensity of evoked allodynia while the rostral part of this structure is a member of a group of structures that appears to encode for the intensity of ongoing clinical pain (Schweinhardt *et al.*, 2006). Variation in the level of spontaneous pain is an important consideration also because the variability of spontaneous pain may vary among chronic pain conditions and this difference in variability may be reflected in imaging studies (Foss *et al.*, 2006). In examining 46 consecutive

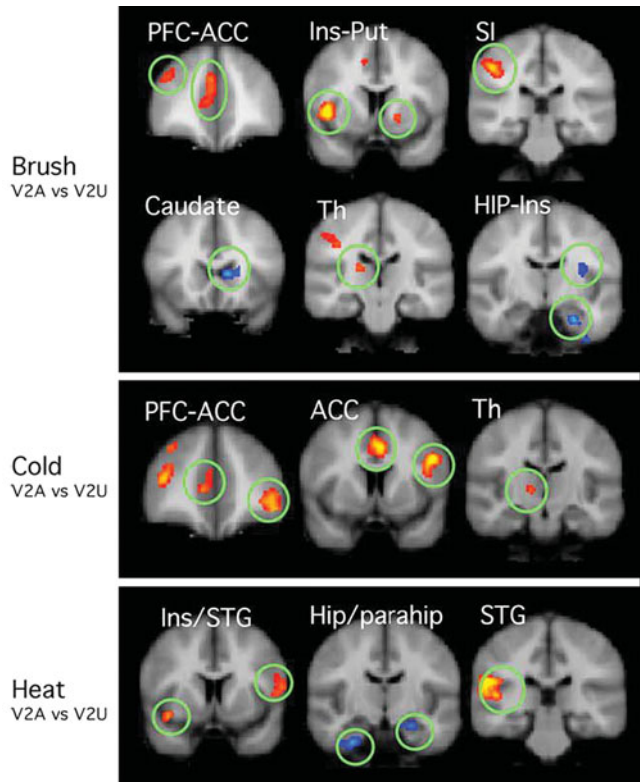


Fig. 8.9. Different forms of allodynia are associated with different activations in six patients with both spontaneous and evoked pain in the right maxillary (V2) division of the trigeminal nerve. During scanning, there was a significant group difference in perceived pain intensity between the affected (V2A) and unaffected (V2U) sides for brush and cold, but not heat, allodynia; however, perceived heat intensity was greater than either brush or cold on both affected and unaffected sides. Group activation differences between V2A and V2U stimulation (V2A – V2U) are shown as increases (red, yellow) and decreases (blue) in the fMRI BOLD signal during brush (top row), cold (middle row) or heat (bottom row) stimulation; right hemisphere on the reader’s right. PFC, prefrontal cortex; ACC, anterior cingulate cortex; Ins, insula; Put, putamen; SI, primary somatosensory cortex; Th, thalamus; HIP, hippocampus; STG, superior temporal gyrus. Adapted from Becerra *et al.* (2006).

patients with syringomyelia, Ducreux *et al.* (2006) found no difference between syringomyelia patients with or without neuropathic pain in the degree or extent of pain and temperature sensory deficits, indicating that a loss of spinothalamic tract function alone was not sufficient for the development of central pain. However, they determined that, within the area of maximum sensory deficit, patients with both spontaneous pain and allodynia (brush, pressure or cold) had lower heat and higher cold detection thresholds than patients with only

spontaneous pain or no pain. This result suggests that allodynia may be mediated by different mechanisms than spontaneous ongoing pain and depends on the integrity of the remaining thermosensory mechanisms. In addition, thermosensory deficits were less severe in patients with cold allodynia compared with those with brush allodynia, suggesting again a difference in underlying mechanisms between these two symptoms. In an fMRI investigation of a subgroup of these patients with cold and/or brush allodynia, allodynic stimulation was associated with an activation pattern similar to that observed in response to noxious cold (4 °C) in healthy participants and different from the activations produced by innocuous cold (22 °C) or brushing in healthy subjects (Fig. 8.10). In summarizing their imaging results, the authors emphasize the consistent activation of the prefrontal cortex, especially the DLPFC, as a distinguishing feature of the pathological allodynia in these patients with central pain. It is notable that, in contrast with an fMRI study of spinal cord injury patients without central pain, these prefrontal activations were not observed in response to noxious electrical stimulation; there was, however, evidence for an enhanced activation, compared with healthy subjects, of the dorsal anterior cingulate cortex and medial midbrain during fear conditioning (Nicotra *et al.*, 2006).

Modulation and treatment of neuropathic pain

The heat-capsaicin model was used to examine the effect of a demanding cognitive task (visual memory/recognition) on tonic heat hyperalgesia in healthy individuals (Wiech *et al.*, 2005). When the tonic heat pain (21 s duration) was near intolerable intensities during fMRI acquisition, there was increased activation (compared with low intensity pain) of the orbitofrontal, medial frontal, insular and cerebellar cortices; these activations were attenuated during the most demanding version of the task, which alone activated the premotor, lateral and medial prefrontal, insular, parietal, visual and cerebellar cortices. This result demonstrated modulation of the brain responses to hyperalgesia by cognitive mechanisms in normal subjects.

To examine treatment effects in chronic pathological conditions, Geha *et al.* (2007) extracted the fMRI BOLD responses during increases of spontaneous pain in 11 patients with post-herpetic neuralgia. The patients tracked the variations in pain intensity with a visual tracking device during scanning sessions; a separate visual tracking task served as a control. Questionnaires were used to document changes in other aspects of their clinical pain. Patients were scanned before, 6 hours after and 2 weeks after the application of a 5% lidocaine patch to the affected region. Significant BOLD responses associated with spontaneous pain (compared with the visual tracking task) included the bilateral orbitofrontal, right mid-frontal, mid- and rostral left anterior cingulate, left inferior

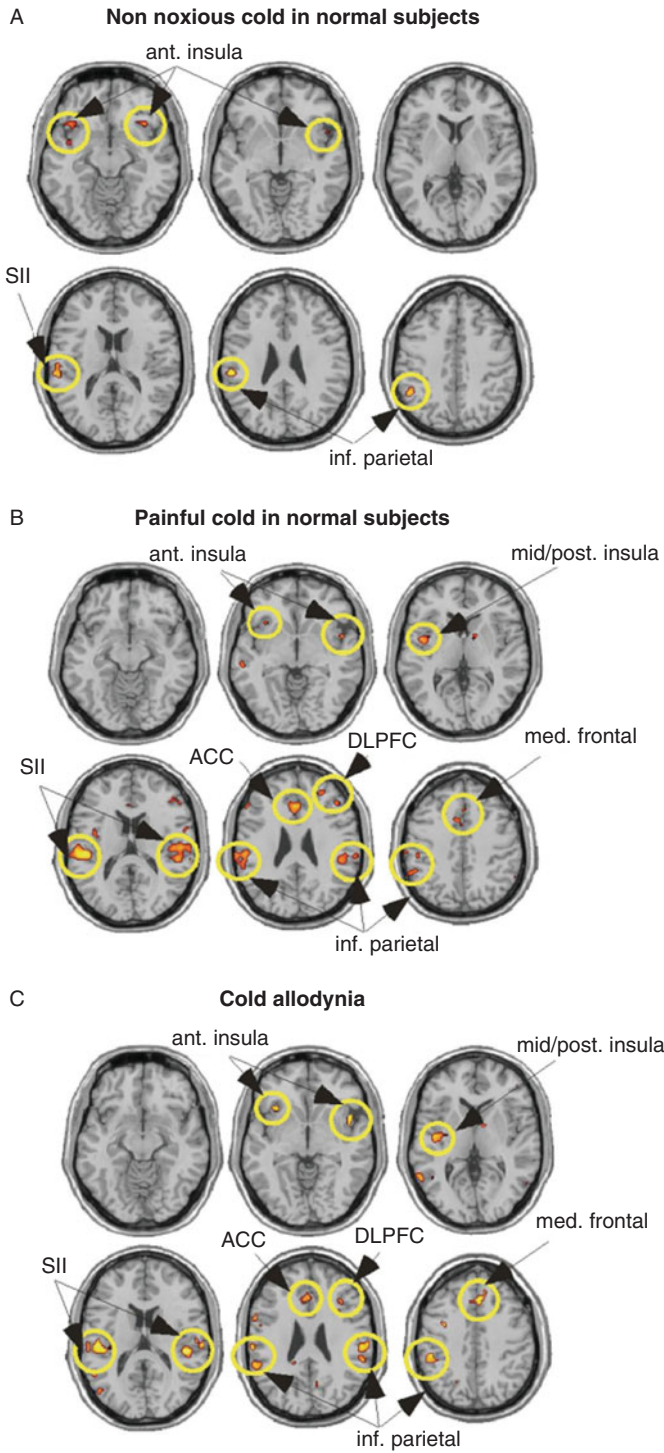


Fig. 8.10.

temporal, bilateral insular and bilateral secondary somatosensory (SII) cortices; subcortical structures included the left cerebellum, bilateral amygdala, right hypothalamus, bilateral ventral striatum and, before treatment, the thalamus. Over the course of treatment, the sensory-discriminative and hedonic aspects of pain were reduced as shown by the rating scores and questionnaire responses. Based on the decreased ratings for spontaneous pain, the lidocaine effect was modeled as a decrease across treatment sessions and correlated with the activity in brain regions showing positive activity during increases in spontaneous pain. This analysis revealed decreasing activity during treatment in the bilateral ventral striatum, midline ventral tegmentum, left thalamus, hypothalamus, and the left insular and somatosensory and somatomotor cortices (M1/SI, SII); increased BOLD activity was noted in the right inferior frontal and insular cortices (Fig. 8.11). When the correlation analysis included seven neuropathic pain descriptors that included “unpleasant,” “sensitive” and “intense,” activations in the bilateral ventral striatum, left insular cortex and left amygdala were seen to increase and activations in the anterior cingulate cortex decrease related to the treatment effect. The authors emphasize the close relationship of activity in the bilateral ventral striatum with the hedonic aspects of pain and the probable rewarding effects of treatment. As the authors note, the mechanism of the treatment effect could include a placebo effect because a placebo control could not be included in this experimental design.

Several studies have examined the effect of stimulation over the motor cortex area in the treatment of neuropathic pain. In a PET activation study, Garcia-Larrea *et al.* (1999) examined rCBF responses during motor cortex stimulation (MCS) in ten patients with intractable neuropathic pain. Stimulation-related increases in rCBF were found in the ventrolateral and medial thalamus as well as in the anterior insula, upper midbrain, anterior perigenual cingulate and orbitofrontal cortex. The authors suggested that MCS activates a circuit that includes a corticothalamic pathway to the medial thalamus which could attenuate the emotional and affective component of chronic pain. In a review of this

Caption for Fig. 8.10. Parallel comparisons of BOLD activations during (A) innocuous (22 °C) cold stimulation or (B) noxious (4 °C) cold stimulation of the right hand in normal subjects with (C) allodynic (22 °C) cold stimulation of the right hand in patients with central pain and allodynia. Labeled structures include the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC). Left brain is on reader's left. Cold allodynia in patients is associated with an activation pattern that is similar to that during cold pain in normal subjects and differs from normal innocuous cold activations primarily by the activation of the DLPFC and ACC. Adapted from Ducreux *et al.* (2006).

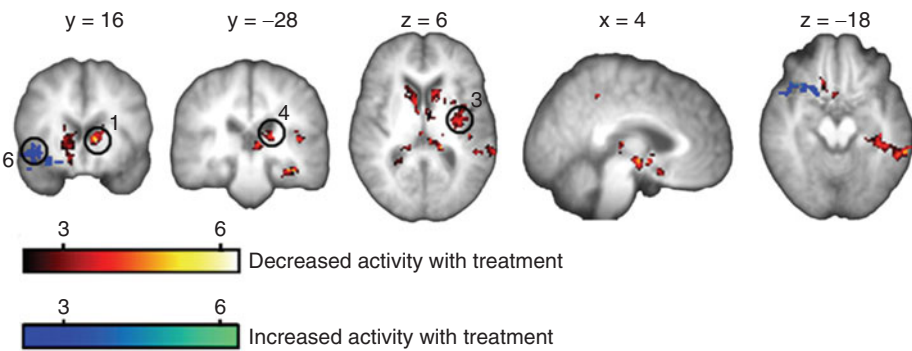


Fig. 8.11. Brain regions showing a positive (red) or negative (blue) BOLD activation during spontaneous increases in post-herpetic neuralgia pain and significant correlations with reduced spontaneous pain during lidocaine patch treatment. BOLD responses are contrasted with activations during a control visual tracking task. Circled regions were selected for additional analysis (see text; 1, L ventral striatum; 3, L mid-insula; 4, L posterior thalamus; and 6, R anterior insula). Adapted from Geha *et al.* (2007).

subject, two of the authors suggest that, based on imaging and electrophysiological studies, a delayed MCS-mediated activation of this circuit involves the midbrain periaqueductal gray and could explain the delayed and prolonged effect of MCS in the relief of clinical pain for hours or days after the stimulation is terminated (Garcia-Larrea and Peyron, 2007). This suggestion receives some support from the PET investigation of six patients with chronic deafferentation pain (Kishima *et al.*, 2007). These investigators also observed immediate MCS activation of the posterior thalamus and insula followed, in the early post-stimulus phase, by rCBF increases in the orbitofrontal cortex and posterior insula and later by activations in the anterior cingulate cortex.

Additional support for MCS-mediated activation of a medial descending control mechanism comes from another PET $H_2^{15}O$ study of 19 patients with medically refractory neuropathic pain of both peripheral and central origin (Peyron *et al.*, 2007). When compared with the baseline condition, MCS activated the contralateral anterior mid-cingulate and dorsolateral prefrontal cortices. However, activations continued to appear in the mid-, pregenual cingulate and orbitofrontal cortices as well as the thalamus and medial midbrain (periaqueductal or PAG region) for as long as 75 minutes after MCS was terminated; these late, but not the early, activations showed a positive relationship with the degree of clinical pain relief (regression analysis). A functional connectivity analysis (Fig. 8.12) revealed a significant correlation among the pregenual anterior cingulate, medial midbrain (PAG) and basal ganglia during this post-MCS period of hypalgesia.

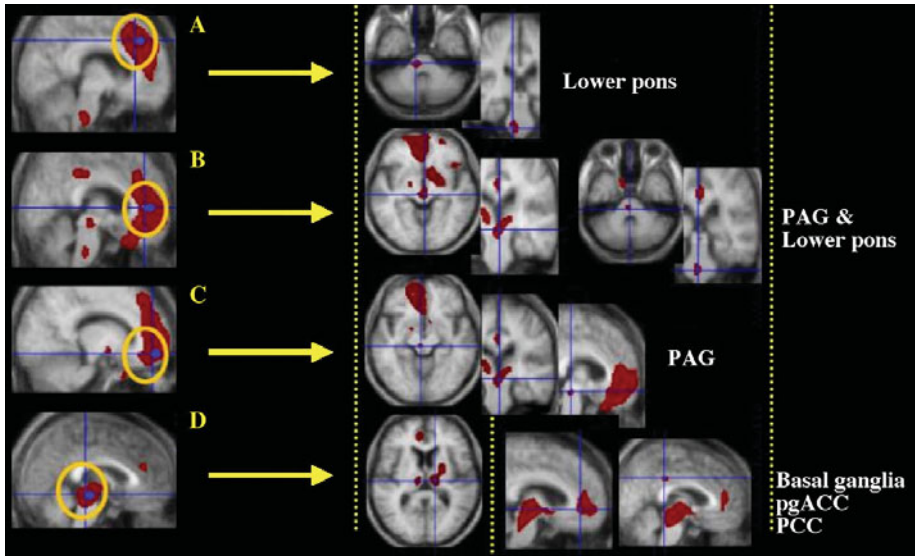


Fig. 8.12. Functional connectivity analysis of structures activated during the delayed hypalgesic effect on neuropathic pain following the termination of motor cortex stimulation. Left column shows the activations in contrast with the baseline (prestimulus) condition: A, mid-anterior cingulate cortex; B, pregenual anterior cingulate cortex (pg ACC); C, orbitofrontal cortex; and D, medial rostral brainstem. Arrows point to significantly correlated activity in the structures shown and listed in the adjacent column. The major connectivity is among the pregenual ACC and mesencephalon, basal ganglia, right insula and posterior cingulate. Adapted from Peyron *et al.* (2007).

To investigate further the mechanisms underlying this effect of MCS, Maarrawi and colleagues examined the binding potential (BP) of opioid receptors in eight neuropathic pain patients (Maarrawi *et al.*, 2007b). In comparing pre- and post-operative PET scans, these investigators observed that clinical pain relief was correlated with decreased opioid receptor BP (consistent with release of endogenous opioid) in the mid-anterior cingulate cortex and medial rostral midbrain (PAG region). Taken together, the observations cited above suggest that MCS pain relief is attributable in large part to the activation of a medial frontal cortical system that releases endogenous opioids for the relief of both hedonic and discriminative aspects of clinical pain.

Electrical stimulation in the thalamus has been used also in the treatment of neuropathic pain (Chapter 7). The results of some studies suggest that the mechanisms associated with pain relief during thalamic stimulation may be distinct from those involved in the effect of MCS. In a PET activation study of five neuropathic pain patients with a history of successful pain relief, thalamic

stimulation produced thermal paresthesias and activation in the vicinity of the electrodes and in the insular cortex contralateral to the pain (Duncan *et al.*, 1998). The authors suggest that the pain-relieving effects may be due to thermosensory modulation of nociceptive pathways. In another PET activation study, thalamic stimulation produced immediate and sustained activation of the anterior cingulate cortex and a more posterior delayed activation in addition to activations in the motor cortex, globus pallidus and cerebellum; however only two of the five patients in this study obtained pain relief during or after thalamic stimulation (Davis *et al.*, 2000).

A PET activation study of a patient with refractory facial pain following removal of an adenocarcinoma revealed a different activation pattern associated with clinically significant pain relief (Kupers *et al.*, 2000). This patient's pain had clinical characteristics consistent with a neuropathic origin (pinprick and thermosensory loss with stinging and shooting pain); he obtained pain relief within minutes of stimulation in the territory of the ventral posterior medial thalamus. The pain relief persisted for 2–4 hours after stimulation terminated but then the pain returned to the previous near-intolerable level (8–10/10 level). In a single-subject PET activation study (3D, $H_2^{15}O$), the contrast of the baseline (prestimulation pain) condition with the pain-free condition following stimulus termination revealed increased rCBF in the prefrontal (including orbitofrontal and cingulate) and anterior insular cortices and in the hypothalamus and rostral medial midbrain (PAG area; Fig. 8.13). These structures are therefore active during the painful state and show reduced activity following the stimulation. The thalamic stimulation alone (stimulation on vs. stimulation off, both without pain) activated the amygdala and the ventromedial and anterior insular cortices. The authors emphasize the significance of activity in the frontal cortex and limbic system structures (hypothalamus, PAG) in this chronic pain condition.

Group differences in hypothalamic and amygdala activations between healthy individuals and patients with carpal tunnel syndrome were found also in an fMRI comparison of acupuncture and sham acupuncture (Napadow *et al.*, 2007); however, although acupuncture is associated with the activation of structures that are active in acute pain and pain modulation (Biella *et al.*, 2001), the relationship of these results to any pain-relieving or clinical effects of this treatment modality is presently uncertain.

Summary

Imaging studies show that chronic neuropathic pain differs from acute pain in several respects. First, at least some chronic neuropathic pain is associated with both functional and structural changes in the “resting” or “default”

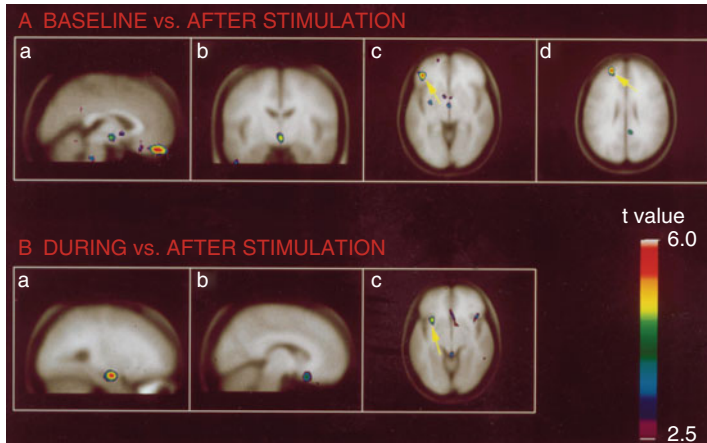


Fig. 8.13. A PET activation study of a patient with refractory facial neuropathic pain relieved by electrical stimulation in the territory of the ventral posterior medial thalamus. (A) Contrast image of baseline (prestimulus) painful condition vs. the pain-free condition after the end of thalamic stimulation. The painful condition is associated with increased rCBF in the orbitofrontal (a), inferior (c) and superior (d) frontal cortices, and the hypothalamus (b). (B) Thalamic stimulation alone (stimulation on – stimulation off, both without pain) activated the amygdala (a), the inferior frontal (b) and anterior insular (c) cortices. Adapted from Kupers *et al.* (2000).

brain that is not consciously engaged in a task. Whether these changes are entirely the direct consequence of the pain itself or of long-term cerebral functions related to the adjustment to pain is yet to be determined. The degree to which these changes persist remains uncertain also. In any case, the changes appear to involve several cerebral structures but perhaps most often the pre-frontal cortex; this may therefore reflect long-term cognitive and emotional adjustments to the presence of abnormal somatic or visceral afferent inputs in an injured nervous system. The extent to which these changes depend on ongoing nociceptive or other sensory input is also uncertain and is likely to vary among clinical conditions.

Second, chronic neuropathic pain alters the response to normally innocuous and noxious stimuli, often resulting in allodynia and hyperalgesia, respectively. To an as yet unknown degree, these abnormalities may depend on the changes in the physiology of the default brain. Whatever the cause, allodynia and hyperalgesia are associated with brain activation patterns that are quite different from the activations during acute, non-neuropathic pain. Many of these response changes are likely to be transient and input dependent but their persistence

remains to be assessed in various clinical conditions. Nonetheless, it cannot be assumed that somatic or visceral afferent inputs are going to be processed by the central nociceptive mechanisms used for acute pain.

Third, in accord with the above observations, the treatments for chronically painful neuropathic conditions cannot be based entirely on the neurobiology of acute nociceptive mechanisms. Although the available information is scanty and somewhat confusing, it appears that some major treatment effects are acting, not on structures associated primarily with nociceptive discriminative sensory mechanisms, but on neural systems mediating hedonic, cognitive and autonomic functions. In addition, it appears that several components of the prefrontal cortex participate in either the maintenance or modulation of chronic neuropathic pain states. Eliminating or reducing nociceptive input will continue to be important but may not be sufficient when central modulatory processes are impaired. Therefore, the development of effective treatments may have to include the recruitment and enhancement of endogenous top-down forebrain modulatory mechanisms, hopefully by implementing physiological, non-invasive strategies.

Other chronically painful conditions

In many of the chronically painful conditions considered below, the pathological source of nociceptive input or abnormal nociceptive function is unclear or at least controversial. In neuropathic pain, clinical evaluation uncovers evidence of injury or disease affecting the peripheral or central nervous system. When pain occurs in patients with arthritis or cancer, clinical evaluation usually reveals evidence for extra-neuronal tissue damage with an associated inflammatory process. But there is no broad consensus about the pathology leading to pain in patients with fibromyalgia, irritable bowel syndrome, burning mouth syndrome, primary headache disorders or “idiopathic” low back pain. Any resolution of these issues will require far more research and discussion than is possible here. Nonetheless, many of the functional imaging studies of chronic non-neuropathic pain suggest, as in neuropathic pain, that central nociceptive processing in these patients is abnormal and that this abnormality either causes or contributes to the chronic pain they experience. Whether these changes are acquired, developmental, genetic, or due to some combination of these factors cannot be determined from the evidence currently available.

Although cancer is sometimes a cause of chronic pain and is a frequent and important clinical problem, there currently are no functional imaging studies, with the exception of Di Piero *et al.* (1991), cited above, specifically addressing the issue of pain-related brain responses in patients with cancer pain.

Sympathetically maintained pain (SMP) in complex regional pain syndrome 1 (CRPS 1)

According to the IASP Classification of Chronic Pain Syndromes II, CRPS Type I is a syndrome that usually develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is apparently disproportionate to the inciting event. It is associated at some point with evidence of edema, changes in skin blood flow, abnormal sudomotor activity in the region of the pain, or allodynia or hyperalgesia (Merskey and Bogduk, 1994).

Because this syndrome does not clearly involve injury to a major nerve, we consider it under the category of chronic pain (non-neuropathic) and thus distinct from CRPS 2. The syndrome as defined in the above document may follow stroke or other CNS injury but this condition is considered under the category of central pain syndromes and is obviously neuropathic. In some patients with non-neuropathic CRPS 1, the pain appears to be maintained by activity in the sympathetic efferent fibers because the pain is relieved by blocking sympathetic neuronal transmission with a local anesthetic; this is therefore referred to as sympathetically maintained pain (SMP). Apkarian *et al.* (2001) used fMRI to investigate brain activations during evoked heat pain in seven patients with SMP and no evidence for neuropathy according to pre- and post-sympathetic block sensory examination. Healthy participants ($n = 29$) included six subjects who received scans before and after sympathetic blockade; the remainder participated only in the warm vs. heat pain task. Brain activations were measured using a spatial and intensity integrated measure of the BOLD activity (Apkarian *et al.*, 1999). A within-patient group contrast of ongoing pain before and after sympathetic blocks revealed strong activity in the anterior cingulate and prefrontal cortices during spontaneous pain and during evoked heat pain (Fig. 8.14). A parallel VOI comparison with the healthy subjects showed that the patients had stronger prefrontal, but not parietal, cortical activity before sympathetic block. In addition, thalamic activity was reduced contralateral to the painful hand in patients. The authors suggest that these changes reflect a reorganization of cerebral resting activity and nociceptive responsiveness involving the prefrontal cortex and thalamus in this chronic pain condition.

Back pain

In a PET activation study of 16 patients with chronic back pain and 16 healthy control subjects, both groups showed activity in the thalamus, insula, mid-cingulate cortex, medial midbrain (PAG region), lentiform nucleus and cerebellum during cutaneous heat pain (Derbyshire *et al.*, 2002). Group comparisons

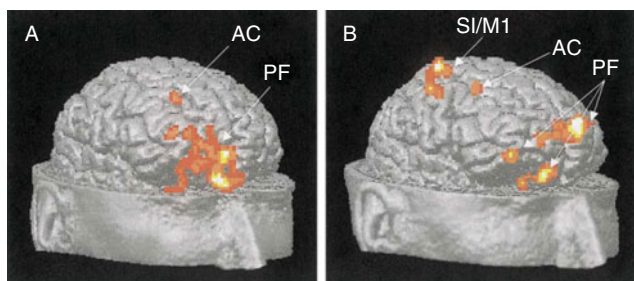


Fig. 8.14. Prefrontal and anterior cingulate cortical BOLD responses to noxious heat applied to the painful hands of seven patients with CRPS 1. (A) Contrast of the eight responses before minus four responses after sympathetic blocks relieved the ongoing pain. (B) Same contrast except for including four clinically unsuccessful sympathetic blocks in the before and after block comparison. The prefrontal and anterior cingulate cortical activations remain after including the unsuccessful blocks (B) but there is additional activation of the sensorimotor cortical areas. Adapted from Apkarian *et al.* (2001).

revealed small but statistically greater responses in the mid-cingulate, prefrontal and insular cortices among the healthy control group and a trend of greater response in the posterior cingulate cortex in the patient group. The authors did not consider these response differences sufficient to suggest abnormal nociceptive functions among the patients. However, Giesecke *et al.* (2004) found evidence for augmented nociceptive processing among patients with idiopathic low back pain of at least 12 months duration. In an fMRI investigation of healthy subjects, patients with fibromyalgia and patients with chronic back pain (screened to exclude neural damage), thumbnail pressure stimuli that were painless for healthy participants evoked pain in both groups of patients. In a parallel comparison among the three groups receiving these same stimuli, both patient groups had cerebral activations in the somatosensory (SI and SII), inferior parietal and cerebellar cortices; healthy subjects, however, activated only the contralateral SII cortex. When the stimuli were adjusted to be equally painful among the groups, qualitatively similar activations were present in all groups (contralateral SI and SII somatosensory, inferior parietal, insular and anterior cingulate cortices; ipsilateral SII and cerebellar cortices). Although direct among-group comparisons were not made, these results support the hypothesis that both groups of chronic pain patients have augmented central nociceptive processing systems.

Baliki and colleagues, however, did not find psychophysical or brain activity group differences when acutely noxious heat was applied to the backs of 11 healthy subjects and to 11 patients with chronic low back pain (Baliki *et al.*, 2006). In this fMRI investigation, the investigators examined the differences between

the brain responses during sustained spontaneous pain and transient acute increases in back pain. The participants performed a visual tracking task (control task for all participants) or tracked the intensity changes in ongoing back pain (two groups of 11 and 13 patients). The transient phase of acutely increasing pain was associated with activations in regions typically active during acute pain (right anterior and posterior insula, secondary somatosensory cortex, mid-cingulate cortex, primary somatosensory cortex (foot-leg region) and cerebellum. In contrast, during spontaneous high-level sustained pain, there was increased activity in the medial prefrontal and rostral anterior cingulate cortices (Fig. 8.15). The authors emphasize that the unique prefrontal cortical activity during spontaneous sustained pain may reflect the cognitive and emotional components of chronic, as compared with acute pain. This conjecture receives support from their additional analysis showing that, when contrasted with acute noxious heat stimulation, activity in the insula correlated with heat pain intensity while activity in the medial prefrontal cortex correlated only with the spontaneous pain in patients with low back pain.

In summary, these studies reveal differences in the brain activities of non-neuropathic chronic back pain patients compared with healthy individuals within the same age range. Although the brain activations during acute noxious mechanical stimuli may differ between groups and suggest a hyper-responsiveness among patients (Giesecke *et al.*, 2004), no difference was found when noxious heat stimuli were applied (Baliki *et al.*, 2006). The brain activation pattern during acute pain, however, may not be the distinguishing abnormality in chronic back pain; rather, the intense spontaneous sustained pain that characterizes this condition is associated uniquely with activity in the prefrontal cortex in this sample patient population.

Arthritis

In a PET activation study, the rCBF responses during heat pain of six patients with rheumatoid arthritis (RA) were compared directly with those of six age-matched healthy subjects (Jones and Derbyshire, 1997). The patients showed weaker responses in the medial prefrontal and anterior cingulate cortices. In a subsequent fMRI investigation of 20 RA patients, Schweinhardt *et al.* (2008) also noted reduced prefrontal cortical responses to contact heat pain compared with those evoked during the equally intense pain evoked by pressure over an involved tender joint. The activations during experimental heat pain in RA patients were otherwise similar to those reported in the literature for normal subjects. Of particular interest was the strong activation, only during painful joint stimulation, of the medial prefrontal cortex; this response correlated with measures of clinical depression and joint involvement and with the activation

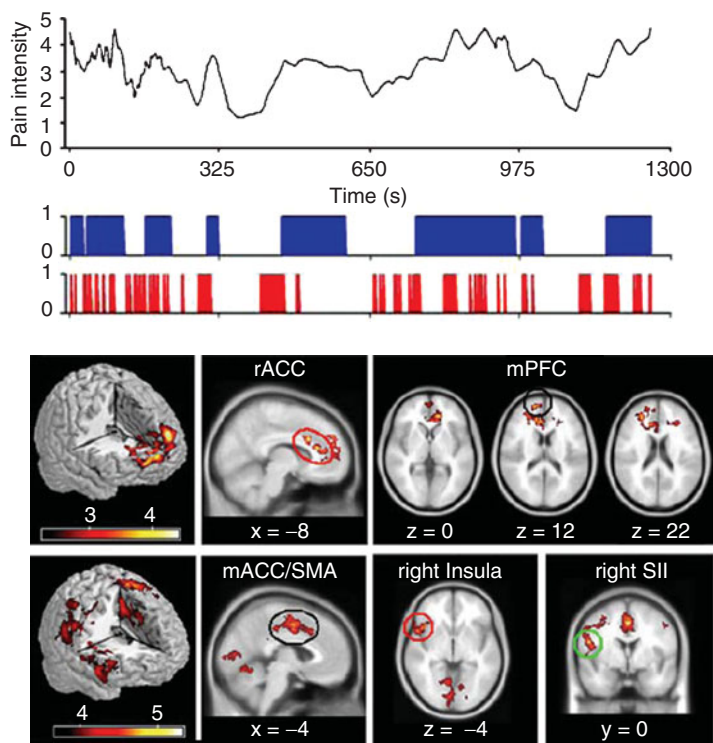


Fig. 8.15. Brain activity during sustained spontaneous and transiently increasing pain in patients with chronic low back pain. Top panel shows an example of a patient visually tracking pain intensity during an fMRI scan (upper tracings). The periods of most intense sustained spontaneous pain are shown in blue and periods of superimposed acute increases in back pain shown in red below the tracking record. Note that the two conditions show overlapping and non-overlapping periods. Middle panel shows BOLD activations during periods of maximum sustained pain. Bottom panel shows activations during transient acute increases in pain. Color bar indicates statistical levels of significance. rACC, rostral anterior cingulate cortex; mPFC, medial prefrontal cortex; mACC, mid-anterior cingulate cortex; SMA, supplementary motor area; SII, secondary somatosensory cortex. The parallel comparison of these two conditions shows that different brain regions are active during these two different conditions. Adapted from Baliki *et al.* (2006).

of several structures including the caudate nucleus and the dorsolateral prefrontal, posterior cingulate, medial temporal and posterior parietal cortices (Fig. 8.16).

These studies again show that the type of stimulation, particularly its relationship to the clinical pain condition, is likely to be critical for revealing the unique brain responses during chronic pain. In addition, as in neuropathic pain,

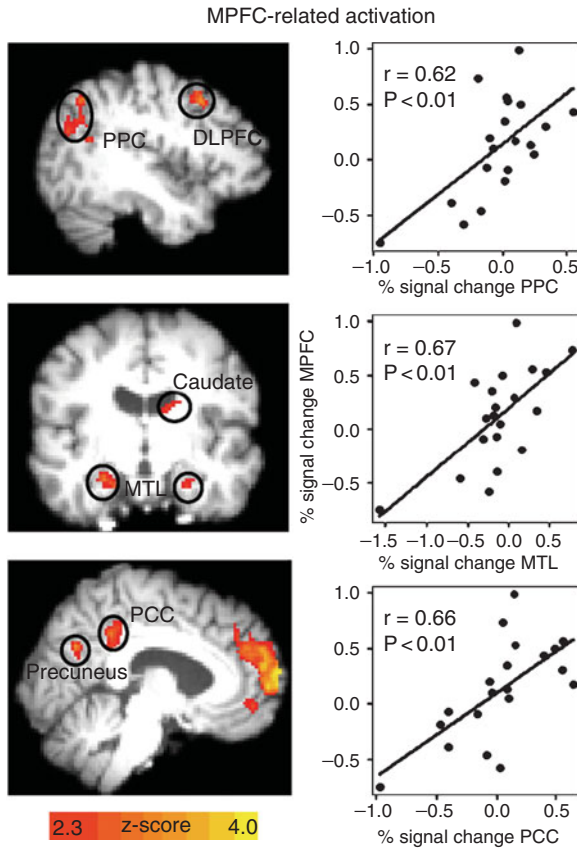


Fig. 8.16. Brain images (right hemisphere on reader's left) show BOLD activations during evoked joint pain in patients with rheumatoid arthritis and correlated with depression-related activation in the medial prefrontal cortex (MPFC) shown in the bottom image. Graphs show the linear regression between the normalized MPFC response and three correlated responses in the posterior parietal cortex (PPC), medial temporal lobe (MTL) and the posterior cingulate cortex (PCC). Color bar indicates the statistical measure (Z-score) of the activations. DLPFC, dorsolateral prefrontal cortex. Adapted from Schweinhardt *et al.* (2008).

abnormalities of prefrontal cortical activity seem to be an important component of the brain mechanisms mediating this type of chronic pain.

Headache

Primary headache disorders are those without a clinically identifiable source of nociceptive input such as an inflammatory meningitis or brain tumor. Examples of primary headache include migraine, cluster headache or “tension-type” headache (International Classification of Headache Disorders II;

<http://his-classification.org/en/>). Primary headaches are typically paroxysmal and brief (hours to days) and may not be widely accepted as chronically painful conditions. However, some patients suffer headaches frequently enough and for durations sufficiently long that they could be considered as having a chronic pain syndrome. Given the preceding evidence for cerebral response abnormalities among patients with chronic pain, it is important to consider whether chronic headache patients have similar differences in response to noxious stimulation. Unfortunately, the unpredictability and limited duration of most primary headaches severely limits the opportunity to examine the above question with functional imaging techniques. Most imaging studies have focused on the interictal or prodromal phases of the headache and not on whether headache patients have an abnormal response to noxious stimuli (Cohen and Goadsby, 2004).

Some studies have investigated the source of nociceptive input during the headache. In a PET activation study ($H_2^{15}O$) of patients with cluster headache, dilation of intracranial extraparenchymal vasculature was observed during nitroglycerine-induced headache, but this effect was seen also in the absence of headache and in capsaicin-induced head pain in healthy subjects (May *et al.*, 1999b). The pain-related brain activation during headache induction was similar to that reported in healthy individuals. In a PET (^{15}O butanol) study of nitroglycerine-induced cluster headache in four of seven patients, cerebral activations appeared in the right motor and premotor, right anterior cingulate, right insular and right inferior frontal cortices during headache compared with the resting pain-free condition. Dilation of intracranial extraparenchymal blood vessels was observed in both headache-responsive and non-responsive participants and, other than the right-sided predominance of the brain activations, there was no evidence for abnormal brain activation during pain (Hsieh *et al.*, 1996).

In a PET ($H_2^{15}O$) study of nine chronic cluster headache patients, nitroglycerine-evoked headache was accompanied by activation in the hypothalamus in addition to the expected pain-related activations in the contralateral thalamus, bilateral insulae and anterior cingulate cortex (May *et al.*, 1998). Hypothalamic activity was observed also in a single case study of a similar headache syndrome (May *et al.*, 1999a) but not in a case of spontaneous migraine headache (Bahra *et al.*, 2001); the hypothalamic activity may therefore reflect the autonomic accompaniments of some specific headache syndromes, such as cluster headache, but does not appear to be related directly to pain. Similarly, activity in the upper brainstem of patients with migraine headache is probably related to the mechanisms that trigger the migraine attacks and not to the pain of headache (Weiller *et al.*, 1995; Bahra *et al.*, 2001). However, an abnormal response to an applied noxious stimulus was observed in a Xenon-133 SPECT study of seven cluster headache patients in remission and 12 healthy subjects. In that

study, a region of interest analysis revealed a reduced rCBF increase in the contralateral thalamus and sensorimotor cortical area of patients only when the hand ipsilateral to the headache side was immersed in painfully cold water (Di Piero *et al.*, 1997). Otherwise, the evidence thus far does not provide strong support for abnormal nociceptive processing in patients with primary headache disorders.

Orofacial pain conditions

A PET study (inhaled C¹⁵O) of rCBF activity during noxious contact heat stimulation (right hand) was performed in six patients 4 hours following the extraction of a left 3rd molar tooth (Derbyshire *et al.*, 1999). The activations were compared to those obtained in previous studies of the same number of RA patients and healthy subjects (Derbyshire *et al.*, 1994a; Jones and Derbyshire, 1997). Although the psychophysical responses to the heat stimulation were not different among these groups, a parallel comparison suggested a reduced response in the anterior cingulate, prefrontal medial and orbitofrontal cortices in the post-operative surgery patients. This result suggests that, compared with healthy individuals, differences in acutely evoked prefrontal cortical activity can occur within hours of the onset of non-neuronal tissue damage; however, the persistence of these differences is unknown.

As discussed in [Chapter 7](#), sensory or motor deficits are not usually detected in the clinical examination of patients with classical tic douloureux; therefore, we will consider this condition apart from neuropathic pain conditions. Jones *et al.* (1999) measured the total volume distribution of ¹¹C diprenorphine (as an estimate of binding potential) in six patients with “trigeminal neuralgia” (3 to 26 years duration) before and after radiofrequency lesions were placed in the trigeminal ganglion. The patients’ pain scores decreased following the surgery although none were said to be in pain at the time of the scans. The clinical description does not include the temporal characteristics of the patients’ pain, so the extent to which the pre-operative pain was continuous or paroxysmal is not clear. Nonetheless, the surgery was considered clinically successful. A contrast of the pre-operative scans with the 3-month post-operative scans revealed increased ¹¹C diprenorphine binding post-operatively, which was interpreted as indicating reduced endogenous opioid binding (consistent with increased endogenous opioid release) during the more painful pre-operative period. The regions with significant binding differences included the bilateral anterior insular, mid and anterior cingulate, parietal, medial frontal and prefrontal cortices as well as the bilateral putamen and right medial thalamus. These regions are commonly active during pain in healthy subjects, so there was no indication of response abnormalities in these patients. As the authors note, it is not possible to

determine whether the reduced binding is a consequence of endogenous opioid release or a reduction of receptors available for occupancy.

A patient with clear paroxysms of pain and a diagnosis of tic douloureux was studied with fMRI during brief (1–2 second) periods of pain in the maxillary division of the trigeminal nerve (Borsook *et al.*, 2007). This patient had spontaneous paroxysms of pain but also was able to trigger a pain paroxysm by tapping her teeth together on command; this condition made it possible to compare the BOLD responses to spontaneous and voluntarily triggered pain episodes. Both types of pain paroxysms were associated with positive BOLD in structures that would be expected to respond in otherwise normal individuals; negative BOLD responses were also observed in the anterior and posterior cingulate, primary motor, and temporal cortices, medulla, hypothalamus, amygdala and hippocampus. The BOLD response to the evoked paroxysms was of larger amplitude than to the spontaneous episodes and there were more total activations during the evoked pain. A direct within-subject contrast comparison revealed that evoked pain was associated with larger and more extensive activations in the anterior cingulate, insular, primary somatosensory and motor, parietal, temporal and prefrontal cortices; the authors interpret this result as reflecting "... the expectation of certain pain" (p. 13). It is not possible to determine whether the responses in this patient are abnormal, however, because there can be no direct comparison of the brain activations to this particular type of pain in healthy individuals.

The pain of atypical facial pain (AFP) does not conform to the diagnostic criteria of other primary or secondary trigeminal pain syndromes; it is constant but variable in intensity, usually aching, unilateral but poorly localized, and without a clinically identifiable cause on physical, radiological or laboratory examination. A PET activation study of six patients with AFP revealed increased responses in the anterior cingulate cortex and reduced responses in the prefrontal cortex during noxious heat (contralateral to the face pain) in a direct contrast comparison with six healthy individuals (Derbyshire *et al.*, 1994b). The interpretation of these results is difficult, however, because these patients all had other associated symptoms including headache, neck ache, irritable bowel and pruritis; furthermore, there was no significant group difference in the ratings of the heat pain.

Because a previous PET study had demonstrated that D2 dopamine receptor binding potential was inversely related to cold pain threshold in the right putamen and cold pain tolerance in the right medial temporal cortex (Hagelberg *et al.*, 2002), the same group studied seven patients and 11 healthy subjects with AFP using the selective D2 receptor antagonist ^{11}C raclopride to estimate dopamine D2 receptor availability (binding potential) (Hagelberg *et al.*, 2003a).

A direct, VOI-based, voxelwise comparison with the control group revealed increased D2 binding potential in the left putamen, suggesting that D2 receptor-mediated analgesic mechanisms might be impaired in some patients with this disorder. An increase in D2 receptors, however, cannot be excluded in this study.

Patients with burning mouth disorder (BMD) have constant, bilateral, intraoral burning pain of unknown etiology. Hagelberg and colleagues used the same PET methods described above to investigate the status of the dopamine system (receptor binding potential) in ten women with burning mouth syndrome and compared the results with those obtained from 11 healthy women (Hagelberg *et al.*, 2003b). As in the atypical facial pain patients, a direct, VOI-directed, voxelwise comparison with the control group showed that the D2, but not D1, binding potential was increased, this time in the left putamen, consistent with reduced endogenous dopamine release. Because psychophysical measurements were not obtained in this study, it is not possible to relate this finding to abnormalities in nociceptive processing. However, the fMRI BOLD response to noxious heat was studied in eight women with BMD and compared with the responses of eight healthy women (Albuquerque *et al.*, 2006). Heat pain thresholds and heat pain ratings did not differ between these groups but, in a direct comparison with healthy control subjects, the BMD patients showed increased activation in the bilateral thalamus, middle frontal, precentral and lingual gyrus and the cerebellum. Patients with BMD had relatively reduced pain-related responses in the anterior cingulate cortex and precuneus. In addition, a group comparison of the total activation volume revealed less total activation in the BMD patients. In both patients and healthy participants, activation of the left insula and bilateral posterior cingulate cortex correlated positively with measures of somatization, obsessive-compulsive trait, interpersonal sensitivity, depression and anxiety. However, BMD patients differed in showing a relatively stronger positive correlation of anxiety with bilateral precuneus activity and a negative correlation of bilateral thalamic activity with anxiety. It is notable that, in normal subjects, activity in the posterior cingulate and precuneus region is decreased in proportion to the expectation of pain (Chapter 5) (Koyama *et al.*, 2005). As the authors note, the overall pattern of activation is not different from that expected in normal subjects. Within this small sample, however, there appear to be response differences related to psychological variables that influence pain, although the hedonic aspect of pain was not specifically examined in this study.

In summary, the heterogeneity and small sample size of the facial pain conditions considered above does not lead to a unifying conclusion. However, it seems likely that at least some of the chronic pain conditions represented here

are associated with abnormal brain responses to noxious or possibly even innocuous stimuli. The evidence for an abnormality in dopaminergic pain modulation in some of these conditions (atypical facial pain, burning mouth disorder) gains significance given the clinical, neurophysiological and surgical evidence for the central origin of pain in patients with Parkinson's disease (Sage *et al.*, 1990; Starkstein *et al.*, 1991; Chudler and Dong, 1995; Ford *et al.*, 1996; Honey *et al.*, 1999; Djaldetti *et al.*, 2004; Schestatsky *et al.*, 2007). How these abnormal brain responses differ among conditions and how they may be related to the genesis or modulation of the clinical pain condition remains to be determined.

Fibromyalgia

Patients with fibromyalgia (FM) experience chronic, deep, usually aching or cramping pain that is widely distributed throughout the body; they also have lowered thresholds for pressure-evoked pain at several body sites including the trunk and extremities. The disorder affects women primarily. General agreement about the cause of the pain is lacking and remains a subject of intense debate (Bohr, 1996; Edwards, 2005; Vierck, Jr., 2006). Among the considerations is the hypothesis that patients with FM have a disorder of nociceptive processing in the central nervous system. This hypothesis gained some support when SPECT studies first identified resting rCBF abnormalities in patients with FM: bilaterally reduced perfusion in the thalamus and caudate nuclei in one study of ten patients and seven healthy subjects (Mountz *et al.*, 1995). This finding was subsequently confirmed but with additional resting hypoperfusion noted in the pontine tegmentum of 17 patients compared with 22 healthy women (Kwiatk *et al.*, 2000). Lowered pain thresholds in the FM patients were found in the former, but not the latter study. Resting rCBF was examined also with PET in eight patients with FM. When compared with a similar healthy control group, FM patients were found to have a higher rCBF bilaterally in the retrosplenial cortex and a lower rCBF in the left frontal, temporal, parietal and occipital cortices (Wik *et al.*, 2003). These investigators subsequently reported retrosplenial deactivation during acute pain in FM patients (Wik *et al.*, 2006).

In examining the response to evoked pain, Gracely and colleagues found both psychophysical and brain activation abnormalities during evoked pressure pain in an fMRI investigation of 16 FM patients and 16 healthy participants (Gracely *et al.*, 2002). When thumbnail pressure stimuli that were painless for the control group, but painful for FM patients, were applied to each group, a direct comparison of the activations showed significant BOLD responses only among FM patients in the contralateral primary somatosensory cortex (SI), inferior parietal lobule, insula, superior temporal gyrus, anterior and posterior cingulate

cortex and cerebellum. Ipsilateral activity was detected in the secondary (SII) somatosensory cortex, superior temporal gyrus and cerebellum. Only the medial frontal gyrus was active in the healthy control group during this low pressure stimulus (Fig. 8.17). Pressure stimuli that were equally painful in both groups evoked similar BOLD activation patterns. Although the activation pattern during evoked pain in these FM patients is similar to that observed in many studies of normal subjects, the level of stimulation required to produce that activation is much lower and suggests an augmentation of normal nociceptive processing mechanisms.

Cook and colleagues examined fMRI BOLD responses during the application of contact heat to nine FM patients and nine healthy subjects (Cook *et al.*, 2004). Stimuli that were perceived as equally warm and equal on an unpleasantness scale by both groups nonetheless resulted in activations only among FM patients bilaterally in the prefrontal and supplementary motor cortex and contralaterally in the anterior cingulate cortex when compared directly with control subjects. During the application of a normally painful 47°C stimulus to both groups, a direct comparison showed that, although this stimulus was perceived equally by both groups, only the patients with FM had significant activity in the right (contralateral) insular cortex. These results are in general agreement with those of Gracely *et al.* (2002) in suggesting an augmentation of otherwise normal nociceptive processing. Some of this augmentation may be related specifically to the perception of the pain as having especially negative consequences for personal survival (catastrophizing and depression) (Gracely *et al.*, 2004; Giesecke *et al.*, 2005).

Position emission tomography studies suggest that patients with FM may have abnormalities of endogenous opioid or dopaminergic control of nociceptive processing. Harris and colleagues, for example, found that, in direct comparison with an equal number of healthy subjects, 17 patients with FM had a greater reduction of opioid binding potential (BP of ^{11}C carfentanyl) in the nucleus accumbens, amygdala and the dorsal cingulate cortex; the BP was negatively correlated with indicators of the negative affective, but not sensory, dimension of pain (Harris *et al.*, 2007). These results could be interpreted as a reduction of available μ opioid receptors or as increased μ opioid receptor occupancy due to the release of endogenous opioids during pain. Wood and colleagues have presented evidence for the impaired release of dopamine, as measured by a VOI analysis of the ^{11}C raclopride (D2/D3 receptor ligand) binding potential (BP), from the striatum in 11 FM patients during the painful intramuscular infusion of hypertonic saline (Wood *et al.*, 2007). During pain, the BP decreased significantly in the globus pallidus, putamen and caudate nucleus in the 11 healthy participants but not among patients with FM. In addition, the decrease

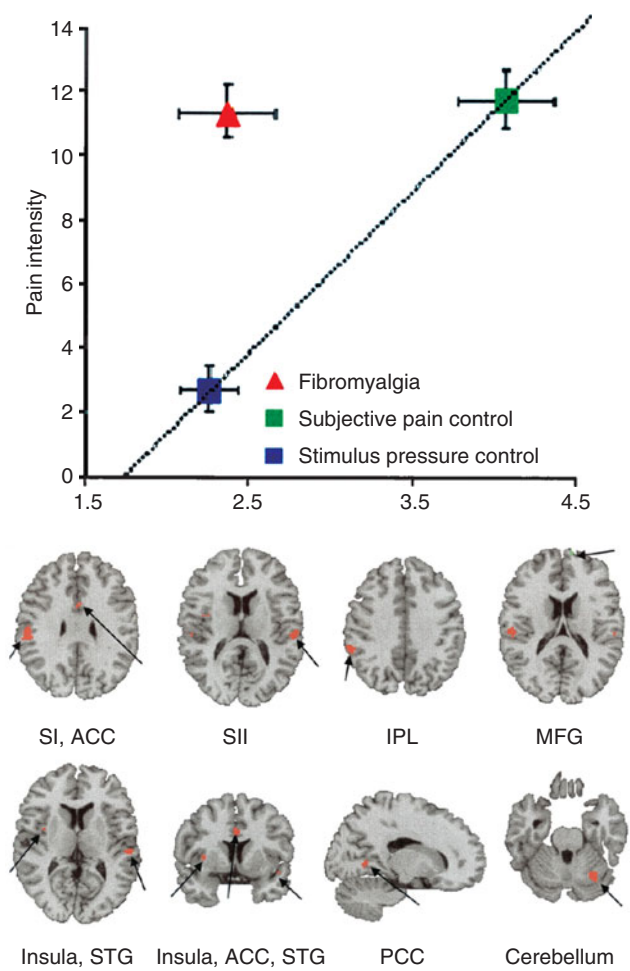


Fig. 8.17. Examination of brain responses of patients with fibromyalgia (FM). Upper panel shows sensory testing results. Red triangle shows average pain rating given by FM patients for left thumbnail pressure at low stimulus intensity (abscissa). Blue and green squares show the ratings given by healthy individuals at both low and high (painful) stimulus intensities. Note the intensity differences required to evoke pain in FM and healthy participants. Lower panel shows contrast images of cerebral activations (fMRI BOLD) found in a direct comparison between patients with FM and healthy individuals ($n = 16$ both groups) when painful pressure is contrasted also with innocuous touch stimulation of the left hand. Right hemisphere shown on the left. Activations greater in patients are shown in red; the single activation greater in healthy subjects is shown in green. SI, primary somatosensory cortex; ACC, anterior cingulate cortex; SII, secondary somatosensory cortex; IPL, inferior parietal lobule; MFG, middle frontal gyrus; STG, superior temporal gyrus; PCC, posterior cingulate cortex. Adapted from Gracely *et al.* (2002).

in BP was correlated with the increase in pain ratings in the control, but not the patient, group. The pain rating of the 11 FM patients, however, was not significantly greater than that of the healthy participants.

Irritable bowel syndrome

The criteria for the diagnosis of irritable bowel syndrome (IBS) includes recurrent abdominal pain or discomfort of at least 3 days/month in the last 3 months associated with improvement following defecation and change in frequency or form of stool, all without clinically identifiable cause (iasp-pain.org/irritable-bowel) (Merskey and Bogduk, 1994). A PET activation study ($H_2^{15}O$) of patients with IBS alone and patients with IBS and FM found that patients with both disorders rated rectal distension and somatic stimuli as equally unpleasant while patients with IBS only found the visceral stimulus relatively more unpleasant. Group comparisons revealed a greater rCBF response to the visceral stimulus in the mid-ACC among patients with IBS only; the same region showed a greater response to noxious somatic stimuli among patients with IBS and FM (Chang *et al.*, 2003).

The rCBF (PET) responses of seven IBS patients were compared also with those of eight patients with ulcerative colitis (UC, symptomatically inactive) and seven healthy subjects (Mayer *et al.*, 2005). The study design included anticipation as well as stimulus conditions. Ratings of intensity and unpleasantness were given about 10 min after each rectal distension. There were no significant group differences in stimulus-related sensations, but IBS patients reported greater sensory and unpleasantness ratings during anticipation than either the healthy or UC groups. Because the weaker (45 mmHg) and stronger (60 mmHg) stimuli were combined in the analysis, the degree of pain during the study is not clear. Nonetheless, a VOI-directed group contrast revealed that, during rectal distension, IBS patients showed greater activation of the bilateral anterior cingulate cortex (ACC), and the left amygdala, subgenual anterior cingulate cortex and dorsomedial prefrontal cortex (DMPFC). Patients with UC uniquely activated a region encompassing the dorsal pons and periaqueductal gray (PAG) in contrast with IBS patients and the left DMPFC in contrast with healthy subjects. In the main effects analysis, healthy subjects also activated the dorsal pons/PAG region and deactivated the left rostral ACC and bilateral DMPFC. During anticipation, IBS patients, compared with UC patients, activated the bilateral ACC and left DMPFC; UC patients had greater activation of the dorsal pons/PAG region. Patients with UC had greater activation of the DMPFC than healthy subjects. After the healthy and UC groups were combined, a connectivity analysis revealed a positive correlation between activations in the right lateral frontal cortex (RLFC) and the region of the dorsal pons and PAG. With structural equation

modeling, the authors showed that this frontal-brainstem correlation is probably mediated through the medial frontal cortex. These results show that the brain responses to visceral stimulation during a chronic inflammatory condition are different from those of both healthy persons and IBS patients, suggesting that the differences are not likely to be determined largely by input from inflammation-sensitized visceral afferents. The activation differences appear to be more related to differences in the hedonic component of the sensations and the degree to which visceral sensory processing is controlled by circuits connecting the frontal forebrain and brainstem. In a 12-month duration follow-up PET study of IBS patients, the investigators found that the increased psychophysical responses during rectal distension, but not clinical symptoms, became normal during a year of repeated testing while the major pain-related activation patterns persisted (Naliboff *et al.*, 2006). Stimulus-related activity in the limbic cortical and brainstem regions decreased and activity in the amygdala, dorsal anterior cingulate cortex and dorsal brainstem decreased during the anticipation condition. The results show that, although the brain response abnormalities and clinical symptoms persist in IBS patients, they may be reduced during repeated stimulation along with the affective component of stimulus-evoked sensations.

In a psychophysical study, the perceptual responses of IBS patients during the tracking of rectal distension sensations were found to be different from those of healthy individuals in the higher ratings of relative unpleasantness, the persistence of sensation, and higher ratings of unpleasantness during painful tonic distensions (Kwan *et al.*, 2005a). Eleven IBS patients and nine healthy subjects from this sample population participated in a PET (H_2^{15}O) study in which rectal distension sensations were tracked continuously during scanning (Kwan *et al.*, 2005b). Both contrast and parallel comparisons were used to identify major group differences in stimulus and perception-related brain activation. Patients with IBS, but not healthy subjects, activated the primary somatosensory cortex during “urge” sensations and the medial thalamus and hippocampus during painful sensations. Healthy subjects, however, uniquely activated the right anterior insular and anterior cingulate cortices during both urge and pain sensations. The authors interpret these findings as indicating abnormal visceral sensory and visceral nociceptive processing among IBS patients.

To investigate further the possibility of a more generalized hypersensitivity in this patient population, Verne and colleagues compared the responses to visceral distension and noxious somatic heat stimuli (water immersion), using fMRI in a study of nine patients with IBS and the same number of healthy subjects (Verne *et al.*, 2003). Patients with IBS rated both the visceral and somatic stimuli as more intense and unpleasant than healthy participants; the patients also had much

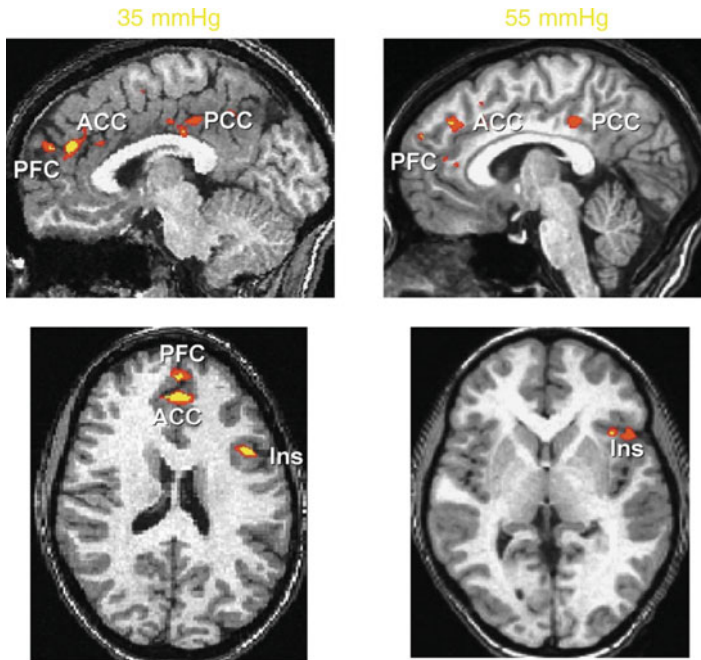


Fig. 8.18. Brain activations during rectal distention (35 and 55 mmHg) in patients with irritable bowel syndrome contrasted with those in healthy subjects. Left hemisphere on reader's right. Similar response differences were observed during somatic heat pain (not shown). PFC, prefrontal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; Ins, insula. Adapted from Verne *et al.* (2003).

higher ratings of stimulus-related fear and anxiety during the study. In response to noxious heat (47 °C) and visceral distention (55 mmHg) stimuli, a direct group-contrast comparison revealed stronger activation of the thalamus, insula and the somatosensory (SI), cingulate and prefrontal cortices among IBS patients (Fig. 8.18). The authors suggest that the exaggerated response to both somatic and visceral stimuli within the same brain structures reflects a generalized hyper-responsiveness to the stimulation of nociceptive afferents among IBS patients, perhaps related to increased fear and anxiety. Additional fMRI studies show that IBS patients have a strong placebo behavioral response as reflected by the attenuation of pain-related brain responses through a network of structures associated with affective and cognitive functions (Craggs *et al.*, 2007; Price *et al.*, 2007).

Although the strong placebo effect among IBS patients shows that at least some endogenous pain modulatory mechanisms are intact in this patient population, there is evidence that others may be deficient. Thus Song and colleagues found that the mechanism of diffuse noxious inhibitory control (DNIC; see Chapter 5) may be impaired in IBS patients (Song *et al.*, 2006). These investigators

examined changes in the psychophysical and fMRI BOLD responses of 12 patients with IBS and 12 healthy subjects to 30 seconds of rectal distension while a foot was immersed in painfully cold water (heterotopic stimulation). The pain ratings for the cold pain, rectal pain and sham rectal stimulation were not different between groups but the IBS patients had lower thresholds for painless and painful rectal stimulation and failed to show a decrease in rectal pain scores during the combined (cold + rectal) stimulation. In a parallel group comparison, there were several differences in brain activation patterns in each of the stimulus conditions (rectal, combined and sham stimulation). Random effects within-group direct contrasts of the combined minus rectal stimulation conditions followed by a parallel statistical comparison (their table 4) showed that IBS patients had greater activation in the right inferior parietal lobule and greater deactivation in the right medial precuneus cortex. Healthy subjects, however, showed greater deactivation in the left primary somatosensory cortex. This particular comparison is most closely related to the relevant perceptual difference between the groups and may offer some insight into its possible neurophysiological basis.

To investigate further the mechanisms that may underlie the abnormal visceral perceptions of IBS patients, Berman and associates focused on the anticipation of pain among a group of 14 patients with IBS-C (C = constipation predominant) and 12 healthy participants (Berman *et al.*, 2008). These investigators measured the BOLD responses to the cued anticipation of mild to moderate rectal distension (5, 25 or 45 mmHg). The groups did not differ in the within-scan ratings of maximum rectal distension intensity or unpleasantness but the IBS patients reported more anxiety and depression before and after the fMRI sessions than healthy subjects. A VOI-directed group comparison (Fig. 8.19), based on an earlier study (Mayer *et al.*, 2005), showed that, during cued anticipation, healthy subjects had significantly greater deactivation in the right posterior insula, and bilateral dorsal brainstem (DBS). The attenuated decrease in DBS deactivation in IBS patients was inversely correlated with measures of negative affect. During the most intense rectal distension, IBS patients had greater responses in the left DBS and, based on spatial extent, in the dorsal anterior cingulate cortex. Covariate analysis showed also that the degree of DBS deactivation during anticipation was associated with activation of the right orbitofrontal and bilateral subgenual anterior cingulate cortices. Accordingly, the authors suggest that IBS patients have a defective cortico-limbic modulatory system that acts through brainstem mechanisms to attenuate visceral sensory input.

Another fMRI study by Ringel and colleagues (Ringel *et al.*, 2008) shows that female IBS patients with a history of abuse report greater pain than healthy subjects and patients without abuse histories. The IBS-abuse patients also show

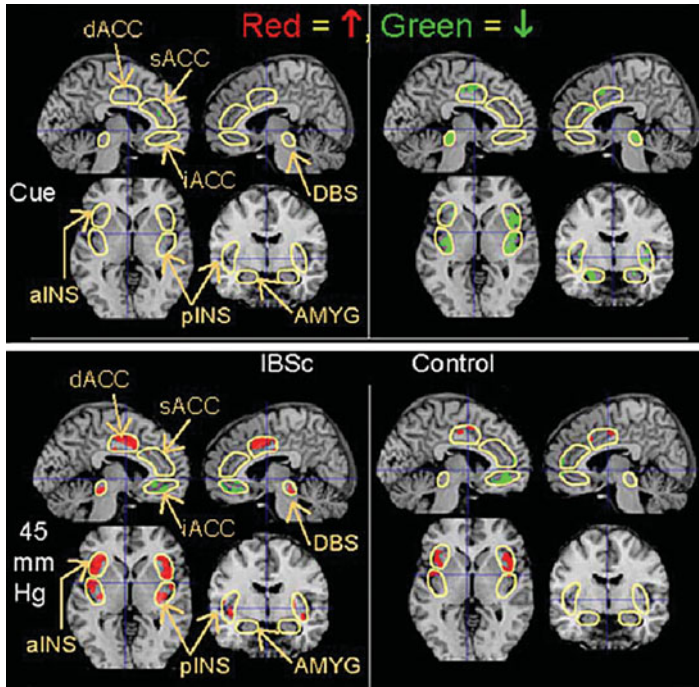


Fig. 8.19. Group analysis of BOLD activations (red) and deactivations (green) in patients with irritable bowel syndrome (left column) and healthy individuals (right column) during the cued anticipation (top panels) of rectal distension (bottom panels). Volumes of interest are shown as outlines on sagittal and transverse brain images (left hemisphere on reader's left). During the anticipation period there is more extensive deactivation among the healthy subjects. During rectal stimulation, there is more activation among the patients; both groups show deactivation in the subgenual anterior cingulate cortex. See text for more details. Adapted from Berman *et al.* (2008).

greater rectal stimulation responses in the left medial frontal cortex and less activation in the left supragenual anterior cingulate cortex. These results suggest that adverse personal experiences are associated with the abnormal brain responses and defective modulation of visceral sensory inputs.

Conversion and somatoform disorders

In these psychiatric disorders, there is usually a loss of somatic sensation, ranging from hypoesthesia to complete analgesia in some area of the body. Pain, if present, varies widely in location, character and the environmental circumstances in which it occurs. In every instance, however, there is a lack of clinically detectable evidence for a neurological, somatic or visceral abnormality. Mailis-Gagnon *et al.* (2003) conducted an fMRI investigation of four patients

with chronic pain symptoms and somatosensory deficits (hypoesthesia and hypalgesia) that did not fit into a dermatomal or peripheral nerve distribution. BOLD activations during noxious mechanical and brush stimulation of the involved and normal limbs were compared in a fixed-effects analysis with confirmation by subsequent conjunction analysis. Stimuli that were not perceived did not activate the thalamic, anterior cingulate, or frontal and prefrontal cortical areas that were activated during both noxious and innocuous stimulation. This result shows that the somatosensory perceptual abnormality that the patients report, whatever the cause, is linked to abnormal brain responses in this sample group of patients.

Patients with somatoform disorder (SD) generally do not have sensory loss but, like patients with conversion disorder, complain of pain without a clinically detectable cause. In an fMRI study of 17 patients with SD and 17 healthy subjects, mechanical quantitative pinprick stimulation was applied as part of an investigation that included an examination of brain response group differences to cognitive and emotional stress (Stoeter *et al.*, 2007). The noxious stimuli were applied first in a sequence of tests that included cognitive and emotional stimuli interleaved with the second and third set of noxious stimuli. Both groups, however, scored within the normal range in tests of anxiety and depression. Within-scan scoring of pain and of cognitive and emotional stress was not different between groups. Nonetheless, a random effects direct group comparison with healthy subjects showed that, during the first set of noxious stimuli, SD patients had greater activation in the anterior insular, dorsal and ventral frontal, temporo-occipital and inferior parietal cortices as well as the hippocampus, thalamus and putamen. These pain-related differences did not appear during the subsequent stimulus applications. These results again reveal some brain response differences that are associated with a clinically defined condition but do not appear to be related to differences in the perception of applied noxious stimuli.

Summary of chronic (non-neuropathic) pain imaging

Functional imaging of the chronic pain conditions reviewed above suggests some differences with similar studies of neuropathic pain. First, with the exception of sympathetically maintained pain (SMP) (Apkarian *et al.*, 2001) and fibromyalgia (FM) (Mountz *et al.*, 1995; Wik *et al.*, 2003), the evidence for functional or structural changes in the default resting brain is quite limited. Second, possibly because of the heterogeneous range of clinical conditions that have been studied, there is a wide range of abnormal responses to applied or spontaneous ongoing noxious stimulation. In neuropathic pain, abnormal prefrontal cortical activity was often found at rest or in response to stimulation; this

appears to be less commonly observed in chronic (non-neuropathic) pain. However, it is premature to draw conclusions from the limited number of studies in this mixed population of clinical pain syndromes. Finally, by definition, the response (or resting) abnormalities in these pain syndromes cannot be attributed to clinically identifiable lesions in the peripheral or central nervous system. In some conditions, there is an obvious source of constant or intermittent chronic pain that may, over time, alter the physiology of central nociceptive processing at several levels of the neuraxis. In others (e.g. fibromyalgia, burning mouth, conversion syndrome), evidence for any source of nociceptive input is lacking, leading to the suggestion that other factors in the patient's developmental or life experience are responsible for the abnormalities seen in functional imaging studies. Overall, however, the evidence thus far shows that, however uncertain the causes, aberrations in the experience of pain are likely to be reflected in the results of functional imaging studies.

Concluding summary

Chronically painful conditions are often associated with changes in the brain's resting (default) state, the response to innocuous or noxious stimuli, or with changes in both the resting and responsive conditions. Functional brain imaging has begun to identify these changes with increasing detail. When the peripheral or central nervous system is injured, it is reasonable to consider that some or all of these changes are attributable to the direct effects of the injury on the physiology of nociceptive processing, including endogenous pain modulation. But it is also possible that these upstream changes are due to constant or periodic afferent input from the periphery or generated within the central nervous system. In chronic, non-neuropathic pain, for example, there may be a clinically identifiable source of nociceptive input (e.g. arthritis or other sites of inflammation) that could initiate and sustain changes in central nociceptive function. In these cases, monitoring, with functional imaging, the effect of treatments directed specifically at the source of afferent activity could help address this question by revealing a normalization of brain function. The interpretation of the results is often complicated by ongoing, superimposed central and peripheral adaptive changes. Nonetheless, experiments in that direction could provide much-needed information about the duration of changes in brain responsiveness and the degree to which they are input-dependent. In the central pain syndromes, the problem is complicated by the distributed effects of focal lesions and their direct effect on endogenous pain modulation mechanisms (Casey, 2004). The problem is still different in cases of chronic pain without a clinically identifiable afferent source (e.g. fibromyalgia, irritable bowel

syndrome, burning mouth disorder, some types of headache). Here, the changes in brain responsiveness may be more heterogeneous and there is no identified focal pathology to treat. The responsive or resting brain abnormalities revealed by functional imaging thus far suggest pathology intrinsic to the central nervous system and reflected primarily, but perhaps not exclusively, in nociceptive dysfunction. In fact, when there are no group differences in the perception of pain, as in some examples above, it is impossible to be certain about what is being imaged in the contrast comparisons. Perhaps a source of nociceptive input will be found eventually, or future functional imaging studies, perhaps focusing on neurotransmitter systems, will elucidate the pathophysiology of these conditions.

Whatever the proximate or remote causes of the chronic pain, the associated changes in brain function have implications for treatment. In chronic pain, the altered central mechanisms could sustain the pain by enhancing responses to both noxious and innocuous inputs. The increased sensitivity may be due to spontaneous, ongoing activity in neural systems specifically dedicated to nociceptive processing, to impaired endogenous modulation, or some combination of these mechanisms. Treatment strategies will have to take these possibilities into consideration and may be guided to some degree by the results of functional imaging studies.

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Functional implications of spinal and forebrain procedures for the treatment of chronic pain

The clinical descriptions of cordotomy played a major role in elucidating the function and the anatomy of the human spinothalamic tract (STT) (Chapter 1). There are a number of other examples of surgical interventions which have informed our understanding of the pain system. In particular, the pain-related role of the cingulate gyrus is suggested by imaging studies and by the effect of cingulotomy on experimental pain (Rainville *et al.*, 1997; Gildenberg, 2004). Similarly the role of the motor cortex in these systems has suggested the effects of stimulation on activity throughout the pain system (Brown and Barbaro, 2003; Brown, 2004; Peyron *et al.*, 2007). The purpose of this chapter is to examine these surgical interventions in terms of the anatomy and function of structures involved in these interventions. The inclusion of procedures in this chapter is arbitrary and many other such procedures which might have been included have been excluded.

Cordotomy and myelotomy

Percutaneous cordotomy produces relief of pain by interrupting the transmission of signals in the STT from below the level of intervention (Tasker, 1988; Tasker, 2004). The anterolateral quadrant of the spinal cord has long been recognized as the location of the STT (Chapter 1). Recent findings indicate that the dorsal column system also has an important role in visceral nociception (Nauta *et al.*, 1997; Willis *et al.*, 1999). The STT terminates in the primate thalamus, brainstem and other structures such as the hypothalamus and amygdala whereas the dorsal column system terminates in the dorsal column nuclei (Newman *et al.*, 1996).

Cordotomy was initially carried out as an open, bilateral procedure at T1–2 for relief of pain secondary to cancer. Percutaneous cordotomy is frequently carried out now using intravenous sedation, with myelography or computed tomography to identify the STT anatomically (Mullan *et al.*, 1965; Onofrio, 1971; Tasker *et al.*, 1974; Kanpolat, 2002). The lesion is made by radiofrequency coagulation (Rosomoff *et al.*, 1965). Percutaneous cordotomy is currently done by the dorsal approach at the C1–2 interspace, the low anterior cervical approach (C5–6) or the lateral cervical approach at C1–2. The high lateral cervical approach seems to be the most popular at present.

The physiology and psychophysics of STT function have been significantly clarified by studies carried out on patients undergoing cordotomy. Clinical observations of the sensory level after anterolateral cordotomy demonstrate that the pain/thermal pathway ascends for two segments before decussating (Mehler, 1974). Stimulation for localization prior to cordotomy demonstrates a somatotopic organization with sacral fibers forming a band at the level of the dentate ligament (Taren *et al.*, 1969; Tasker, 1976) (Chapter 3). More rostral levels of the body are located successively in more ventral circumferential bands around the cord. In the medulla the face is represented medially by fibers from the spinal trigeminal nucleus, while more caudal structures are represented successively further laterally (Schwartz and O’Leary, 1941, 1942). In the midbrain, similar stimulation mapping demonstrates that the face is dorsally adjacent to the medial lemniscus and caudal parts of the body are located successively more laterally (White and Sweet, 1955; Tasker *et al.*, 1982).

Nathan’s published work is a signal contribution, including a review of clinical–anatomic correlations of cordotomy in more than 60 patients (Nathan *et al.*, 2001). The findings of this study confirmed that complete anterolateral cordotomy results in a zone of total anesthesia beginning one level below the cordotomy. Partial analgesia was identified by altered pain and thermal thresholds and was associated with lesions extending from one segment below to one or two segments above the cordotomy. The zone of partial anesthesia was accounted for by the fact that not all fibers had yet crossed in the anterior commissure of the spinal cord, and so some were spared in the other half of the cord. Anterior commissure fibers cross transversely (within a segment in the cord) rather than diagonally. The levels of partial and total sensory loss are partially accounted for by the fact that dorsal root filaments ascend or descend a level before entering the cord.

Studies of patients with lesions of the posterior columns had preserved light touch and pressure sensation but poor discrimination, and impaired active touch (Nathan *et al.*, 1986). Lesions of the STT caused no deficits in tactile sensation whereas lesions of both pathways led to total loss of touch and

pressure. Lesions of the dorsal columns with spared STT led to increased pain sensation, as well as enhanced sensations of tickle, warmth and cold, suggesting that the transmission of pain and temperature in the STT is inhibited by dorsal-column input.

Findings in three patients with bilateral dorsal column destruction and unilateral anterolateral quadrant destruction suggest the anatomic substrate of central pain (Wall and Noordenbos, 1977; Beric *et al.*, 1988). In one patient, pressure stimulation in the leg contralateral to the intact STT and ipsilateral to a lesioned dorsal column was painful. Repeated stimulation that was non-painful would summate so that the stimulus became painful after multiple stimuli, i.e. “windup.” There was also a general, constant state of “unpleasantness” on the side contralateral to the lesioned STT. The heightened baseline pain state reached a peak at 3 weeks post-injury, and diminished back to baseline by 1 year, consistent with studies demonstrating that all patients with central pain have abnormal pain or temperature sensations, or both (Beric *et al.*, 1988; Boivie *et al.*, 1989; Vestergaard *et al.*, 1995).

Spinothalamic tract stimulation leads to different responses in patients with neuropathic pain and those with nociceptive pain, which arises from tissue damage or stimuli which threaten such damage. Stimulation of the STT at the cervico-medullary junction in patients with nociceptive pain almost always produces a sensation of warmth, coolness or burning (Hitchcock, 1972; Hitchcock and Tsukamoto, 1973; Tasker, 1976; Tasker *et al.*, 1977, 1982). Stimulation of the STT commonly produces pain in patients with neuropathic pain (Tasker *et al.*, 1982).

An elegant study by Mayer *et al.* (1975) estimated the conduction velocity of fibers mediating the sensation of pain by measuring the refractory period during paired-pulse stimulation in the STT at the cervico-medullary junction during cordotomy. Successively longer interpulse intervals were applied until the sensation of pain increased stepwise as the fibers reported both pulses for the first time. The conduction velocity corresponding to this interpulse interval was compared with estimates of the conduction velocities for fibers originating in lamina I versus laminae IV and V (Price and Mayer, 1975). The conduction velocity for axons subserving the sensory-discriminative aspect of pain was found to correspond to that measured for axons originating in the deep lamina of the spinal cord in monkeys (Mayer *et al.*, 1975; Price and Dubner, 1977).

Indications, results and complications

Percutaneous cordotomy is most clearly indicated for the relief of nociceptive pain located below the level of the cordotomy. It is particularly effective

for leg pain secondary to cancer in patients with a limited expected survival time (Tasker, 1988, 2004). The effectiveness of this technique in severe cancer pain makes it a valuable procedure in patients with a short expected survival. Cordotomy may relieve the hypersensitivity (allodynia, hyperalgesia, neuralgic pain) of neuropathic pain, but is less effective for the steady burning component of neuropathic pain (Tasker and Dostrovsky, 1989; Tasker *et al.*, 1992). The indications for cordotomy in large series included pain from cancer of the cervix in approximately 20%, rectum in 15%, colon in 10%, lung in 10%, breast in 5%, other cancers in 30% and central pain of spinal cord origin in 10% (Gildenberg, 1974; Tasker, 1988; Tasker, 2004). Pain above the C5 vertebra will not usually respond to lower cervical cordotomy.

Overall published data indicate 60–80% complete contralateral pain relief and 70–95% significant pain relief (Tasker, 1988). Complete pain relief diminished from 90% of patients immediately post-operatively, to 85% after 3 months, to 60% at 1 year, to 40% between 1 and 5 years, and finally to 40% at 5 to 10 years (Tasker, 1988).

The bilateral procedure is often proposed since cancer pain is uncommonly unilateral (Tasker, 1988). The two procedures should be staged by a week, or more. The success of the bilateral procedure may be estimated at 64% ($80\% \times 80\%$), assuming that the rate of pain relief with unilateral cordotomy is 80%.

The complications of cordotomy are often the result of damage to structures in the cord near the STT (Tasker, 1988; Tasker, 2004). The chief complication is respiratory failure related to loss of ipsilateral, automatic respiration (Ondine's curse). This is the result of a lesion of the ipsilaterally distributed reticulospinal tract, which is located among the axons of the cervical STT. Significant reversible respiratory complications occur in up to 10% and death due to respiratory complications will occur in 0–5% of patients after unilateral cordotomy. When the first procedure of a proposed bilateral cordotomy interferes with automatic respiration, then cordotomy on the second side must be considered carefully.

Following a unilateral procedure persistent paresis of the ipsilateral leg, or ataxia, will occur in up to 10%. Dysfunction of micturition occurs in up to 15% of patients after unilateral procedures, and is more common after bilateral procedures (Tasker, 1988). Ipsilateral, partial, ptosis results from damage to the axons of preganglionic sympathetic neurons in the intermediolateral cell column in the thoracic and upper lumbar spinal cord. It is a frequent complication which is of little consequence.

Midline myelotomy is a procedure which involves section of pathways in midline of the spinal cord approximately at the radicular level of the cord corresponding to the level of the visceral pain. This procedure is unlike cordotomy which involves section of the STT – an ascending pathway. Myelotomy was

initially thought to produce analgesia as a result of section of the STT fibers as they decussate in the spinal cord (Noordenbos, 1959; Uddenberg, 1968; Hitchcock, 1974; Rustioni *et al.*, 1979; Willis and Coggeshall, 1991). Recent studies have identified the lesioned pathway as one that arises from cell bodies near the central canal and that ascends near the midline in the dorsal column (Al-Chaer *et al.*, 1997) (Chapter 3). Nauta *et al.* (2000) demonstrated that medically intractable pelvic pain could be effectively relieved by a small, midline lesion above the painful level. Similar success was achieved for pain of stomach cancer following a midline myelotomy at the upper thoracic level (Kim and Kwon, 2000).

Spinal cord stimulation

Spinal cord stimulation (SCS) had its origin in the 1960s as a therapeutic option for pain based upon the gate control theory (Melzack and Wall, 1965; White and Sweet, 1969). As a result of many refinements this technique is now an effective treatment for painful and ischemic conditions as described below. At present, SCS is carried out with permanently implanted electrodes following a successful test of stimulation by percutaneous placement of a temporary lead. This lead is a linear electrode with several contacts along its length, and is placed in the epidural space usually over the lower spinal cord and conus. If this test is successful (pain relief >50%), then this lead is replaced with a permanent lead which is attached to a pulse generator and battery. Thereafter, programming is carried out to find the pattern of electrodes and parameters of stimulation that produce an optimal therapeutic effect.

Spinal cord stimulation: mechanisms

The hypothesis that the efficacy of SCS is based upon gate control theory (Melzack and Wall, 1965; White and Sweet, 1969) gives no clear explanation of clinical observations such as the effectiveness for the treatment of neuropathic but not nociceptive pain (Meyerson and Linderorth, 2003). It is also unclear how SCS produces analgesia for ischemia of somatic and cardiac muscle. Neurons in the canine thoracic dorsal horn demonstrate increased activity during both acute ischemia and reperfusion of cardiac muscle (Foreman *et al.*, 2000), although this activity is unrelated to parameters of cardiac function. A similar effect upon vascular parameters has been observed in peripheral ischemia (Meyerson and Linderorth, 2003).

Studies in rodent models of neuropathic pain have clarified the mechanism of analgesia in neuropathic syndromes (Linderorth and Foreman, 1999; Meyerson and Linderorth, 2003). Spinal cord stimulation in these models decreases the hypersensitivity to mechanical stimuli (hyperalgesia or allodynia), and may

concomitantly decrease dorsal horn neuronal hypersensitivity. Spinal cord stimulation is associated with increased release of excitatory amino acids from the spinal cord. Systemic administration of GABA_B antagonists or agonists is associated with decreased or increased effects of SCS stimulation on behavioral measures of hypersensitivity respectively.

In the case of ischemic pain in the extremities it seems likely that the analgesic effect of SCS results from vascular dilatation leading to decreased ischemia (Linderöth and Foreman, 1999). This effect may be the result of retrograde activation of primary afferent fibers in the dorsal column or may be mediated through activation of sympathetic fibers. It has also been suggested that activation of primary afferent fibers results from peripheral release of calcitonin gene related peptide (CGRP) (Croom *et al.*, 1997).

In the case of angina pectoris, the analgesic effect of SCS may be due to correction of myocardial blood flow. The onset of angina in response to increased heart rate, produced by *external pacing* or by exercise, can be delayed by SCS, which also can lead to reversal of STT segment depression and myocardial production of lactate (Mannheimer *et al.*, 1993). These effects may be due to alteration of coronary artery blood flow, to reduction of coronary oxygen consumption and to decreased sympathetic activity in the myocardium (Jessurun *et al.*, 1996; Foreman *et al.*, 2000).

Cardiac origin of the benefit of SCS for treatment of angina is also suggested by a randomized controlled trial of SCS stimulation for the treatment of patients with chronic intractable angina pectoris (Hautvast *et al.*, 1998). Improvement was noted in assessments of exercise tolerance, frequency of angina attacks, amount of medical treatment and pain. Placebo stimulation did not produce any of these effects.

An independent factor in the effect of SCS upon angina pectoris is the effect upon the activity of intrinsic cardiac neurons located in right atrial cardiac plexus (Foreman *et al.*, 2000). Spinal cord stimulation led to decreases in the activity of these neurons evoked by myocardial ischemia during ventricular ischemia and reperfusion in a canine model. These changes in intrinsic cardiac neuronal activity occurred in the absence of changes in indices of cardiac function. This effect of lumbosacral SCS upon the intrinsic cardiac neurons may be related to the activity of sympathetic afferent and efferent fibers (Foreman *et al.*, 2000).

Indications, results and complications

Spinal cord stimulation applied either for neuropathic, peripheral ischemic pain or angina pectoris is indicated only when medical or surgical

treatment options have been exhausted. In the USA, permanent SCS implantation for pain must be preceded by a successful response to a percutaneous trial of stimulation.

The most common indication for SCS is nociceptive back pain and neuropathic pain associated with lumbosacral degenerative spinal disease and with sequelae of its surgical treatment. A proof of principle study of clinical and experimental heat pain ratings has been carried out in a placebo controlled design, in a small number of patients (Marchand *et al.*, 1991). Spinal cord stimulation was associated with significant decreases in ratings of experimental pain, clinical pain and detection of heat stimuli. Visual tasks including ratings and detection of light intensity were unaffected, suggesting that these effects are not due to changes in the rating performance.

There are very few randomized, prospective SCS studies and placebo-controlled trials are difficult due to the presence of paresthesias. There are a larger number of studies of SCS applied in the treatment of neuropathic pain, comprising large patient groups with long-term follow-up, which are often in agreement with each other. In these studies a good result was defined by >50% pain reduction, and by secondary measures such as amount of analgesic intake or the patients' estimate of satisfaction, which were also improved in the majority of patients (Simpson, 1994). The analgesia resulting from SCS stimulation is often long lasting without habituation, fatigue or tolerance of benefit.

A randomized trial of SCS versus reoperation for treatment of failed back syndrome demonstrated significance for lower subjective pain ratings, opiate intake and crossovers to the other limb of the study, e.g. patients requesting SCS after first being randomized to reoperation (North *et al.*, 2005). Similar results were obtained in a large prospective multicenter trial which obtained complete data at 1 year in 70 of 182 patients implanted with a permanent SCS system (Burchiel *et al.*, 1996). There was a significant improvement in measures of subjective pain and of quality of life. Among these patients 55% had a significant improvement which was defined as a 50% decrease in a subjective pain rating. Approximately 15% of patients had non-surgical complications, often resolved by adjustment of the stimulation parameters. Surgical complications often required replacement or repositioning of a component of the implanted SCS hardware.

A study of prognostic factors in the treatment of lumbar radiculopathy has revealed that increased age and indexes of depression correlated negatively with post-operative pain levels. High scores on the evaluative scale of the McGill pain questionnaire correlated positively with clinical success of SCS (Torgerson *et al.*, 1988; Burchiel *et al.*, 1995).

A literature review including multiple retrospective studies of SCS for the treatment of low back pain found an aggregate success rate of almost 60% (Turner *et al.*, 1995). Database searches that reviewed the literature on neurostimulation for the treatment of pain including SCS have been published (Coffey and Lozano, 2006; Cruccu *et al.*, 2007). In randomized controlled trials of SCS for lumbosacral radiculopathy and failed back syndrome, the percentages of responders (> 50% pain relief) were 47–48% versus 9–12% for reoperation or best remedial therapy (Cruccu *et al.*, 2007).

Chronic pain and trophic changes due to trauma with or without nerve injury can be described as the complex regional pain syndrome (CRPS) (Kozin *et al.*, 1976; Meyer *et al.*, 1994; Campbell, 2004). This typically occurs after trauma without injury to a nerve (CRPS type 1), or with injury to a nerve (CRPS type 2). A recent randomized, controlled study of failed back syndrome or CRPS found that patient pain was significantly reduced 24 months after SCS plus physical therapy compared with physical therapy alone; the effect size did not reach the standard of 50% relief in 50% of patients (Turner *et al.*, 2004).

Another randomized controlled study examined the effectiveness of SCS versus physical therapy for sympathetically maintained pain, a subcategory of CRPS (Kemler *et al.*, 2000). In a randomized, controlled trial of SCS plus physical therapy (n = 36) versus physical therapy alone (n = 18), 24 patients in the first group had implantation of the permanent stimulation system after a successful trial of stimulation. In the SCS group versus the physical therapy group there was a significant decrease in pain ratings and a significant increase in who reported “much improved.” Twenty-five percent of patients with permanent stimulators had complications including infection and technical problems leading to reoperation (Kemler *et al.*, 2000).

Spinal cord stimulation for the management of ischemic pain in the extremities is currently practiced in relatively few centers. Provided the treatment is applied only with stringent selection criteria, the overall outcome is favorable with 60–70% of the patients enjoying substantial pain relief (Simpson, 1994). There is also a marked amelioration of claudication and increased walking distance. Further, SCS may facilitate the healing of small ulcers and thus improve limb salvage.

Intractable angina pectoris has emerged as an important indication for SCS since successful outcomes are reported in up to 85% of studies (Ten Vaarwerk *et al.*, 1999). Outcome was defined by the number of attacks of angina, consumption of nitrates, visits to the emergency room and quality of life. A randomized controlled study comparing the outcome of stimulation to controls with inactive SCS confirmed the remarkably favorable outcome of the treatment (Hautvast *et al.*, 1998). Spinal cord stimulation is a well established minimally invasive stimulation technique that is well tolerated and may offer effective pain management of

pain conditions for which there is often no alternative treatment available. It has also been shown to be cost-effective in a number of studies.

Deep brain stimulation

Deep brain stimulation for treatment of chronic pain began with reports of hypothalamic stimulation for the treatment of chronic pain (Pool *et al.*, 1956). At present, the main targets are the somatic sensory thalamus, i.e. the ventral posterior (VP) or Hassler's ventral caudal nucleus (Vc) (Chapters 2 and 3), and the periaqueductal gray (Richardson, 1985; Young *et al.*, 1985; Hosobuchi, 1986; Levy *et al.*, 1988; Weiss *et al.*, 2004).

In 1969, Reynolds demonstrated in rats that focal stimulation at the lateral margin of the PAG prevented nociceptive responses during abdominal surgery without concomitant drug administration (Reynolds, 1969). Mayer *et al.* (1971) demonstrated similar results. Subsequently, the reversal of these effects was demonstrated following the administration of opioid antagonists (Akil *et al.*, 1984). After numerous reports of the analgesic effect of PAG stimulation in rodents these results were confirmed in humans (Hosobuchi *et al.*, 1977; Richardson and Akil, 1977).

In humans, effects of PVG stimulation can be reversed by opioid antagonists (Hosobuchi *et al.*, 1977) and can be associated with increased levels of endogenous opioids in the third ventricle (Akil *et al.*, 1978; Hosobuchi *et al.*, 1979), which could be an artifact of the use of contrast media during the collection of cerebrospinal fluid (Fessler *et al.*, 1984). More recently it has been shown that both beta-endorphin and met-enkephalin levels also increase after PAG stimulation (Young and Chambi, 1987). In man infusion of opiates into the intraventricular or spinal subarachoid space causes analgesia (Yaksh, 1981; Dougherty and Staats, 1999).

Mechanism of analgesia produced by PAG stimulation

Several lines of evidence suggest that the mechanism of analgesia in PAG stimulation involves connections from PAG to the medullary raphe nuclei which send a serotonergic connection to the spinal cord (reviewed by Basbaum and Fields, 1984; see also Maciewicz and Fields, 1986). First, the PAG neurons rarely project directly to the spinal cord but project monosynaptically to the nucleus raphe magnus (NRM). Medullary NRM sends a strong serotonergic connection to the dorsal horn (see Chapter 6). Second, the analgesic effect of PAG stimulation is abolished by cutting descending pathways to the spinal cord. Depletion of monoaminergic neurotransmitters in rodents leads to reduction in the analgesia produced by PAG stimulation in rodents (Akil and Liebeskind, 1975). The PAG, medullary NRM and dorsal horn all contain high levels of opiates

(see [Chapter 6](#)) and opiate receptors suggesting that these structures mediate the opiate-induced analgesia.

A study in Old World monkeys examined the effect of stimulation in the monkey periventricular gray (PVG) just lateral and anterior to the junction of the posterior commissure and the wall of the third ventricle ([Chapter 6](#)) (Gerhart *et al.*, 1984). This stimulation inhibited responses to noxious stimulation, perhaps due to an inhibitory effect on transmission of impulses encoding these stimuli through the STT neurons mediated through serotonergic pathways (Gerhart *et al.*, 1984). Recordings were made from STT cells in the lumbosacral enlargement of anesthetized monkeys. The cells were identified by antidromic activation from the contralateral ventroposterolateral nucleus of the thalamus. Electrical stimulation at sites within the periaqueductal gray, the adjacent midbrain reticular formation or the deep layers of the tectum were found to inhibit the activity of STT cells.

In general, midbrain stimulation inhibited the background discharges and the responses of wide dynamic range cells evoked by innocuous and noxious cutaneous stimulation. However, in a subpopulation, midbrain stimulation preferentially inhibited the responses to noxious stimulation. Midbrain stimulation inhibited the responses of STT cells to volleys in both the A fibers and the C fibers although the effect on C fibers was much stronger. The effects of lesions of the spinal cord led to the conclusion that the inhibition is mediated by pathways descending in the dorsal lateral funiculus, rather than by descending through the ventral spinal cord.

Pharmacologic tests to predict the effectiveness of PAG versus Vc DBS stimulation for treatment of chronic pain

Unlike nociceptive pain which responds best to both opiates and PAG stimulation (Hosobuchi, 1986; Arner and Meyerson, 1988), neuropathic pain may not respond to opiates. Therefore, acute tests showing an analgesic effect of opiates have been interpreted as identifying patients with a nociceptive versus a neuropathic mechanism of chronic pain; these patients would be considered responders to PAG versus Vc stimulation. As the therapeutic effect of opiates upon neuropathic pain has been tested in controlled trials, the validity of this test has been questioned. Therefore, before examining the mechanism of Vc stimulation we explore the validity of the opiate test to predict the effectiveness of PAG versus Vc stimulation in individuals with chronic pain.

The effect of intrathecal opioids on central neuropathic pain syndromes is a critical test of this idea, since there is seldom a component of nociceptive pain to confuse the issue. Studies employing intrathecal drug delivery have reported no

effect or limited effects of IV morphine and IV fentanyl on CPSP (Tasker, 1984; Scott *et al.*, 1986; Arner and Meyerson, 1988; Portenoy *et al.*, 1990; Kupers and Gybels, 1992; DelleMijn and Vanneste, 1997; Mailis *et al.*, 1997). However, intravenous infusion of alfentanil led to a significant decrease in spontaneous and evoked pain (Eide *et al.*, 1995).

In combination, intrathecal morphine and clonazepam led to significant pain relief, although neither agent was effective individually (Backonja *et al.*, 1994). A double-blind, placebo-controlled trial of intravenous naloxone did not produce analgesia in patients with CPSP (Bainton *et al.*, 1992). However, an open-label trial of intravenous naloxone reported that “pain and hyperpathia were completely obtunded” in seven out of 13 CPSP patients studied, and “partially obtunded” in one patient (Budd, 1985).

In the case of central pain syndromes due to spinal cord injury intraspinal delivery of opioids (alfentanil) was found to be effective for the treatment of spontaneous and evoked pain (Eide *et al.*, 1995) while morphine was reported to be ineffective except in combination with clonidine (Siddall *et al.*, 2000).

Studies of oral opioids for treatment of neuropathic pain have also cast doubt upon the validity of opioid tests as a way to identify patients with neuropathic pain. These patients would then be selected for Vc DBS rather than PAG DBS. A recent randomized, controlled clinical trial of an opioid to treat a mixed population of patients with central or peripheral neuropathic pain found a significant analgesia for the oral mu opioid levorphanol (Rowbotham *et al.*, 2003). Patients with refractory neuropathic pain were assigned to one of two different dosages of levorphanol for 8 weeks under double-blind conditions. Across all categories of neuropathic pain the high-dose levorphanol regimen decreased the pain rating significantly (36%). All doses produced reduction in affective distress and interference both with functioning and with sleep. Patients with CPSP were the least likely to report benefit. As these studies have demonstrated a therapeutic effect of opiates upon neuropathic pain the validity of opiate tests prior to DBS implantation has been called into question. Furthermore, there is evidence that the mechanism of analgesia produced by Vc DBS stimulation may involve opiates.

Mechanism of analgesia produced by Vc DBS stimulation

Neuropathic pain seems to respond best to stimulation of the somatosensory thalamus, although the mechanisms are not fully understood (Hosobuchi, 1986; Levy *et al.*, 1987; Bendok and Levy, 1998; Rasche *et al.*, 2006a). A proof of principle study of clinical and experimental heat pain ratings has been carried out in a placebo-controlled design, in a small number of patients with neuropathic pain (Marchand *et al.*, 2003). Thalamic stimulation significantly decreased clinical and

experimental pain perception, and it also had a significant placebo effect. Neither thalamic nor placebo stimulation significantly affected ratings of cutaneous air puff stimuli or of light intensity, demonstrating that these stimuli did not affect rating performance which can be affected by attention.

Benabid *et al.* (1983) reported that stimulation of the ventroposterolateral (VPL) nucleus of the rat inhibits the nucleus parafascicularis (Pf) response to noxious stimuli through an opioid independent mechanism. Furthermore, the inhibition did not appear to involve dorsal horn neurons of the spinal cord since stimuli that inhibited Pf neurons did not affect the responses of a limited sample of dorsal horn interneurons. Gerhart and co-workers demonstrated the inhibitory effect of thalamic stimulation on lamina I to V spinothalamic tract (STT) neurons (Gerhart *et al.*, 1983). The mechanism of this effect was thought to involve either orthodromic or antidromic mechanisms.

Stimulation-evoked STT activation could antidromically activate PVG which projects to NRM or nearby reticulospinal pathways (see above), or it could activate NRM directly. The NRM has a serotonergic spinal projection which could inhibit STT cells (Yeziarski *et al.*, 1983). Alternatively any of these descending systems could activate propriospinal systems (Gerhart *et al.*, 1983). Sorkin and co-workers have demonstrated that stimulation of the VPL nucleus elicited increases in extracellular serotonin concentration in the monkey spinal cord (Sorkin *et al.*, 1992). They hypothesized that thalamic stimulation retrogradely activates the NRM-spinal tract, in turn releasing serotonin which acts as a pain modulator. Thus a large variety of mechanisms may explain the efficacy of thalamic stimulation for the relief of pain.

Indications, results and complications

Patients selected for placement of deep brain stimulation for the treatment of pain should have chronic pain unresponsive to medical or surgical therapies over several years, and have been assessed in an inpatient pain clinic. Candidates for the procedure should have no evidence of psychological issues or of secondary gain from the procedure (Gildenberg and DeVaul, 1985). The opiate test (see above) has been used (Levy *et al.*, 1987). In many published studies, patients were studied by intravenous morphine infusion test (Boivie and Meyerson, 1982; Hosobuchi, 1986; Bendok and Levy, 1998; Weiss *et al.*, 2004). Significant naloxone-reversible analgesia in response to morphine was used to identify patients with nociceptive pain best treated with PAG stimulation. Failure of opiate analgesia was used to identify “neuropathic” pain best treated by thalamic stimulation and electrode location in Vc, or both in Vc and PAG in patients with a partial response.

In an early study, success was measured by regular use of the stimulator, and by this criterion success was measured at 60% initially (6 weeks) and at 30% in longer term (greater than 6 weeks) follow-up (Levy *et al.*, 1987). Patients with nociceptive pain had a 60% initial success rate and a 30% long-term success rate, while patients with neuropathic pain experienced 50% and 20% success rates. In another study, patients with DBS placed in Vc for chronic pain had 68% initial and 57% long-term success rates (Hosobuchi, 1986).

The most recent study included 56 patients with different forms of neuropathic and mixed nociceptive/neuropathic pain with blinded, long-term follow-up (mean 3.5 years, range 1–8 years) (Rasche *et al.*, 2006a). Electrodes were routinely implanted both in the somatosensory thalamus and the periventricular gray region, and before implantation of the stimulation device, a double-blinded evaluation tested the efficacy of stimulation alone and in combination. The best long-term results were attained in patients with chronic low back and leg pain, who had greater than 50% relief in 8/18 cases, and in those with CRPS type 2 (4/6 cases). Least benefit was found in patients with central pain (spinal cord injury pain 0/12 cases, CPSP 1/11 cases).

Opiate screening tests were initially used to determine the target for DBS in another large series (Young and Rinaldi, 1997) and electrodes were subsequently implanted in both PAG and Vc. In the latter case the best electrode was determined by optimal stimulation parameters during the trial of stimulation. Of the 89 patients with a permanent implant, 62% experienced long-term pain relief, which included 70% of patients with nociceptive pain, and 50% of patients with neuropathic pain.

A meta-analysis of DBS for treatment of chronic pain (13 reports including a total of 1114 patients) concluded that 50% of patients had long-term relief from pain overall. Long-term relief was achieved in 60% of patients with PAG stimulation for nociceptive pain and in 56% with Vc stimulation for neuropathic pain (Bendok and Levy, 1998). A database study of the European Association of Neurology Panel on Neurostimulation for the Treatment of Pain identified two recent studies using current standards of MRI target localization in thalamus or PAG/PVG (Cruccu *et al.*, 2007). The first described results in 15 patients with CPSP who identified success (pain relief > 30%) in 67% of patients in the long term. The other included 21 patients with mixed neuropathic pain syndromes, and concluded that only 24% of patients had durable pain relief as defined by use of DBS for over 5 years. Overall, they considered that there was weak positive evidence for use of DBS in peripheral neuropathic pain.

A low rate of significant complications was reported. Hemorrhage occurred in 14/441 cases (three deaths) due to the design of the electrode, which has now been improved (Modelo 3387, Medtronic, Minneapolis, MN) (Hosobuchi, 1986;

Levy *et al.*, 1987; Young and Rinaldi, 1997). Neurological side effects were reported in 7% of cases, including diplopia, oscillopsia, hemineglect and hemiparesis. Persistent headache occurred commonly in one study (Young and Rinaldi, 1997).

Infections occurred in up to 12% of cases (Hosobuchi, 1986; Levy *et al.*, 1987; Young and Rinaldi, 1997). This included both subdural or subgaleal infections which responded readily to antibiotic treatment and hardware infections which responded to removal of the hardware and antibiotics. Ventriculitis and subdural empyema occurred rarely. Technical failures were reported in all studies, including migration of the electrode (up to 10%) and fracture of the insulation (up to 4%). Skin erosions occurred in 2% of cases. The technical complications and hemorrhage rates have decreased with the introduction of the newly designed electrode system (Benabid *et al.*, 1996). In the meta-analysis, the complications were summarized for 649 patients in eight series and included hemorrhage rates (1.9–4.1%), infection (3.3–13.3%), mechanical problems (2–9.9%) and erosions occurred in 1.4% overall.

Motor cortex stimulation

Epidural motor cortex stimulation (MCS) emerged as a treatment for chronic pain as a result of Tsubokawa's studies of the analgesic effects of stimulation of a number of structures in the brain (Tsubokawa *et al.*, 1987). Motor cortex stimulation produced long-term inhibition of the abnormal neuronal activity recorded in the thalamus of cats after cordotomy, which presumably results in post-cordotomy dysesthesias. Thereafter, the same group reported success with this technique in a pilot study of seven patients with chronic, neuropathic pain (Tsubokawa *et al.*, 1991). Excellent or good pain control was obtained in all cases without any complications or side effects. They also reported an increased temperature of the painful skin, and an increased range of movement of the painful limbs. As a result of these studies motor cortical stimulation emerged as a surgical therapy for chronic pain (Brown, 2003, 2004; Brown and Barbaro, 2003).

The surgical technique requires a small craniotomy over the central sulcus under local anesthesia (Brown and Barbaro, 2003). Motor cortex is identified by multiple radiological and physiological techniques. The target for facial pain is thought to be in the inferior, lateral precentral sulcus adjacent to the inferior frontal gyrus (Nguyen *et al.*, 2000b). The target for upper extremity is the precentral gyrus about 3 cm lateral to the midline over the cortical gyrus subserving hand motor function. The effect of MCS on the patient's pain is assessed by intra-operative and post-operative trials of stimulation; the latter is accomplished through a temporary extension cable which is led through the skin. If a greater

than 50% decrease in pain can be evoked by stimulation at some parameters during an extra-operative trial, then the electrode is internalized and attached to an internal pulse generator. Subthreshold stimulation is then carried out chronically at parameters of approximately 70–90 Hz, 120–200 ms pulse-width and 3–6 volts (Nguyen *et al.*, 2000b; Brown and Barbaro, 2003; Rasche *et al.*, 2006b).

Mechanisms of motor cortex stimulation

Motor cortex stimulation has been shown to modulate neuronal activity in the dorsal horn of the spinal cord. Electrical stimulation of the motor cortex inhibited responses to noxious pressure and pinch stimuli in a graded fashion, so that higher voltages produced greater reductions in the responses to these stimuli. Stimulation did not affect the responses to an innocuous brush stimulus, as recorded from wide dynamic neurons in lumbar spinal dorsal horn in rats (Senapati *et al.*, 2005). However, mixed results from MCS have been reported in monkeys so that MCS resulted in excitation, or excitation followed by inhibition, of STT cells (Yeziarski *et al.*, 1983).

A recent PET study demonstrated that MCS in chronic neuropathic pain patients induced activation, partly during the stimulation period but mainly in the poststimulation period in many areas. These areas included the anterior cingulate gyrus adjacent to the central sulcus or the anterior aspect of the corpus callosum, orbitofrontal cortex, putamen, thalamus and brainstem (PAG and pons) (Peyron *et al.*, 2007). Regional CBF changes during this poststimulation period correlated with pain relief. A functional connectivity analysis suggested that these areas are all connected and form a network that was influenced by motor cortex activation. Lack of efficacy of MCS in a subset of patients may be due to damaged corticospinal tracts or intra-cortical connections.

Changes in the endogenous opioid system have also been reported to be related to the analgesia produced by MCS (Maarrawi *et al.*, 2007). Changes in opioid receptor binding resulting from MCS were studied by PET scans using the non-selective opiate antagonist-labeled diprenorphine in patients ($n = 8$) with neuropathic pain with different etiologies, with replication. Post-operative PET scans revealed significant decreases in binding of diprenorphine in the anterior cingulate cortex, periaqueductal gray, prefrontal cortex and cerebellum. The decrease in diprenorphine binding suggests that endogenous opioids are released by stimulation and so occupy more receptors. This correlation strongly supports the suggestion that the effect of MCS is mediated through the endogenous opioid system.

Transcranial magnetic stimulation (TMS) is a relatively new technology that offers the possibility of transiently stimulating or “resetting” the brain non-invasively. Since the outcome of MCS varies between patients and this procedure is invasive, the TMS procedure may be of value to screen patients that may be

responders for the electrical MCS. A recent study showed that repeated sessions of repetitive transcranial magnetic stimulation (rTMS at 20 Hz for 10 minutes each day for 5 successive days) over the motor cortex reduced pain by about 40% compared with baseline and sham rTMS in patients with post-stroke central pain for at least 2 weeks after the end of the treatment (Khedr *et al.*, 2005).

Indications, results and complications

The best indication for MCS is neuropathic pain in a trigeminal distribution or CPSP, although a number of characteristics predicting success have been reported (Brown and Barbaro, 2003). Satisfactory pain relief has been found in 73% of patients without motor weakness, but in only 15% of those with moderate to severe motor weakness (Katayama *et al.*, 1998). If motor responses cannot be induced by stimulation, then only 8% of patients will obtain pain relief. The conclusion to be drawn is that MCS requires an intact motor system to be effective, but not an intact somatosensory system. Studies of pharmacological, pre-operative predictors of success have found that satisfactory pain relief by MCS is found in patients with at least 40% pain relief in response to incremental infusions of intravenous thiamylol to a maximum dose of 250 mg but not with morphine in doses of up to 18 mg given over 5 hours (Yamamoto *et al.*, 1997).

An early clinical report presented the initial results from treatment of 12 patients with CPSP (Tsubokawa *et al.*, 1991). Among this group eight patients had durable pain relief lasting at least 1 year. Similar results were described by Meyerson who reported greater than 50% pain relief in each of five patients with trigeminal neuropathic pain. Dysesthesia and hyperesthesia/allodynia were also decreased during stimulation (Meyerson *et al.*, 1993). A series of three patients with CPSP secondary to lateral medullary infarctions (Wallenberg syndrome) were treated with MCS (Katayama *et al.*, 1994). Two out of three patients obtained “satisfactory pain relief” from motor cortex stimulation, while none obtained relief from thalamic DBS.

A retrospective study with long-term follow-up (3.6 years, range 1–10 years) has confirmed these results. Chronic neuropathic pain in 17 patients was treated with epidural stimulation electrodes. In ten cases, trigeminal neuropathic pain (TNP) and in seven cases post-stroke pain (PSP) were diagnosed. The placement of the electrodes was followed by a stimulation trial including double-blind assessment of pain intensity which identified a positive response in three of ten patients with facial neuropathic pain and three of seven with CPSP. These results were apparently maintained at last follow-up (Rasche *et al.*, 2006b; see also Nguyen *et al.*, 2000a).

The overall level of evidence supporting the use of motor cortical stimulation for the treatment of pain has been assessed in detail. The European Database Study of Neurostimulation for the Treatment of Pain concluded that the use of motor

cortical stimulation was supported by multiple retrospective studies without validated measures of outcome in amputation pain (phantom and stump), post-stroke, facial pain and headache (Cruccu *et al.*, 2007; see also Coffey and Lozano, 2006). This database study concluded that there is convincing evidence that MCS is useful in 50–60% of patients with CPSP and trigeminal neuropathic pain.

Complications are frequent, and include seizures which may occur in as many as 41% of patients, usually during implantation of the stimulator (Rasche *et al.*, 2006b). Kindling and epilepsy have not occurred. Bezard *et al.* (1999) have studied the effect of MCS in monkeys. Though stimulation could cause reversible seizures, neither epilepsy nor a reduced threshold for kindling of seizures occurred. Epidural hematomas have been associated with the MCS surgery, but not with neurological injury. Stimulator pocket infections and electrode wire fractures have occurred, all known complications of the implantation of neuromodulation equipment and not unique to MCS (Rasche *et al.*, 2006b; Cruccu *et al.*, 2007).

Cingulotomy for pain

The ACC and associated structures were first suggested to be a target for psychiatric surgery by Fulton, based on studies in monkeys (Pribram and Fulton, 1954). This approach was subsequently adopted for treatment of chronic pain (Foltz and White, 1962; Ballantine, Jr. *et al.*, 1967). These early papers reported that following cingulotomy chronic pain was reported to be less “bothersome” or unpleasant (Foltz and White, 1962). These studies demonstrated an effect of cingulotomy on chronic pain which is seemingly opposite to that in studies of experimental pain before and after cingulotomy (Davis *et al.*, 1994; Talbot *et al.*, 1995).

The advent of modern imaging techniques has led to MRI-guided cingulotomy (Hassenbusch *et al.*, 1990; Cosgrove and Rauch, 2003). This procedure is based on MRI mapping spanning the entire anterior cingulate cortex and frontal horns of the lateral ventricles. Targets are chosen 2–5 mm above the roof of the lateral ventricle, 7 mm from the midline and 20–25 mm posterior to the tip of the frontal horn. A radiofrequency electrode is introduced to the target, and the lesions are made (Cosgrove and Rauch, 2003).

Mechanisms of cingulotomy

Functional imaging

Our understanding of the role of the ACC in pain perception is largely based upon functional imaging and neurophysiological studies. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have shown multiple areas of increased regional cerebral blood flow (rCBF) or blood oxygenation level dependent (BOLD) signal increases in response to painful stimuli.

These cortical areas include: the primary somatosensory cortex (SI), cortex around the sylvian fissure (PS, parasyllian cortex), prefrontal cortex, supplementary motor area (SMA) and the cingulate gyrus. These studies provide evidence to support the role of the posterior ACC, just anterior to the central sulcus in the processing of pain (Jones *et al.*, 1991; Talbot *et al.*, 1991; Casey *et al.*, 1994, 1996; Coghill *et al.*, 1994; Craig *et al.*, 1996; Vogt *et al.*, 1996; Derbyshire *et al.*, 1997; Rainville *et al.*, 1997; Ploghaus *et al.*, 1999; Lorenz *et al.*, 2003; Moulton *et al.*, 2005).

Activation during painful stimulation has been identified in multiple locations within the cingulate cortex anterior to the marginal branch of the cingulate sulcus (see Chapter 4) (Davis *et al.*, 1995, 1997; Rainville *et al.*, 1997; Becerra *et al.*, 1999; Ploghaus *et al.*, 1999; Moulton *et al.*, 2005). These studies have also demonstrated widespread cortical areas apparently encoding the actual and perceived intensity of the painful stimulus (Coghill *et al.*, 1999).

Imaging studies have also demonstrated functional differences which depend on location along the anterior-posterior axis of the cingulate gyrus. Pain-related cerebral blood flow increase or BOLD activation is frequently found in the posterior ACC (Hsieh *et al.*, 1995; Davis *et al.*, 1997; Derbyshire and Jones, 1998). This area is also activated when the unpleasantness of pain is increased by hypnosis, without altering the intensity of the pain (Rainville *et al.*, 1997).

Attention-related tasks (e.g. verbal fluency or Stroop tests; Lezak, 1995) activate posterior ACC based on group analysis, but individual responses showed more widespread activation of the medial frontal cortex (Davis *et al.*, 1997; Derbyshire *et al.*, 1998). Direct comparisons indicate that separate regions within the ACC are activated more strongly by attention tasks than by pain (Davis *et al.*, 1997; Derbyshire *et al.*, 1998). The ACC is activated when subjects experience capsaicin-induced heat allodynia, but not when experiencing normal (non-sensitized) heat pain (Lorenz *et al.*, 2002). Finally, the ACC can be activated by the expectation of pain (Ploghaus *et al.*, 1999), anxiety surrounding pain (Ploghaus *et al.*, 2001) or by intravenous opiates (Wagner *et al.*, 2001).

Neurophysiology

Animal and human electrophysiological evidence also supports a role of the medial thalamus and cingulate gyrus in pain processing. The presence of neurons which respond to painful stimuli has been demonstrated in the medial thalamus (Bushnell and Duncan, 1989). Anatomical confirmation of such cells has been demonstrated in the central lateral, the parafascicular and the medial dorsal nuclei of monkeys (Perl and Whitlock, 1961; Casey, 1966). In monkeys, these cells responded exclusively to noxious stimulation in large receptive fields (Perl and Whitlock, 1961; Casey, 1966), although during some states of consciousness there was convergence with other sensory modalities.

Studies of the human medial thalamus have identified nociceptive neurons in the centre médian/parafascicularis nuclear complex (Sano *et al.*, 1970; Ishijima *et al.*, 1975; Tsubokawa and Moriyasu, 1975). One group of cells responded at a short latency to the application of noxious stimuli. A second group of cells responded following a long latency and showed prolonged after-discharges. Both types of cells had receptive fields that were large and often bilateral. Analogous neurons in the monkey medial thalamus showed the capacity to encode noxious stimulus intensity, despite having large, spatially diffuse receptive fields (Bushnell and Duncan, 1989). Thus, these cells may be involved in the sensoridiscriminative aspect of pain. Nociceptive cells were not reported in more recent human microelectrode studies, apparently directed toward the same nuclei (Rinaldi *et al.*, 1991; Jeanmonod *et al.*, 1993).

Pain has been reported in response to stimulation of the medial thalamus during thalamotomy in patients with chronic pain (Sugita *et al.*, 1972; Sano, 1979). Two types of stimulation-evoked sensation have been reported following stimulation in medial thalamus (Sano, 1979). The first type was described as a diffuse, burning pain referred to the contralateral half of the body or on occasion the whole body which may have been evoked by stimulation of the centre médian/parafascicularis nuclei. The patient's chronic pain was said to be exacerbated by stimulation at these sites. The second type of sensation was a generalized "unpleasant" sensation, not localized to a particular body part which may have been evoked by stimulation of the medial dorsal and periventricular nuclei. Stimulation-evoked pain was not reported in the more recent human microelectrode studies directed toward the medial and intralaminar thalamus (Rinaldi *et al.*, 1991; Jeanmonod *et al.*, 1993).

Cortical responses to noxious stimuli have been reported in human and animal studies. Neurons in ACC of rabbits and rats respond to noxious stimuli (Sikes and Vogt, 1992; Yamamura *et al.*, 1996). Based on observations made just prior to cingulotomy, neurons in the human ACC responded to painful cutaneous stimuli, or to pain-related events, such as observation or anticipation of the application of a painful stimulus (Hutchison *et al.*, 1999). Similar anticipatory and nociceptive neuronal responses were recorded in the ACC of monkeys while performing an avoidance task (Koyama *et al.*, 1998).

Nociceptive inputs to the ACC based on EEG potentials recorded directly from the cortex (electrocorticography) have been demonstrated in response to application of a painful cutaneous laser (laser-evoked potentials – LEPs) (Lenz *et al.*, 1998) (see Chapter 8). These consist of a negative wave (N2) followed by a positive wave (P2). Scalp LEPs having vertex maximums (Carmon *et al.*, 1978; Bromm and Treede, 1984) may arise in part from generators in the ACC, as assessed by scalp source analysis (Tarkka and Treede, 1993; Chen and Bromm, 1995; Kitamura *et al.*, 1995).

Laser-evoked potential N2 and P2 peaks were also recorded from the high lateral convexity near the primary somatic sensory cortex hand area (SI region; see [Chapter 8](#)), and near the sylvian fissure (parasyllian region) (Ohara *et al.*, 2004a, 2004b). The LEP N2 and P2 peaks in the SI region were distributed over both pre- and postcentral cortical areas. For the PS cortex, both N2 and P2 were maximal near the junction of the central sulcus and sylvian fissure with polarity reversal (see [Fig. 4.14](#)). Over the medial frontal region, both N2 and P2 peaks were distributed over the cingulate sulcus and the supplementary motor area, with polarity reversal near the cingulate sulcus.

The effect of ACC lesions upon pain-related behaviors or pain perception

The rationale for cingulotomy for pain is related to imaging studies (see above) and to studies of rodent models of subacute or chronic pain (Donahue *et al.*, 2001; Lagraize *et al.*, 2004; Senapati *et al.*, 2005). A model of inflammatory pain was produced by injection of formalin into the forepaw, and a model of neuropathic, chronic pain and mechanical hypersensitivity was produced by an L5 nerve root ligation. Pain-related behaviors were decreased by an electrolytic lesion of the ACC in the inflammatory pain model (Donahue *et al.*, 2001). In the neuropathic pain model mechanical hypersensitivity was unchanged while escape/avoidance behaviors were decreased (Lagraize *et al.*, 2004).

A study of experimental pain before and after cingulotomy in a patient with psychiatric disease (Davis *et al.*, 1994) yielded results different from those anticipated by the early literature of cingulotomy for chronic pain (Foltz and White, 1962). The Davis *et al.* (1994) study demonstrated increased perceptions of both the intensity and unpleasantness of painful hot stimuli post-cingulotomy although the heat pain threshold was increased (Davis *et al.*, 1994). That is to say, there was decreased sensitivity to heat at threshold, but increased intensity and unpleasantness of suprathreshold stimuli. The cold pain threshold was also increased, i.e. decreased sensitivity, although the patient was unusually sensitive to cold pain pre-operatively.

A similar study of experimental thermal and pain stimuli was carried out before and after a cingulotomy in a patient with obsessive-compulsive disorder (Greenspan *et al.*, 2008). Thresholds were not significantly different between these two time points, as compared with a test-retest database in controls. However, (suprathreshold) heat pain and cold pain intensity ratings were increased during water bath testing. The unpleasantness ratings were increased post-cingulotomy for heat but not cold pain. Among these two studies of the effect of cingulotomy upon experimental pain the consistent finding is the increased ratings of intensity and unpleasantness of thermal pain (Davis *et al.*, 1994; Greenspan *et al.*, 2008).

Another psychophysical study examined the effects on experimental pain of anterior capsulotomy in a patient with psychiatric disease. This lesion interrupts afferent and efferent fibers to the anterior portion of the ACC and other frontal lobe structures (Talbot *et al.*, 1995). Post-capsulotomy effects upon thermal pain perception included decreased intensity and unpleasantness ratings for supra-threshold stimuli. When tested by the cold pressor test, which involves immersing one hand in an ice water bath, the patient rated the ice water as less painful, but he had much shorter immersion times, consistent with decreased tolerance. His behavioral reactions, however, were not consistent with decreased tolerance, as he was perplexed that his hand came out of the water bath so quickly. The capsulotomy may have disrupted pathways that altered voluntary motor control, such that the subject was no longer able to inhibit spinal withdrawal reflexes.

It was suggested that capsulotomy blocks the subcortical input to and so disinhibits anterior cingulate cortex which reduces both the intensity and unpleasantness of noxious stimuli (Talbot *et al.*, 1995). This interpretation could reconcile the decreased ratings following capsulotomy with the increased ratings following cingulotomy. The effect of cingulotomy would decrease cingulate activity leading to increased intensity and unpleasantness. Post-capsulotomy, decreased unpleasantness ratings of thermal stimuli, including the cold pressor, are more consistent with the less “bothersome” or unpleasant nature of chronic pain which may occur following capsulotomy. Clearly the relationship between the ACC and experimental pain versus chronic or cancer pain is more complicated than assumed initially (Foltz and White, 1962).

The dichotomy between the effects of cingulotomy on acute and chronic pain is difficult to reconcile. However, recent functional imaging studies examining pain and expectations may provide some insight (Porro *et al.*, 2002; Koyama *et al.*, 2005). Both studies identified an overlap between pain and expectation-related activation in the anterior cingulate cortex. Koyama *et al.* (2005) proposed that this overlap may reflect a crucial interface between cognitive information and afferent processing of nociceptive information. Surgical disruption of the ACC may substantially alter this interaction. Thus, pain with substantial cognitive involvement, such as chronic pain, may be more susceptible to disruption of the ACC than acute pain that is driven largely by a rapid burst of nociceptive activity. In this way, the ACC may mediate the subjective experience of pain which is heavily influenced by cognitive factors.

Indications, results and complications

The largest reported series of cingulotomy for chronic pain treated 123 patients, and included both the ventriculogram (air or contrast) era and the MRI

era (Ballantine, Jr. and Giriunas, 1988). Procedures were judged to be successful if the patient reported no pain without any intake of analgesic medication or was comfortable on non-narcotic analgesics. Among 35 patients with cancer, 57% had significant relief. Among 98 patients with non-cancer pain the largest group was those with failed back syndrome (61 patients) of whom 74% benefited from cingulotomy. Numbers were much smaller in other groups such as patients with chronic abdominal pain, of whom 5/6 were improved, or phantom limb pain, of whom 3/5 reported improvement. Patients with pain from post-herpetic neuralgia or post-stroke pain never benefited, although numbers were very small (Ballantine, Jr. and Giriunas, 1988).

There are several recent reports of series of cases in which cingulotomy was performed for treatment of chronic neuropathic pain and cancer pain. A study of MRI stereotactic bilateral cingulotomy for treatment of three patients with widespread metastatic cancer reported significant relief of pain in two out of the three patients, based on reduction in pain medication requirements and subjective pain relief (Wong *et al.*, 1997). Wilkinson and colleagues reported 23 patients who underwent 28 bilateral cingulotomies for chronic neuropathic pain, including five who had enlargement of the lesion. These patients had a variety of pain syndromes, including phantom limb pain, "failed back syndrome," vascular claudication and atypical facial pain. Seventy-two percent of patients reported significant improvement in their pain, and 55% of patients discontinued opiates (Wilkinson *et al.*, 1999).

Another series of cingulotomy cases for pain included patients with cancer and nociceptive ($n = 6$) and neuropathic pain ($n = 2$) of which four had an excellent result and four had a poor to fair result (Pillay and Hassenbusch, 1992). The remaining patients had pain secondary to neurofibromatosis and post-stroke central pain with excellent and poor results, respectively. There do not appear to have been complications in this series. Finally, transient benefit was reported in a case of "whole body sympathetically maintained pain" (Santo *et al.*, 1990).

The complications of this procedure are those that can occur with any stereotactic neurosurgical procedure including intracranial hemorrhage, infection and seizure. In Wilkinson *et al.*'s series of 23 patients, two patients had seizures intra-operatively, and five had late seizures. Four of those patients were placed on phenytoin with adequate control of their seizures and one had pseudo-seizures not requiring treatment. No hemorrhages were reported, and no patients died as a result of the procedure (Wilkinson *et al.*, 1999).

A lower incidence of complications was reported in a large series (714 cingulotomies, 414 patients) performed for either chronic pain or psychiatric disease. There were no deaths and no infections. Two patients became hemiplegic secondary to acute subdural hematomas, one developed a chronic subdural

hematoma and five patients had seizures controlled by phenytoin (Ballantine, Jr. and Giriunas, 1988).

Neuropsychological testing of patients with bilateral cingulotomy for chronic pain displayed worse executive function, attention and self-initiated behavior, while language, motor control and memory were not affected (Cohen *et al.*, 1999). Another group reported that all patients had a transient flattening of affect post-operatively, and two of 23 patients had an aphasia that resolved in 48 hours. One patient exhibited repetitive hand washing lasting several days (Wilkinson *et al.*, 1999).

In summary, the studies of mechanisms of these procedures have contributed to our understanding of the human pain system. In particular, studies of cordotomy have contributed to our understanding of the function of the STT in acute and chronic pain. Studies of DBS and motor cortical stimulation have informed our understanding of the psychophysics of descending modulatory systems in humans. Finally, studies of patients undergoing cingulotomy have clarified the role of the anterior cingulate cortex in psychological factors related to pain perception.

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