STIMULATION-EVOKED PAIN AND TEMPERATURE SENSATIONS IN THALAMUS OF PAIN AND NON-PAIN PATIENTS

by

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A thesis submitted in conformity with the requirements for the degree of Master's of Science
Graduate Department of Physiology
University of Toronto

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STIMULATION-EVOKED PAIN AND TEMPERATURE SENSATIONS IN THALAMUS OF PAIN AND NON-PAIN PATIENTS

Marosh Manduch, Master's of Science Degree, 1999
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This thesis examined the location and incidence of thalamic microstimulation-evoked painful/thermal sensations in pain and non-pain patients. Awake patients undergoing functional stereotactic surgery were asked to report any sensations evoked by microstimulation (300Hz, 0.2ms, 1 sec. trains) at 1-mm intervals along microelectrode trajectories through ventrocaudal nucleus (Vc) and ventroposterior (VPVc) region.

In 49 movement-disorder and 37 pain patients microstimulation evoked painful/thermal sensations at 6.6% of the 5842 stimulation sites. The majority (77.3%) of these pain/temperature sites was located ventroposterior to Vc. The incidence of pain sites was higher in post-stroke pain patients (PSP, n=11) compared to other patients (15.1% vs 1.6% in Vc; 9.5% vs 2.8% in VPVc). In contrast, thermal sites within VPVc were evoked less frequently in PSP patients (2.3%) than in other groups (7.4%). These data demonstrate that most pain/thermal sites were located in VPVc and suggest that alterations in thalamocortical sensory processing in PSP patients may mediate chronic pain.
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<table>
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<th>Definition</th>
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<tbody>
<tr>
<td>AC</td>
<td>anterior commissure</td>
</tr>
<tr>
<td>ALQ</td>
<td>anterolateral quadrant</td>
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<tr>
<td>AMH</td>
<td>A-delta mechanoheat receptor</td>
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<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
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<tr>
<td>BC</td>
<td>bursting cell</td>
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<tr>
<td>CL</td>
<td>central lateral nucleus</td>
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<tr>
<td>CM</td>
<td>central medial nucleus</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>DBS</td>
<td>deep brain stimulating</td>
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<tr>
<td>DC</td>
<td>direct current</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
</tr>
<tr>
<td>GABA</td>
<td>γ-aminobutyric acid</td>
</tr>
<tr>
<td>HPC</td>
<td>heat pinch cold</td>
</tr>
<tr>
<td>HRP</td>
<td>horseradish peroxidase</td>
</tr>
<tr>
<td>KF</td>
<td>kollinker-fuse nucleus</td>
</tr>
<tr>
<td>LCN</td>
<td>lateral cervical nucleus</td>
</tr>
<tr>
<td>LT</td>
<td>low threshold</td>
</tr>
<tr>
<td>MDvc</td>
<td>ventral caudal aspect of medial dorsal nucleus</td>
</tr>
<tr>
<td>MG</td>
<td>medial geniculate</td>
</tr>
<tr>
<td>MS</td>
<td>multiple sclerosis</td>
</tr>
<tr>
<td>NG</td>
<td>nucleus gracilis</td>
</tr>
<tr>
<td>NS</td>
<td>nociceptive specific</td>
</tr>
<tr>
<td>NSP</td>
<td>non-stroke pain</td>
</tr>
<tr>
<td>PAG</td>
<td>pariaquaductal grey</td>
</tr>
<tr>
<td>PB</td>
<td>parabrachial nucleus</td>
</tr>
<tr>
<td>PC</td>
<td>posterior commissure</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>Pf</td>
<td>Parafascicular nucleus</td>
</tr>
<tr>
<td>PF</td>
<td>projected field</td>
</tr>
<tr>
<td>PHA-L</td>
<td>phaseolus vulgaris leukoagglutinin</td>
</tr>
<tr>
<td>PSDC</td>
<td>postsynaptic dorsal column</td>
</tr>
<tr>
<td>PSP</td>
<td>post-stroke pain</td>
</tr>
<tr>
<td>RF</td>
<td>receptive field</td>
</tr>
<tr>
<td>SHT</td>
<td>spinohypothalamic tract</td>
</tr>
<tr>
<td>SI</td>
<td>primary somatosensory cortex</td>
</tr>
<tr>
<td>SII</td>
<td>secondary somatosensory cortex</td>
</tr>
<tr>
<td>SPA</td>
<td>stimulation produced analgesia</td>
</tr>
<tr>
<td>SRD</td>
<td>subnucleus reticularis dorsalis</td>
</tr>
<tr>
<td>STT</td>
<td>spinothalamic tract</td>
</tr>
<tr>
<td>VB</td>
<td>ventrobasal complex</td>
</tr>
<tr>
<td>Vc</td>
<td>ventral caudal nucleus</td>
</tr>
<tr>
<td>Vcpc</td>
<td>parvicellular region of ventral caudal nucleus</td>
</tr>
</tbody>
</table>
Vim - ventral intermediate nucleus
VL - ventral lateral nucleus
VMb - ventromedial basal nucleus
VMpo - posterior part of ventromedial nucleus
Vop - posterior part of ventral oral nucleus
VP - ventral posterior nucleus
VPI - ventroposterior inferior nucleus
VPL - ventroposterior lateral nucleus
VPM - ventroposterior medial nucleus
WDR - wide dynamic range
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**Section 1. Introduction**

The sensation of pain is generally perceived in a negative connotation mainly due to its association with physical damage to the body and its highly unpleasant affective quality. However, physiologic pain serves a function that is imperative for the survival and well being of an individual. The usefulness of physiologic pain is illustrated by accounts of people born without the ability to feel pain. Such people are shortchanged of the valuable warning signal provided by pain and as a result are unable to avoid inflicting severe wounds on themselves. For example, individuals with a congenital insensitivity to pain often sustain extensive burns, bruises and lacerations during childhood, and frequently bite deep into the tongue while chewing food. Melzack and Wall (1982) described a man who did not feel the pain after a ruptured appendix and almost died as a result. Thus it is evident that normal functioning of the pain system is necessary for the body's well being.

Under normal conditions, the somatosensory system uses pain to alert the organism to actual or potential tissue damage. The pain that occurs before any serious injury takes place allows the organism to escape the damaging stimulus and avoid potentially serious repercussions. Such painful experiences force the organism to make associations between the noxious stimulus and pain thus allowing the organism to prevent them in the future. Also, pain that persists after the initial injury has taken place may serve to aid in the healing process by keeping the damaged body part stress-free. The pain that is perceived is a direct consequence of activation of peripheral receptors in response to noxious stimulation. For example, various conditions such as trauma, ischemia,
inflammation and tissue damage will result in the activation of nociceptors and thus pain. Such pain occurring under normal physiological conditions is termed nociceptive pain.

However, occasionally pain may persist long after the natural repair of the damaged tissue has taken place with no obvious physiological value to the organism. For example, some people undergoing amputation of a limb may experience excruciating pain in their phantom limb long after the initial surgery. Such chronic pain may last for years or even for the remainder of their lives. The pain is no longer a symptom of a disease but becomes a medical problem in itself. This type of pain is called neuropathic pain and is thought to result due to a malfunction of the pain sensing system itself. It is believed that the disruption of the pain system is usually caused by peripheral tissue or nerve damage, or damage of the central nervous system (CNS), although the precise mechanisms are largely unknown.

The purpose of this review is to examine the physiologic and pathologic mechanisms of pain. The anatomy and physiology of the nociceptive pathways will be discussed first. The review will then focus on the clinical characteristics of central pain. Finally, some of the theories regarding thalamic mechanisms of central pain will be examined.
Section 2. Literature Review

1. The Peripheral Nervous System Involved in Perception of Pain and Temperature

1.1. Nociceptors

The primary function of the pain system is to prevent bodily injury. For example, when a person touches a hot stove, the noxious (harmful) stimulus elicits a painful signal and the body responds with an appropriate action, such as a withdrawal reflex. The initial contact of the body with the noxious stimulus occurs via the receptor. The nociceptive-specific receptors, referred to as nociceptors, were originally proposed to respond exclusively to injurious or potentially harmful stimuli by Sherrington (1906). Burgess and Perl (1973) later expanded upon this definition by stating that such a sensory pain unit must be able to effectively distinguish between innocuous and noxious stimuli. In support of this criterion, it has been shown that the stimulation threshold for nociceptors is significantly higher than for mechanoreceptive units. For example, Perl (1968) showed that nociceptors responded to a sharp point when 10-100g of force was used to press against the skin at their most sensitive points. In contrast, mechanoreceptors, signaling innocuous tactile information, responded well to a 0.025g von Frey hair (Iggo, 1963).

Furthermore, nociceptors have been shown to respond in a graded manner to increasingly more noxious stimulation, whereas mechanoreceptor discharges tend to level off or even decrease as the stimulus becomes more intense (Perl 1968). There are two main classes of nociceptors:
1.1.1. A-delta Mechanical Nociceptors

The first main class of cutaneous nociceptors is termed the A-delta mechanical nociceptors and has two distinguishing characteristics (Willis 1985). First, the axons of these receptors are of the thinly myelinated type, commonly referred to as A-delta, which conduct action potentials at velocities in the range of 3-30 m/s. Second, the A-delta mechanical receptors have been shown to have high thresholds specific to mechanical stimulation.

There have been many studies of the A-delta mechanical nociceptors. Burgess and Perl (1967) investigated the characteristics of receptors from the hairy skin on the hind limb of cats by recording from single primary afferent fibers using glass micropipettes. They found 74 fibers with conduction velocities within the A-delta range that responded to noxious mechanical stimulation of the skin delivered using calibrated tweezers or a needle, but failed to respond to 3.3g von Frey hair stimulation at any spot within their receptive field. Furthermore, these receptors were almost completely insensitive to noxious heat, producing only an occasional impulse even when the heat setting was at its highest. Lastly, the receptors were tested for sensitivity to chemical stimuli. It was found that neither strong acid nor bradykinin applied to the receptive field evoked little or no response. In the absence of stimulation, these receptors exhibited rare or no spontaneous activity.

The receptive fields of the A-delta mechanical nociceptors consist of small areas located on both glabrous and hairy skin (Perl 1968). Perl (1968) studied the functional
characteristics of cutaneous nociceptors in the primate by recording discharges of single myelinated afferent fibers with microelectrodes. He identified a number of fibers conducting under 30 m/s which could not be excited by gentle mechanical stimulation of the skin, cooling of the skin to 10°C, nor heating to 50°C. However, these fibers consistently responded to noxious stimuli applied to the skin using a needle or serrated forceps. The receptive fields of all fibers within this group consisted of high-threshold mechanically sensitive small spots (under 1 mm in diameter) separated by areas which were unresponsive to identical stimuli. The number of excitable spots ranged from 3 to 20 per receptive field and the overall shape of the receptive field was roughly circular or oval and extended from under 10 mm to over 20 mm in the longest dimension.

A number of studies have noted the tendency of the A-delta mechanical nociceptors to alter their firing rate following repetitive stimulation. For example, Burgess and Perl (1967) observed that repeated stimulation of a given point in the receptive field of the A-delta nociceptive fibers with serrated forceps or the needle resulted in decreased responsiveness to the point that eventually no discharge could be elicited by stimulation. The opposite phenomenon was also reported, whereby repeated stimulation resulted in sensitization of the receptors. A well-illustrated example of such a case is presented by Fitzgerald and Lynn (1977) who recorded from A-delta nociceptor fibers during repeated noxious heating of the receptive fields. They observed that majority of the fibers did not respond to the initial stimuli. However, a discharge could be elicited from some units following the delivery of several stimuli of 50 or 55°C.
Meyer et al. (1994) suggested that there are in fact two types of A-delta mechanical nociceptors. Type I A-fiber mechano-heat (AMH) nociceptors are characterized by a very high heat threshold in addition to the typically high threshold to mechanical stimuli. Type I AMHs are presumed to correspond to the high threshold A-delta mechanical nociceptors discussed above. It is likely that due to the very high heat threshold of these receptors (e.g. 53°C or greater), their sensitivity to noxious heat stimuli was not documented by many investigators (Burgess and Perl, 1967; Burgess et al., 1968; Perl, 1968). The major distinguishing feature of Type II AMHs is their considerably lower heat threshold compared to the Type I AMHs (Treede et al., 1991). The other characteristics of the Type II AMH receptors are similar to those described for the high threshold A-delta mechanical nociceptors (or Type I AMHs).

Treede et al. (1991) hypothesized that the two types of AMHs have different functions in pain signaling based on their physiologic characteristics. They suggested that Type I AMHs may play an important role in hyperalgesia to heat, whereas the Type II AMHs are probably involved in signaling first pain, commonly described as a sharp stinging type of pain. Lastly, Davis et al. (1993) identified mechanically insensitive nociceptive afferents (MIA) of the A-delta class (and C-fibers, see below) which either failed to respond to any mechanical stimuli tested or had very high mechanical thresholds. Interestingly, some of these nociceptors responded to the application of chemical (algesic/inflammatory chemical mixture) or heat stimuli.
1.1.2. C Polymodal Nociceptors

The second class of nociceptors differs from the A-delta mechanical nociceptors in two major ways. As their name suggests, the C polymodal nociceptors have fibers conducting at velocities below 2.5 m/s which are characteristic of small unmyelinated fibers (C-fibers) (Willis, 1985). Furthermore, these receptors were demonstrated to respond to noxious mechanical, thermal, and chemical stimuli.

This polymodal response of the C-fiber nociceptors has been extensively documented by a number of investigators (Beck et al., 1974; Bessou and Perl, 1969; Kumazawa and Perl, 1977; Torebjork and Hallin, 1974). For instance, Kumazawa and Perl (1977) recorded the responses of sensory units with unmyelinated (C) fibers in the hairy skin of monkeys following mechanical and heat stimulation. They found that the polymodal nociceptors had relatively high mechanical thresholds and were maximally activated only by skin-destructive stimuli. In addition, the receptors were found to respond in a graded manner to graded mechanical stimulation within the tissue-damaging range. A linear relationship between stimulation temperature and the rate of discharge of the C-fiber nociceptors was also demonstrated in a study by Beitel and Dubner (1976). The C-fiber thermal thresholds were found to range from 38 ° to 49 °C with maximum discharge frequencies in the noxious heat range (45-55 °C ). Furthermore, as the stimulation temperature progressively increased beyond the threshold, there was a corresponding increase in the firing frequency, accompanied by a decrease in the latency of the discharge of the polymodal nociceptor fibers. No C-fiber discharges were evoked upon cooling of the skin. C-polymodal nociceptors also appear to be sensitive to noxious chemical stimuli, as
an intradermal injection of bradykinin near the receptive skin region of the polymodal receptors was found to induce a firing activity (Khan et al., 1992). Similar results have been shown following local application of acetylcholine, acids, potassium or histamine (reviewed in Willis, 1985). Finally, in a manner similar to the A-delta mechanical nociceptors, the C polymodal nociceptors exhibited little or no background activity during periods of rest (Bessou and Perl, 1969; Kumazawa and Perl, 1977).

The receptive fields of the C polymodal nociceptors tended to be smaller than those of the A-delta mechanical nociceptors and are not comprised of a large cluster of small spots. For example, Bessou and Perl (1969) found that the receptive fields of the polymodal nociceptors usually consisted of one small area of less than 2 mm². Occasionally, units with very elevated mechanical thresholds had receptive fields comprising of two to three spots of under 1 mm². A similar study by Croze et al. (1976) documented polymodal nociceptor receptive fields consisting of areas of uniform sensitivity of up to 5 mm².

Similar to the A-delta mechanical nociceptors, the C polymodal nociceptors also show both fatigue and sensitization following repeated noxious stimulation. Torebjork and Hallin (1974) provide an example of units that exhibited decreased sensitivity as a consequence of repeated mechanical stimulation. They first applied prolonged pressure using the tip of a pencil onto the receptive field of polymodal nociceptors. This induced a burst of impulses followed by a slowly adapting discharge. However, the units failed to respond when the stimulus was subsequently repeated. In contrast, sensitization of the C
polymodal nociceptors was reported by Beitel and Dubner (1976) who observed an increase in the C-fiber discharge following repeated exposure of the receptive skin area to noxious heat stimuli.

1.2. Thermoreceptors

The original hypothesis by Blix (1884) and von Frey (1895) regarding the existence of functionally specific anatomical substrates responsible for mediation of warm and cold sensations has given rise to a plethora of scientific investigations into the issue of thermoreception. It is now well established that the sensation of innocuous warm and cold are mediated via separate cutaneous receptors. The functional characteristics of each receptor type are discussed below.

1.2.1. Cold Receptors

Hensel et al. (1974) examined the structure and function of cold receptors. They used thin wick electrodes to record from single fibers of the infraorbital nerve of cats in order to analyze the functional characteristics of the cold receptors. The functional specificity of the receptive fields was established using a barrage of stimuli, including heat and cold, as well as mechanical pressure. They found that at normal room temperature the cold receptors exhibited a static discharge that could be inhibited by application of a warm rod or heat radiation. In contrast, touching the cold receptive field with the cold thermode caused a sharp burst of activity. Even when the cold thermode was brought close to the cold spot without any actual contact, a marked frequency in the cold fiber discharge was observed. This seemed to suggest that cold receptors were likely located rather
superficially within the skin. Subsequent removal of the cold thermode from the receptive field of the cold receptor resulted in a transient depression in activity, followed by a gradual reappearance of the spontaneous activity. Similar findings had been reported by Hensel and Zotterman (1950a, 1950b, 1950c).

Kenshalo and Duclaux (1977) described the receptive fields of cold units located in the hairy and glabrous skin of the arm or leg in monkeys. About half of the single fibers investigated were found to innervate single spot receptive fields. The remaining fibers innervated two to five discrete spots of skin located within a 0.5-cm radius or less. The receptive fields were found to vary considerably in shape. For example, most cold spots were of relatively small size, usually 1-2 mm in diameter. However, many individual receptive fields were elongated to form straight, crescent, or right-angle shapes, 2-3 mm wide and up to 5 mm in length. A study by Kenshalo and Gallegos (1967) showed that cold stimulation of several of the multiple cold spots results in summation of their neural activity in the single cold sensitive fiber. They suggested that this summation might be a neural analog of the areal summation of thermal stimuli reported in psychophysical studies (Hardy and Oppel, 1937, 1938; Kenshalo et al., 1967).

A number of studies examined the conduction velocities of the fibers innervating the cutaneous cold receptors in order to estimate their diameter. For example, Fowler et al. (1988) measured the reaction times to cooling stimuli at two different sites on the lower limb of human volunteers. Based on the conduction distance, the estimated mean conduction velocity for the cold fibers was 2.1 m/s. These and other data in primates
suggest that cold sensation is mediated by small myelinated fibers of the A-delta class (Iggo 1969; Darian-Smith et al., 1973; Perl 1968).

Hensel et al. (1974) determined the morphology of the cold receptors, which consisted of a bundle of nonmyelinated nerve branches with receptor axons in the top of the dermal papilla. At that point the receptor branches were observed to leave their Schwann cell envelope and penetrate the basal lamina of the epithelium, so that their tips were envaginated into the cytoplasm of the basal epithelial cells. At a depth of 50-80 um the receptor axons fused to form one small myelinated axon of 2.5-5 um diameter.

1.2.2. Warm Receptors

The second type of thermoreceptor identified in the skin was a receptor that specifically responded to innocuous warming stimuli and was subsequently termed the warm-sensitive receptor. Hensel and Kenshalo (1969) investigated the nature of the functional characteristics of warm receptors in the nasal region of cats. They used platinum or wick electrodes to record from single fibers of the infra-orbital nerve. Thermal radiation from a heating coil was directed to appropriate areas of the skin using small aluminum strips. A steady discharge was recorded from numerous single warm fibers at constant temperatures of 30°C or more. Further increase in the intensity of the thermal stimuli resulted in an increase in the firing frequency of the warm fibers. A maximum frequency discharge was observed at temperatures between 45 and 47°C. Heat stimulation at higher temperatures resulted in an inhibition of the discharge rate. Cooling of the receptive skin produced a transient depression of the neural activity within the warm fibers. Finally,
mechanical stimulation was found to be an inadequate stimulus for the warm-sensitive receptors. This functional specificity of the warm receptors was consistent with the findings from a number of previous studies (Hensel et al., 1960, 1974; Iriuchijima and Zotterman, 1960).

The receptive fields of the warm-sensitive fibers were described by Hensel and Kenshato (1969). By shielding the skin with small aluminum strips of various widths, they were able to localize the receptive fields of the single warm fibers with an accuracy of about 1-mm. They found that the single warm fibers tended to innervate only one peripheral spot whose size did not exceed 1-2 mm in diameter. The location of the warm receptors within the skin was also studied by Hensel et al. (1974) who found that the latency of their response to warm microthermode contact was of a longer latency and the localization was less accurate than that of the cold receptors. This led them to conclude that the warm sensitive structures were situated in the deep layers of the skin.

Numerous electrophysiological studies examined the conduction velocity of the fibers innervating skin receptive fields sensitive to warm stimuli (Hensel et al., 1960; Iriuchijima and Zotterman, 1960). The results of these studies suggest that the warm-sensitive fibers belong to the C-fiber category. Reaction time experiments performed on human subjects provide further evidence in support of this theory. For example, a reaction time study by Fowler et al. (1988) found that the estimated mean conduction velocity for warm stimuli was 0.5 m/s, suggesting that warm sensations were likely conducted via unmyelinated peripheral nerve fibers.
2. The Central Nervous System Involved in Perception of Pain and Temperature

2.1. Spinal Cord and Ascending Pain and Temperature Pathways

The cellular organization of the spinal cord was first documented by Rexed (1952) who showed that the cells of the spinal cord are arranged in laminae in a dorsal-ventral direction and that these laminae run the entire length of the spinal cord. The spinal cord is divided into ten laminae. The first six laminae are found in the dorsal horn and laminae VII, VIII, and IX in the ventral horn. Finally, lamina X is composed of cells clustered around the central canal. The terminations of the primary afferents into the various laminae of the spinal cord was investigated by Perl (1980). In general, it was found that the thicker the primary afferent fiber, the deeper into the laminae it penetrated. The thin unmyelinated C fibers terminated solely in the superficial laminae I and II. In contrast, the thicker myelinated A-delta fibers were found mainly in laminae I and II, but also tended to penetrate more deeply, ending in lamina V. Large myelinated A-beta fibers terminated mainly in the deep dorsal horn laminae III, IV and V. The cells receiving input from these primary afferents send projections to three general locations: (1) cells in the same spinal segment; (2) cells in other spinal segments; and (3) cells in the brain. In the trigeminal system, the subnucleus caudalis in the medullary dorsal horn is analogous to the dorsal horn of the spinal cord in terms of its laminar division and cellular composition. The axons of the subnucleus caudalis cells were shown to travel along side the STT and terminate in the VPM as well as VMpo and the medial thalamus (Darian-Smith 1973). The following section will discuss the ascending fibers and terminations of the spinal cord pathways mediating the transmission of pain and temperature signals. Specifically, the spinothalamic, spinohypothalamic, spinobulbar,
and other indirect pathways will be dealt with. The origin of the cells, the projections, and terminations of each pathway will be discussed.

2.1.1. Spinothalamic Tract

2.1.1.a. Origin of the Spinothalamic Tract Cells

The functional and morphological characteristics of the dorsal horn cells giving rise to projections that make up the main pain and temperature pathway to the brain - the spinothalamic tract (STT) - will be considered first. The STT cells were demonstrated to be located mainly in three areas of the spinal cord: lamina I, laminae IV-V, and laminae VII-VIII.

Lamina I:

Three major cell types have been identified within the lamina I of the spinal cord. The first type is referred to as nociceptive specific (NS). These cells respond to noxious mechanical stimuli, such as firmly squeezing the receptive skin with smooth-surfaced forceps, but do not respond to gentle mechanical stimuli delivered with a brush (Christensen and Perl, 1970). Some NS cells also respond to noxious heat stimulation. For example, Christensen and Perl (1970) reported lamina I NS neurons excited by a temperature step from 40 to 45°C. Temperatures below 45°C failed to evoke any impulses, whereas more intense heat stimulation produced a graded response. This study also demonstrated that the activation of these NS lamina I neurons resulted from activity in slowly conducting A-delta and C-fibers.
A second group of lamina I neurons have a multimodal response profile. These neurons respond to a noxious pinch of the skin, but not to innocuous mechanical stimulation (Christensen and Perl, 1970). In addition, they responded to moderate decreases of the skin temperature produced by an application of ether and noxious heat stimulation. This second type of lamina I neurons have been appropriately named as polymodal nociceptive (heat-pincho-cold, HPC) (see Craig and Dostrovsky, 1997).

Lamina I neurons of the last type are known as the COLD cells. Dostrovsky and Craig (1996a) reported that a cooling step delivered to the receptive field of these cells produced a large phasic excitation that lasted several seconds. These neurons were spontaneously active at normal skin temperature, and were inhibited by radiant warming of the skin. Interestingly, noxious heating resulted in a weak excitation of a few COLD units.

A study by Han et al. (1998) examined the morphological characteristics of the three major types of lamina I neurons and found a corresponding structure-function relationship. They noted that the NS cells were mostly spindle-shaped and longitudinally oriented (bipolar fusiform type). The HPC cells identified within lamina I were multipolar neurons with polygonal somata and multiple dendrites that arborized both longitudinally and mediolaterally. Both of these cell types receive deep and visceral input in addition to input from cutaneous sources (see Dostrovsky and Craig, 1997). Finally, all the COLD lamina I cells showed a general triangular shape and were classified as pyramidal lamina I neurons with three major dendritic poles and three or four dendrites.
The COLD lamina I cells receive cutaneous input (see Dostrovsky and Craig, 1997).

Wide dynamic range cells (see below) have also been identified in lamina I in addition to the three major cell types already discussed (Willis 1985).

*Lamina IV-V:*

Cells found in laminae IV-V generally fall within two categories. The first category consists of neurons that have low thresholds to mechanical stimulation (low-threshold-mechanoreceptive, LTM), such as brushing a hair or surface of the skin (Willis 1974). Noxious mechanical stimuli failed to excite these cells more strongly than low threshold stimulation. Neurons of the second type are multireceptive or wide dynamic range (WDR), and respond to innocuous brushing of the receptive skin (Dubner et al., 1989; Maixner et al., 1989; Willis, 1985), but have greater responses to noxious mechanical stimulation and also usually to noxious heat stimulation. Some studies have also reported the existence of NS cells in lamina V (see Willis 1985). The receptive fields of WDR cells are contralateral and are usually larger than those of NS cells. Willis (1985) showed a typical WDR cell receptive field that extended over the entire lower limb of a monkey, whereas the receptive field of an NS cell was restricted to the side of the foot.

Many of the lamina V cells also receive convergent input from visceral and deep sources. For example, a study by Foreman et al. (1979) examined the effect of chemical stimulation of muscle afferents on primate STT cells. They found that injections of bradykinin, 5-HT, and KCL into the arterial circulation of triceps surae muscles resulted in powerful activation of many STT cells.
Cells found within laminae VII and VIII are complex cells with distinguishing characteristics. The properties of such cells are thoroughly described in a study by Menetrey et al. (1984). These cells responded to proprioceptive (resting position of the ankle or digital joints) and exteroceptive (stimulation of skin) input. Innocuous stimulation such as mild extension of the joints or moderate indentation of the skin tended to produce an excitatory response. In contrast, noxious input consisting of radiant heat from a red-hot filament or pinching of the receptive skin resulted in inhibition of the spontaneous activity. The receptive fields of the lamina VII complex cells were found to be large, widely separated and tended to extend bilaterally. The functional role of these cells was suggested to involve the integration of somatic and motoric afferents with spinal interneuronal activity (Craig and Dostrovsky, 1997).

2.1.1.6. Ascending STT cell projections

The ascending axons originating from the STT cells within the dorsal horn travel rostrally for one to two spinal segments before decussating to the contralateral ventrolateral white matter of the spinal cord via the dorsal or ventral commissure. Studies involving silver stains for degenerating fibers in human autopsy originally showed that the STT is located in two regions of the white matter (Thiele and Horsley, 1901). One STT branch, commonly referred to as the classical 'lateral' spinothalamic tract, is located in the middle of lateral funiculus. The other branch passes through the middle of the anterior funiculus and is known as the classical 'anterior' spinothalamic tract. The two branches have also
been called the 'dorsal' or 'dorsolateral' and the 'ventral' STT (Apkarian and Hodge, 1989a). Recent anterograde and retrograde labeling studies confirmed these original findings and further suggested that the projections arising from lamina I STT cells travel predominantly in the lateral funiculus, whereas axons in the anterior funiculus originate mainly from the deeper laminae (Apkarian and Hodge, 1989a; Craig 1991). A crude somatotopic organization has been documented within the fibers of the spinothalamic tract (see Craig and Dostrovsky, 1997). It has been shown that axons from caudal body regions tend to be located more superficially in the white matter. In contrast axons from rostral body regions are located more medially. Upon reaching the spinomedullary junction, the two branches of the spinothalamic tract merge together and continue to the thalamus (Westlund and Craig, 1996). This is also the point where the trigeminothalamic fibers, which carry input from the face, intermingle with the STT.

2.1.1.c. Terminations of the STT

Numerous studies have used anterograde tracing or silver-stained degeneration techniques to investigate the terminations of the spinothalamic tract (e.g. Bowsher 1961; Apkarian and Hodge, 1989b). With the use of such techniques it has been possible to demonstrate six major termination sites of the STT in the thalamus:

ventral posterior nuclei (ventral posterior medial nucleus VPM; ventral posterior lateral nucleus VPL; ventral posterior inferior nucleus VPI), posterior region of the ventromedial nucleus (VMpo), ventral lateral nucleus (VL), central lateral nucleus (CL), parafascicularis nucleus (Pf), and caudal part of the medial dorsal nucleus (MDvc).
Before discussing each of the above regions, a quick review of the rather complicated terminology (based on different atlases in different species) of the various thalamic nuclei may be in order. The terms VPM and VPL are commonly used when dealing with the monkey thalamus. Their corresponding counterparts in the human thalamus are ventralis caudalis (Vc) internal and external, respectively. The monkey VPI nucleus refers to the parvicellular part of the Vc nucleus of man. The VMpo nucleus is thought to be part of the suprageniculate/posterior complex mentioned in earlier studies (Jones 1985; Olszewski 1952) and is likely equivalent to the posterior VP of Mehler (1966) and the limitans portae or Vc portae of Hassler (1970).

**Ventral posterior nuclei**

The most dense labeling of STT terminations within the VP was described in the dorsal rostral and ventral caudal portions of the nucleus (Apkarian and Hodge, 1989b). The terminals are found throughout the anteroposterior extent of VP and tend to be clumped into densely packed areas or clusters, similar to the 'archipelago' or 'islands' termination pattern described by Mantyh (1983) and Mehler et al. (1960). Apkarian and Hodge (1989b) noted that interspersed between these heavily labeled clumps were terminal structures that were less dense, less numerous and more uniform in distribution. The STT terminations within VP are topographically organized in the mediolateral direction so that VPL receives input from the cervical spinal cord at its medial-most extent and input from progressively more caudal spinal segments as one moves laterally. The cells receiving projections from STT were shown to project to the superficial layers of the primary somatosensory cortex (SI) (Gingold et al., 1991).
The VPI is a cell-sparse nucleus located in the ventral medial region of the VP (i.e. ventral to VPM) that has been shown to receive projections from the lamina I STT cells via the lateral funiculus (Ralston III and Ralston, 1992). The projections of this nucleus have been investigated by Stevens et al. (1993) using retrograde labeling of thalamocortical cells. They showed that the VPI nucleus projects to the secondary somatosensory cortex (SII).

Posterior ventral medial nucleus

Craig et al. (1994) used calbindin staining to identify the region of VMpo in the human thalamus. The posterior region of the VM nucleus that is located posterior to basal VM and VPM nuclei was shown to receive a highly dense STT projection (Craig et al., 1994; Ralston III and Ralston, 1992). The STT fibers terminating in VMpo originated almost exclusively from lamina I STT cells (Craig 1995; Craig et al., 1994). The STT input to VMpo was topographically organized in the anteroposterior direction so that trigeminal input was located most anterior and cervical and lumbar inputs were found progressively more posterior. The ascending projections from the VMpo nucleus were investigated by Craig (1995) and were found to terminate in the dorsal sulcal margin of the anterior insular cortex.

Ventral lateral nucleus

The VL nucleus is located just rostral to the VP nucleus and has also been shown to receive projections from the STT cells (Berkley 1980). The STT cells located in the laminae V and VII have been proposed as the most likely candidates to project to the VL
nucleus. In addition to the STT input, the VL nucleus also receives input from the deep cerebellar nuclei (Asanuma et al., 1983). The VL nucleus projects to the motor cortex and thus is likely involved in somatosensory-motor integration (Jones 1985).

Central lateral nucleus

Apkarian and Hodge (1989b) used anterograde transport of HRP to investigate the thalamic terminations of the STT in monkeys. They noted a dense and uniform HRP labeling in the CL nucleus. The terminal labeling in CL was most concentrated within its most posterior region. They also showed that majority this STT input originated from the deeper layers of the dorsal horn. The CL nucleus has also been shown to receive dense input from the cerebellum, the substantia nigra, the tectum, the globus pallidus, the mesencephalic tegmentum and the motor cortex (Jones 1985). The majority of the cells in the CL nucleus project to the basal ganglia, while others project to the motor and posterior parietal cortices (Jones 1985).

Parafascicular nucleus

Light HRP labeling of STT terminals was identified in the Pf nucleus was also observed by Apkarian and Hodge (1989b). This nucleus has been shown to project to the basal ganglia and to the motor cortex (Jones 1985).

Medial dorsal nucleus

The main nucleus within the medial thalamus that receives STT projections is the MD nucleus. More specifically, Apkarian and Hodge (1989b) found that the highest
concentration of STT terminations within the MD nucleus was concentrated in its posterior region. The origin of these STT termination has been traced to the lamina I of the dorsal horn (Craig et al., 1994). The cortical projections of the posterior region of the MD nucleus were elucidated by Craig and Zhang (1996) who showed that this area terminates in the anterior cingulate cortex.

2.1.2. Spinohypothalamic Pathway

Burstein et al. (1987) antidromically identified nociceptive spinal cord neurons that projected directly to the lateral hypothalamus in rats making up what is known as the spinohypothalamic tract (SHT). The exact origin of the SHT cells was later investigated by Burstein et al. (1990). Using a retrograde tracer to label the cells projecting to the hypothalamus, they found that the spinohypothalamic cells originated mostly bilaterally in the deep dorsal horn. Spinohypothalamic cells were also found in the superficial layers of the dorsal horn, the intermediate zone and the ventral horn. The route traversed by the projections of the spinal cells on their way to the hypothalamus was investigated by combining retrograde tracing with a series of axonal ablations (Burstein et al., 1996). It was found that most SHT neurons reach the hypothalamus through the lateral branch by either crossing the midline of the spinal cord and ascending contralaterally to the contralateral hypothalamus, or ascending to the ipsilateral hypothalamus via an ipsilateral projection. Less than half of the SHT neurons ascend through the medial projection, cross the midline in the spinal cord, ascend on the contralateral side, decussate in the optic chiasm and descend through the ipsilateral hypothalamus. Based on the involvement of the hypothalamus in the regulation of hormonal secretion and the function
of the sympathetic and parasympathetic components of the nervous system, it is hypothesized that the SHT may participate in mediating autonomic, endocrine, and affective responses to somatosensory and nociceptive stimulation (Burstein et al., 1996).

2.1.3. Spinobulbar Pathways

2.1.3.a. Cells of Origin

A number of retrograde staining studies examined the origin of the cells in the spinoreticular and spinomesencephalic pathways (Kevetter et al., 1982; Wiberg and Blomqvist, 1984). For example, Kevetter et al. (1982) mapped the distribution of the cells of origin of the primate spinoreticular tract by following injections of HRP into the pontomedullary reticular formation in monkeys. They found that more than half of the labeled spinoreticular cells were located in laminae VII and VIII. HRP-labeled cells were also found in the dorsal horn, primarily in laminae I and V. Some cells were also found in lamina X. Similar cellular distribution was demonstrated for the spinal projections to the mesencephalon (Wiberg and Blomqvist, 1984) and in the trigeminal system (Darian-Smith 1973).

The functional characteristics of the spinobulbar cells were investigated by Menetry et al. (1980) who antidromically activated spinoreticular tract neurons in the dorsal horn by stimulation at pontine and mesencephalic levels. Once identified, the cells were subjected to a barrage of stimuli to determine their response characteristics. Four separate classes of spinoreticular tract neurons were found. The first class consisted of neurons that responded solely to innocuous mechanical stimulation (LT) such as hair
movement, touch and/or light pressure. The second type were neurons with a wide
dynamic range response. These responded to hair movement, touch, and light pressure,
but were maximally excited by noxious cutaneous stimuli. The majority of these units
also responded to noxious radiant heat stimulation. Neurons in the third class responded
solely to noxious mechanical stimulation (NS) such as strong pinch. Finally, the last
category of cells were activated by innocuous mechanical stimulation, but inhibited by
stimulation of noxious origin. Some of these cells were also activated by proprioceptive
stimuli.

2.1.3.b. Spinobulbar Terminations

The terminations of the spinobulbar pathway have been traced to four major brain stem
areas: brainstem regions containing catecholamine neurons, parabrachial nucleus (PB),
periaqueductal grey (PAG), and brainstem reticular formation (Craig and Dostrovsky,
1997; Wilberg and Blomqvist, 1984; Westlund and Craig, 1996).

It has been shown that the first three termination regions receive projections from lamina
I of the dorsal horn (Westlund and Craig, 1996), whereas the brainstem reticular
formation is innervated by spinoreticular cells located within spinal laminae V and VII
(Kevetter et al., 1992). Each of the four regions will be discussed below.

Catecholamine Cell Regions

Westlund and Craig (1996) used double labeling techniques to examine the terminations
of lamina I neurons in the brain stem. They found that PHA-L (Phaseolus vulgaris
leukoagglutinin) labeled lamina I ascending projections terminated through the medulla and pons and strongly overlapped with catecholamine-containing neurons labeled for tyrosine hydroxylase. These catecholamine cell regions have been shown to be involved in cardiorespiratory and homeostatic functions. For example, Day and Sibbald (1990) induced the release of vasopressin from hypothalamic neurosecretory cells by adequate electrical stimulation of the nociceptive somatic afferents or the application of noxious stimuli. This release was blocked by injections of γ-aminobutyric acid (GABA) into the A1 norepinephrine cell group of the caudal ventrolateral medulla, thus indicating that the activation of neurosecretory vasopressin cells by noxious somatic stimuli requires activation of the A1 region. The catecholamine cell groups may also be involved in the modulation of pain. A report by Young et al. (1992) describes six patients with intractable chronic pain of central or nociceptive origin, in whom an electrode was stereotactically implanted in the region of the Kolliker-Fuse (KF) nucleus. They showed that stimulation of this region provided excellent pain relief in three of the six patients. The modulation of pain may involve the descending projections of the noreadrenergic neurons of the A7 catecholamine cell group (including KF nucleus) to the spinal cord.

Parabrachial Nucleus

Spinal projections to the parabrachial nucleus have been demonstrated by Cechetto et al. (1985) by using anterograde and retrograde transport techniques. These projections were found to originate in the lamina I of the dorsal horn and terminate predominately in the lateral part of the parabrachial nucleus. In addition to numerous interconnections with cell groups in the pontine and medullary reticular formation (Holstege 1988), the
parabrachial nucleus has been shown to project to the hypothalamus, amygdala, and the
intralaminar and ventromedial basal (VMb) nuclei of the thalamus (Saper and Loewy,
1980). Based on the connections of the parabrachial nucleus, it has been suggested that it
is likely involved in the emotional-affective (fear and memory of aggression),
behavioural (vocalization, flight and freezing), and autonomic (pupil dilation,
cardiorespiratory and adrenocortical responses) reactions to noxious events (Bernard and

*Periaqueductal Grey*

Anterograde labeling studies have demonstrated ascending projections from the
medullary and spinal dorsal horn that terminate in the PAG (Mantyh 1983; Wiberg and
Blomqvist, 1984; Yezierski and Blomqvist, 1991). The majority of these projections
originate in lamina I of the spinal cord and terminate in the lateral and ventrolateral
regions of the PAG (Yezierski and Blomqvist, 1991). The PAG has in turn been shown
to project to the hypothalamus and thalamus (Wiberg and Blomqvist, 1984). More
specifically, PAG terminations were observed along the entire thalamic reticular nucleus,
centre median nucleus and nucleus parafascicularis. Descending projections from the
PAG to the raphe magnus in the brainstem have also been documented and are thought to
be involved in descending antinociceptive modulation (Zhang et al., 1997). Electrical
stimulation of the PVG in humans has been shown to result in analgesia and relief of
intractable pain (Adams 1976; Hosobuchi et al., 1977). Several investigators have
suggested that the mechanisms underlying this stimulation-produced-analgesia (SPA)
involve the descending brain stem projection from the PAG (Basbaum and Fields, 1978;
Liebeskind et al., 1973). However, the ascending projection of PAG to the intralaminar nuclei of the thalamus has also been considered to play at least a partial role in PAG-stimulation-induced modulation of pain (Mantyh 1983). The spino-PAG-thalamic pathway could also provide an indirect alternative route for nociceptive signals to the thalamus.

Reticular Formation

Thiele and Horsley (1901) were among the first to document the evidence for a diffuse spinal input to the reticular formation of the brain stem. These findings were later supported by Mehler (1960) who used the silver degeneration techniques to examine the ascending spinal fibers in man. Villanueva et al. (1991) used HRP to retrogradely trace the spinal input into the subnucleus reticularis dorsalis (SRD) of the caudal brainstem reticular formation and found that the projections to SRD originated from all levels of the spinal cord but most densely from laminae I, V-VIII, and X spinal cells of the ipsilateral cervical spinal cord. Bowsher (1975) used physiologically guided stereotactic coagulation to lesion the cellular areas of the midbrain reticular formation in cats. The resulting degeneration was traced to the thalamus, supporting the existence of a spinoreticulothalamic pathway that has been implicated in relaying nociceptive activity to the thalamus.

2.1.4. Other Indirect Pathways

Two additional pathways that carry nociceptive signals to the thalamus are the spinocervicothalamic pathway and the dorsal column postsynaptic pathway. The
spinocervical tract carries ascending input from the second-order cells in laminae IV-V of the spinal cord to the lateral cervical nucleus (LCN) which is a group of neurons located within the dorsal portion of the lateral funiculus of the three rostral-most spinal segments. The majority of the cells in the LCN project via the medial lemniscus to the contralateral ventral posterior nuclei of the thalamus (see Kajander et al., 1987). The physiologic responses of neurons in the LCN of the cat were examined in a study by Kajander et al. (1987). They found that the LCN contained neurons with properties typical of low threshold, wide dynamic range and high threshold types that responded to innocuous and/or noxious stimulation of the skin within discrete receptive fields. The results of this study show that LCN neurons are capable of coding both the intensity and location of noxious stimuli and suggest that the spinocervicothalamic pathway may play an important role in nociception.

The dorsal column-medial lemniscus system has generally been regarded as the major pathway in mammals that signals discriminative tactile information to the brain. The postsynaptic dorsal column pathway (PSDC) has been implicated in the transmission of pain sensation (Bennett et al., 1984; Cliffer and Willis, 1994; Kamogawa and Bennett, 1986). The PSDC pathway originates from second-order cells located in laminae IV-V of the spinal cord. The projections of these cells pass along the base of the dorsal columns and the superficial aspect of the dorsolateral funniculus terminating in the ventral and rostral portions of the dorsal column nuclei. The cells located within the dorsal column nuclei in turn send projections to the contralateral thalamus (Albe-Fessard et al., 1975). Although the majority of the cells in the dorsal column nuclei respond solely to
innocuous mechanical input, nociceptive-responsive cells have also been found. For example, a study by Ferrington et al. (1988) recorded from nucleus gracilis (NG) neurons that were activated antidromically from the ventral posterior lateral nucleus of the contralateral thalamus. They found that 66% of the NG neurons responded to gentle mechanical stimulation. However, 12% of the neurons were activated by both innocuous and noxious mechanical stimulation consistent with the WDR receptive profile. The role of the PSDC pathway has recently been suggested to involve the mediation of nociceptive visceral input into the thalamus (Al-Chaer et al., 1997, 1998).

2.2. Functional Role of Anterolateral Tract Axons

The functional role of the tract fibers traversing within the anterolateral quadrant (ALQ) of the spinal cord (and the trigeminothalamic tract) has been strongly implicated in the mediation of pain and temperature sensations to higher levels of the central nervous system. The evidence in support of this notion include studies demonstrating neuronal activity in the anterolateral tract evoked by noxious stimuli and correlated to pain behaviour, as well as the effects of lesions and direct stimulation on pain behaviour. These will be discussed below.

The activity of the fibers in the anterolateral tract of the spinal cord has been shown to parallel the pain behaviour in animals. For example, a study by Simone et al. (1991) examined the effects of intradermal injection of capsaicin on the activity of the STT neurons in monkeys. The profile of the neuronal activity post-injection was compared with standardized magnitude estimates of pain in human subjects obtained after an
identical administration of capsaicin. The results showed that the time course of discharge rates of the STT WDR neurons correlated with the magnitude estimates of pain in humans. Both pain magnitude and WDR activity were highest within 15 sec after injection and then declined over the next five minutes. Similar findings were obtained by Dubner et al. (1989) who examined the relationship between the activity of medullary dorsal horn nociceptive neurons and the ability of monkeys to detect noxious heat stimuli. They found a significant correlation between the detection speed in a temperature detection task and the neuronal discharge for WDR neurons. The detection speed was previously established to be a reliable measure of the perceived intensity of noxious thermal stimuli (Kenshalo et al., 1989). These studies suggest that activity of some nociceptive cells projecting within the anterolateral quadrant are involved in the encoding of pain intensity.

Studies involving direct electrical stimulation of the anterolateral tract have also provided evidence in support of its involvement in mediation of pain and temperature signals. Mayer et al. (1975) reported that electrical stimulation of the ALQ in patients undergoing percutaneous anterolateral cordotomy for relief of intractable pain evoked pain referred to the contralateral dermatomes at levels below the segments of the stimulation. Sensations of tingling, warmth or cooling were typically reported by the patients at stimulation intensities below those required to produce pain, suggesting that pain and temperature signals are mediated by the fibers in the ALQ of the spinal cord.
Lesions of the ALQ have also been documented to affect the perception of pain and temperature. For example, Vierck et al. (1990) performed unilateral lesions of the ALQ of the monkey spinal cord. The responses of the monkeys to nociceptive electrocutaneous stimulation were monitored pre- and post-operatively in an operant escape task. It was found that the chordotomy produced a contralateral decrease in nociception in all the animals, as assessed by significantly decreased speed and force of the responses to electrocutaneous stimulation of the contralateral leg. A similar study by Norrsell (1989) tested adult cats for behavioural thermosensitivity in a temperature discrimination task before and after unilateral lesions of the lateral funiculus of the cervical spinal cord. Contralateral thermosensory deficiencies were found following lesions involving the middle part of the lateral funiculus. The results from the above studies strongly implicate the ascending pathways in the ALQ in the transmission of pain and thermosensory information.

2.3. Functional Characteristics of STT-Termination Regions in Thalamus

Numerous functional and clinical studies strongly implicate the thalamus in the processing of pain and temperature sensations. Classically, two major subdivisions of the thalamus – medial and lateral – have been suggested to be involved in mediation of different components of nociceptive pain.

The earliest concept of functional differentiation of pain processing between the medial and lateral thalamus was introduced by Head and Holmes in 1911 who reported careful neurological analysis of patients with intractable chronic pain often accompanied by
sensory abnormalities, known as the thalamic pain syndrome. These patients often exhibited diminished tactile, thermal, and pain sensibility, which led Head and Holmes (1911) to conclude that their infarcts were localized to the posterolateral thalamus. On the basis of their observations they proposed that the medial thalamus mediated the affective-motivational aspects of pain, whereas the lateral thalamus is involved in the processing of the sensory-discriminative components of pain. Recent animal recording studies have provided evidence in support of this notion. For example, nociceptive neurons in the medial thalamus have large and often bilateral receptive fields, making them unlikely candidates for precise localization of nociceptive stimuli (Bushnell and Duncan, 1989; Craig 1998; Craig and Dostrovsky, 1997; Willis 1985). Furthermore, many studies have described nociceptive neurons within the ventroposterior nuclei (VP, equivalent to Vc in humans) of the lateral thalamus of primates (Chung et al., 1986; Kenshalo et al., 1980) with small contralateral RFs and graded responses to noxious mechanical and thermal stimulation. Consequently, it is believed that the lateral thalamus is involved in the processing of the sensory-discriminative components of pain and that the medial thalamus is involved in processing of affective aspects of pain.

In contrast to the well-documented representation of pain in the thalamus, little is known about the thalamic mechanisms responsible for the processing of temperature information. However, based on results from a number of animal and clinical studies it is assumed that the two sensory systems are closely associated. For example, stimulation of the STT fibers has been shown to produce sensations of temperature as well as pain (Mayer et al., 1975). Furthermore, thermoreceptive specific cells (COLD cells) have
been found in the dorsal horn lamina I of the spinal cord that project to the thalamus (Christensen and Perl, 1970; Dostrovsky and Craig, 1996a; Han et al., 1998). Lastly, lesions of the STT in monkeys have been reported to produce thermaesthesia and a marked decrease in nociception (Norrsell 1989; Vierck et al., 1990). Lesions of the anterolateral quadrant in humans have also been documented to result in contralateral loss of pain and temperature sensibility (Spiller and Martin, 1912). Thus it is likely that much of the information learned about the pain pathways is to a large extent applicable to the neural systems responsible for temperature processing.

At present few studies have provided direct evidence for the role of the thalamus in temperature sensation. Auen et al. (1980) showed that neurons in the VPM responded to cool stimulation applied to the cat's face and tongue. Similarly, Bushnell et al. (1993) identified neurons within the monkey VPM that responded to innocuous mechanical stimuli and innocuous skin cooling (Mechano-Cool). Mechanical-cool responsive neurons have also been found in human Vc (Lenz and Dougherty, 1998). Stimulation within the Vc and the ventroposterior region of awake human patients has been shown to occasionally produce sensations of warm and cold (Lenz et al., 1993b). Cold-specific neurons have also been identified in the VMpo nucleus in monkeys (Craig et al., 1994). More recently, Davis et al. (1999) identified neurons in the region of VMpo in humans that responded to innocuous cooling of the skin. Microstimulation of this region evoked sensations of cold in the corresponding region of the body.
Thus the medial and lateral thalamus have been implicated in the processing of pain and/or temperature perception; including the intralaminar nuclei and MDvc of the medial thalamus and VP, VPI, and VMpo of the lateral thalamus. Each of these nuclei will be discussed below, however the discussion will focus mainly on primate data.

2.3.1. Ventral Posterior Nuclei

The ventral posterior nuclei, consisting of VPM and VPL, are the major somatosensory regions of the thalamus. It is within these nuclei that the contralateral somatosensory body representation is contained in a somatotopically-organized manner (Jones 1985). Consistent with the trigeminal and medial lemniscal input to the VPM and VPL, respectively, the contralateral limbs and trunk are represented in the VPL and the head, face, and intraoral structures in VPM. Each body part is represented in a curved lamella-like fashion, with a lateral convexity and with concentrically arranged neighboring lamellae representing neighboring body parts. The lower extremities are represented most laterally in VPL and the mouth and pharynx most medially in VPM. The rest of the body is represented in a systematic fashion from medial to lateral: face, head, upper extremities, trunk and lower extremities. The largest VP surface is devoted to the representation of the hand, followed in size by the face, and the VP representation of the trunk and lower limbs is proportionally small.

Scattered among these low threshold VP neurons in the non-human primates are cells responsive to nociceptive stimuli (Bushnell et al., 1993; Chung et al., 1986; Kenshalo et al., 1980). The majority of these nociceptive neurons are WDRs, responding to
innocuous and noxious mechanical stimulation. Some of the WDR neurons responded to heat stimuli as well. Nociceptive specific neurons were also encountered in the VP of the thalamus. These neurons responded in a graded manner to noxious heat stimulation but not to stimuli below 45°C, suggesting that VP may play a role in the sensory-discriminative aspects of pain perception. The receptive fields of these nociceptive neurons were small in size and generally consistent with the somatotopography of VP described above. Kenshalo et al. (1980) described the RFs of nociceptive neurons within the VPL of monkeys. Nociceptive neurons with RFs on the hindlimb were found in the lateral part of the VPL nucleus, whereas neurons with RFs located on the forelimb were in the medial part of the VPL. The nociceptive neurons were most concentrated near the dorsomedial and ventral borders of VPM and the caudal portion of VPL (Bushnell et al., 1993; Kenshalo et al., 1980). The locations of these neurons corresponded to the known terminations of the STT, which suggested that the VP nociceptive neurons received direct input from the STT (Apkarian and Hodge, 1989b). Neurons responding to innocuous and noxious stimuli including brush, pressure, pinch and squeeze were also found in VPI which is known to project to the second somatosensory cortical area (Apkarian et al., 1991).

The somatotopic organization of nociceptive neurons of the cat differs markedly from that of the primates. In contrast to the primate, the nociceptive neurons are not scattered throughout VP, instead they are found in a specific arrangement surrounding the VP. This pattern of nociceptive representation was demonstrated by a number of studies (see Willis 1985). For example, a study by Yokota et al. (1985, 1988) recorded from single
units in the VP complex of anesthetized cats. A series of innocuous and noxious mechanical stimuli were used to test each isolated unit to determine its modality-response and receptive field. The recording sites of nociceptive units were marked and subsequently identified histologically. Both NS and WDR cell types were identified along with low threshold neurons. These nociceptive neurons were located at or near the margin of the VP proper in an area referred to as the shell region. A crude topographical organization of the nociceptive units was also noted. The trigeminal units were located in VPM while units responding to stimulation of the neck, upper limbs, trunk, and lower limbs were located progressively more laterally in VPL.

Lesions in the VP nuclei have also provided support for the role of VP in pain processing. Bogousslavsky et al. (1988) studied the location and effect of thalamic infarcts in a large number of patients. They found that lesions within the area of VP resulted in thalamic pain syndrome. Animal studies also investigated the effect of VP lesions on nociception. For example, Kayser et al. (1985) injected kainic acid unilaterally into VP nuclei of rats and tested their nociceptive thresholds with graded noxious mechanical stimuli both pre- and post-lesion. They found that the rats exhibited an increased vocalization threshold to noxious stimuli on the side contralateral to the lesion but not ipsilaterally. Together these data show that the VP nuclei are integral components of the pain pathway.

Few clinical studies support the notion that the VP complex is involved in the perception of pain. Microstimulation within the Vc of human patients can occasionally evoke painful or unpleasant sensations (Dostrovsky et al., 1993). Paradoxically, chronic
electrical stimulation has been used to alleviate a number of chronic pain conditions including deafferentation pain (Gybels et al., 1993; Gybels and Sweet, 1989; Kuroda et al., 1991; Kumar et al., 1990). The mechanisms underlying this macrostimulation-induced pain relief are largely unknown.

However, the incidence of nociceptive neurons in awake human and monkey Vc is surprisingly low. For example, Lenz et al. 1993a found that only 6% (6/108) of neurons recorded in the cutaneous core of Vc responded to noxious heat stimulation. Nociceptive neurons in human Vc have been documented only in one other study (Lenz et al., 1994). Furthermore, with the exception of chronic pain patients, stimulation within human Vc only rarely evokes sensations of pain (Davis et al., 1996; Lenz et al. 1993b, 1998a). It has been suggested that perhaps structures posterior and inferior to Vc (eg. VMpo) may also be involved in nociception (Craig et al., 1994). This claim has obtained support from a number of recent studies that showed that microstimulation posterior and inferior to Vc produced sensations of pain and temperature (Lenz et al., 1993b, 1998a) (see below).

2.3.2. Posterior-Inferior Region

The primate posterior region contains a distinct nucleus, VMpo, which has been functionally identified as a specific sensory relay nucleus for pain and temperature. The VMpo nucleus has been characterized by Craig et al. (1994) using anterograde and retrograde tracing techniques and single unit recordings in the thalamus of the macaque monkey. Antidromic stimulation was used to show that VMpo receives a prominent projection from STT cells in lamina I of the spinal cord (Craig et al., 1994; Dostrovsky
and Craig, 1996a). The projections of VMpo have been proposed to terminate in the posterior aspect of the insular cortex (see Craig 1998). The VMpo nucleus was found to contain thermo-receptive specific units that were inhibited by radiant warming and excited by cooling. Nociceptive-specific neurons responding in a graded fashion to noxious heat were also found. The receptive fields of both the thermo-receptive and nociceptive-specific units were small, extending over the tip of the tongue or part of the hand, respectively. A recent study by Davis et al. (1999) has provided further support for these findings in the human. They delivered microstimulation within the region of VMpo and found that it evoked cold sensations referred to a circumscribed body part. In addition, it was found that at some of these sites neurons responded to innocuous cooling delivered to the skin area corresponding to location of the stimulation-evoked cold sensations.

According to Craig and Dostrovsky (1997), the location of VMpo in primates is consistent with the general region in the human thalamus in which infarcts were reported to produce hypalgesia and thermanaesthesia. These sensory changes included decreased sensibility to pin-prick, noxious heat or cold, and innocuous temperatures. In some patients, the sensory abnormalities were accompanied by the development of a thalamic pain syndrome characterized by an intractable burning pain localized within the region of affected sensibility (Leijon et al., 1988). Similar changes in sensory discrimination were reported in monkeys which received lidocaine injections into VPM that likely spread into the region of VMpo (Duncan et al., 1993). It was found that the microinjection of lidocaine resulted in profound deficits in noxious heat discrimination, and lesser deficits
in the discrimination of cooling stimuli. These findings, along with the human data, strongly suggest that VMpo plays an integral part in the processing of pain and temperature information along the lamina I spinothalamocortical pathway.

The location of VMpo as characterized by Craig et al. (1994) in the primate is consistent with some of the older literature dealing with the effects of stimulation in this general region. Hassler and Riechert (1959) were the first to present evidence that the parvicellular portion of the ventral caudal nucleus (Vcpc), which is located posteriorly and inferiorly to Vc, was the specific relay for the neospinothalamic tract. In support of this notion they found that stimulation within this region evoked sensations of cramp-like burning pain. Further support for this concept was provided by the observations of Halliday and Logue (1972) who found a region at the caudal end of Vc in five Parkinson disorder patients where electrical stimulation produced unpleasant dysesthesias, which were described as sharp pain, or a burning sensation. Although Vcpc most likely considerably overlaps with the VMpo nucleus, at present time it is still unclear whether this region delineates a homologous functional nucleus.

2.3.3. Intralaminar Nuclei

Nociceptive neurons have been recorded in most intralaminar nuclei of monkeys, rats, and cats (Willis 1985). For example, Bushnell and Duncan (1989) recorded from neurons in the intralaminar nuclei (CL, CM, Pf) of awake monkeys during a temperature discrimination task. The receptive fields of the nociceptive neurons were found to be large and usually bilateral, suggesting that it is unlikely that they transmit information
concerning the localization of nociceptive stimuli. These findings were in agreement with the concept that the medial thalamus subserves affective-motivational components of pain (Melzack and Casey, 1968). However, because some nociceptive intralaminar neurons were found to respond differentially to small changes in noxious temperatures, Bushnell and Duncan (1989) suggested that they may in fact participate in the perception of pain intensity in addition to their role in the affective dimensions of pain.

Further support for the role of the intralaminar nuclei in pain has been provided by clinical studies showing that lesions of the intralaminar nuclei can reduce chronic pain. For example, Jeanmonod et al. (1994) reported that medial thalamotomy, directed mostly at CL-PF nuclei, resulted in a 50-100% pain improvement in 67% of the patients. Furthermore, the majority of the patients showed no postoperative somatosensory deficits. Unfortunately, the results from lesions of the intralaminar nuclei have not been consistently reproduced in other reports and thus their effectiveness in providing pain relief is controversial (see Gybels and Sweet, 1989). Interestingly, lesions of the intralaminar nuclei have been reported not to cause the Dejerine-Roussy (thalamic pain) syndrome post-operatively (Bogousslavsky et al., 1988). Electrical stimulation within the general region of the intralaminar nuclei in human patients has been documented to evoked sensations of pain further supporting the role of these nuclei in the perception of pain (Sano, 1979).
2.3.4. Medial Dorsal Nucleus

Neurons recorded in the primate and rat MD nucleus have been shown to respond to nociceptive stimulation. For example, Craig (1998) reported nociceptive-specific neurons in the ventrocaudal portion of MD of barbituate-anesthetized monkeys that have large, sometimes bilateral receptive fields. They also showed that the ongoing activity of many MDvc neurons can be inhibited by innocuous cool and warm stimuli, and some by pinch applied outside their excitatory receptive field. Furthermore, some of the nociceptive units identified by Bushnell and Duncan (1989) may have been recorded from the MD nucleus in addition to the intralaminar nuclei.

In the cat and the rat, nociceptive neurons have been demonstrated in the medial thalamic submedius (Sm) nucleus, which like the MD nucleus, receives lamina I input and may be functionally similar. Craig (1990) recorded from Sm neurons in the cat and found that many of the units responded to pinch or to noxious heat stimuli. Similar findings were demonstrated in the rat, where a number of studies found Sm neurons with large, bilateral RFs, that were responsive to noxious stimulation (Dostrovsky and Guilbaud, 1990; Miletic and Coffield, 1989). Neurons responsive to low-threshold stimulation were also found in the Sm of the rat (Miletic and Coffield, 1989).

Neurosurgical lesions of the medial thalamus directed at the CM-Pf complex were often used to alleviate pain in some chronic pain patients (Jeamond et al., 1994; Rinaldi et al., 1991). It is possible that these lesions may have involved the ventral caudal portion of the MD nucleus (Craig and Dostrovsky, 1997). It is also notable that lesions in the
medial thalamus reportedly never cause central pain (Bogousslavsky et al., 1988). However, stimulation in awake humans rarely evokes pain (Tasker et al., 1982).

2.4. Cerebral Cortex

The role of the cerebral cortex in pain and temperature sensation has been an issue of controversy for a greater part of this century. Head and Holmes were among the first proponents of the notion that the cerebral cortex plays no essential role in pain. This view was based on their observations of a lack of a permanent deficit in pain and temperature sensibility in patients with parietal lobe lesions (Head and Holmes, 1920). Thus, Head and Holmes suggested that pain and nondiscriminative temperature sensations reached consciousness at the level of the thalamus. This conclusion was later supported by Penfield and Jasper (1954) who observed that electrical stimulation of the primary somatosensory area (SI) of the cortex produced pain in only a small number of patients undergoing surgical removal of their epileptic foci (Penfield and Bödrey, 1937).

However, evidence provided by recent imaging studies failed to support the original proposition of Head and Holmes. Studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) techniques have demonstrated altered blood flow and oxygenation in a number of cortical areas in response to noxious stimuli (Casey et al., 1996; Coghill et al., 1994; Craig et al., 1996b; Davis et al., 1995, 1997; Jones et al., 1991; Talbot et al., 1991) suggesting that the cortex is involved in mediating the sensation of pain. The cortical areas activated included the primary and secondary somatosensory cortical areas (SI and SII), the anterior cingulate cortex, and the anterior
insula. These data are in agreement with the anatomic and physiologic findings regarding the thalamocortical projections discussed above. Thus it appears likely that these cortical areas receive nociceptive inputs from the thalamus: SI from VP; SII from VPI; anterior cingulate from MDvc; and the insula from VMpo. The clinical and physiologic characteristics of each of the pain-activated cortical areas will be discussed below.

2.4.1. Somatosensory Cortex (SI/SII)

A number of studies have reported SI and SII cortical neurons responsive to noxious stimulation of the skin. For example, Kenshalo and Isensee (1983) recorded from single SI cortical neurons in anesthetized macaque monkeys. Each isolated neuron was tested for responses to innocuous mechanical and noxious mechanical and thermal stimuli. They found that the majority of the cortical neurons responded solely to light brushing of the receptive skin, but they also found neurons in areas 3b and 1 that responded maximally to pinching and/or noxious heating of the receptive field. The nociceptive neurons included both NS and WDR cells. The receptive fields of the SI nociceptive neurons had contralateral restricted receptive fields suggesting that they mediated the sensory-discriminative aspects of nociception. Nociceptive neurons in the primary somatosensory cortex have also been reported in the cat (Iwata et al., 1990; Roos et al., 1983).

Although somatosensory cortex lesions do not usually cause a permanent reduction in pain sensation (Head and Holmes, 1920), a number of clinical investigators found that such lesions may cause hypalgesia. For example, surgical resection of the postcentral
gyrus in a patient with pachymeningitis in this region resulted in a marked loss, but not
abolition, of pain and temperature sensations (Russel and Horsley, 1906). Furthermore,
lesions of the somatosensory cortex have been used for the treatment of phantom limb
pain and pain due to central nervous system damage (Horrax, 1946; Lewin and Phillips,
1952). However, the procedure is no longer considered a viable option in the treatment
of pain due to the recurrence of pain several months following the operation.

Extensive evidence from functional imaging studies also supports the role of the
somatosensory cortex in pain perception. For example, Casey et al. (1994) used PET to
measure cerebral blood flow (CBF) to identify brain structures that are active during
acute heat pain in humans and found increases in the CBF in the SI and SII cortex during
application of noxious heat (50°C) to the skin. Using fMRI, Davis et al. (1995) also
detected changes in blood flow and oxygenation in the SI cortex during electrical nerve
stimulation that evoked painful sensations. Similar findings were documented by a
various other imaging studies (Casey et al., 1996; Coghhill et al., 1994; Craig et al., 1996;
Davis et al., 1997; Talbot et al., 1991) thus further supporting the involvement of SI and
SII cortex in the processing of pain.

2.4.2. Insula

Growing evidence from functional imaging studies support the role of the insula in pain
and temperature perception. Coghhill et al. (1994) performed one of the first studies that
investigated the role of the insula in pain processing. They used positron emission
tomography (PET) to indirectly measure the cortical activity in response to painful
stimulation. Blood flow increases were reported in the region of the anterior insular cortex during the application of a painful heat stimulus. Davis et al. (1997) used fMRI to examine the cortical activations in response to cutaneous heat and cold stimuli. They found that painful thermal stimuli activated discrete regions located predominately in the anterior insula. In contrast, innocuous thermal stimuli were found to activate the posterior region of the insula. In agreement with the results of the above imaging study, Dostrovsky and Craig (1996b) demonstrated that neurons recorded in the primate insular cortex respond to noxious mechanical and in some cases thermal stimulation. Collectively, these findings provide support for a role of the insula in the perception of pain.

Further support for the role of the insular cortex in pain and temperature perception is provided by a clinical study describing a patient with a well-circumscribed tumor located just inferior and posterior to the retroinsular cortex of the right hemisphere (Greenspan and Winfield, 1992). Prior to the removal of the tumor the patient experienced sensory deficits on the left hand when compared to the right hand, including higher mechanical, heat, and cold pain thresholds. Upon reexamination 2.5 months after the surgery, the patient was found to have regained normal sensitivity in his left hand. This reversible pain deficit associated with a cerebral tumor compressing the posterior insula suggests an essential role of the insular cortex in normal pain perception.
2.4.3. Anterior Cingulate

Neurons responding to nociceptive stimulation have been identified in the anterior cingulate. A study by Hutchison (1999) used microelectrodes to record from neurons in the anterior cingulate of human patients undergoing bilateral cingulotomy for chronic depression or obsessive-compulsive disorder. During the exploratory part of the surgical procedure they examined the effects of noxious mechanical and thermal stimulation on the response of the cingulate neurons. They found that some neurons responded to noxious pinch, cold and heat stimuli delivered to the contralateral and/or ipsilateral receptive field. Similar findings have previously been demonstrated in the rabbit cingulate cortex (Sikes and Vogt, 1992). Evoked potentials were also recorded over the anterior cingulate cortex in patients following painful cutaneous stimulation (Lenz et al., 1998b). These results provide direct evidence for the involvement of the anterior cingulate in pain and temperature perception.

Lesions of the anterior cingulate have been used by some neurosurgeons to provide relief from certain chronic pain conditions such as intractable cancer pain (Hassenbusch et al., 1990; Pillay and Hassenbusch, 1992; Wong et al., 1997). Cingulotomy has also been associated with post-operative changes in pain and temperature sensibility. Such alterations in pain and temperature perception have been investigated by Davis et al. (1994). They performed detailed psychophysical testing pre- and post-cingulotomy and capsulotomy on a patient with a schizoaffective disorder. It was found that compared to pre-operative levels, the patient exhibited a moderately diminished perception of warmth,
an elevated pain threshold, and increased intensity and affect ratings to suprathreshold noxious heat stimuli following the cingulotomy/capsulotomy.

A number of imaging studies have also implicated the anterior cingulate in the perception of pain. For example, a PET study by Jones et al. (1991) demonstrated increases in blood flow in the cingulate cortex correlated with administration of painful heat stimuli. Similar results were noted by others (e.g. Davis et al., 1997, Talbot et al., 1991).

Rainville et al. (1997) investigated the cortical areas involved in the processing of pain affect. They used hypnotic suggestions to selectively alter the unpleasantness of noxious stimuli without changing the perceived intensity. Using PET they found that hypnotic suggestions for increased or decreased unpleasantness altered both the perception of pain affect and the metabolic activation of the anterior cingulate cortex. The results of this study provide evidence that links the anterior cingulate activity with pain affect.

3. Central Pain and Thalamus

3.1. Introduction

A large number of clinical studies have provided data that suggest differing roles for the medial and lateral thalamus in generation and/or mediation of chronic pain. For example, Bogousslavsky et al., (1988) noted that lesions of the lateral thalamus often result in thalamic pain previously known as Dejerine-Roussy syndrome. In contrast, lesions of the medial thalamus were reported not to produce thalamic pain. These findings are in agreement with the initial observations of Head and Holmes (1911) which led them to propose the disinhibition hypothesis of central pain (see below).
3.2. Clinical Characteristics of Central Pain

The quality of the central pain - which is defined as intractable pain caused by CNS injury - can vary greatly from patient to patient although some qualities are experienced more frequently than others. Boivie (1994) documented the most common qualities of pain reported by patients with central pain. These pain qualities included burning, aching, lancinating, pricking, and pressing. Furthermore, more than one of these qualities may be experienced together. For example, Boivie (1994) described patients with central poststroke pain who experienced burning and aching in the leg and arm, and burning and stinging pain in the face.

Central pain is often stated to be diffusely located encompassing large areas of the body. For example, central pain patients may experience pain in the whole right or left hemibody, or the entire lower half of the body. The pain can be unilateral or bilateral. However, central pain does not need to extend over large body regions. Instead, it can involve discrete areas of the body such as one hand or one side of the face.

The intensity of the central pain can range from low to extremely high, although it is almost always rated as severely unpleasant by the patients due to its constant, unrelenting presence. According to a study by Nepomuceno et al. (1979), central pain patients with minor motor deficits due to spinal cord injury would prefer to trade their pain for severe paresis if it were possible. The intensity of the pain was also found to vary with the location of the lesion. This was demonstrated by Leijon et al. (1989) who found that pain
intensity was rated highest in central poststroke patients with thalamic and brain stem lesions.

The neurological symptoms that tend to accompany central pain include various somatosensory abnormalities (Boivie, 1994). Hypoesthessias, denoting raised thresholds to somatosensory stimuli or total loss of sensibility are common in central pain. Hypoesthessias to innocuous temperature (heat and cold), noxious thermal and mechanical stimuli, and touch have been noted in central pain patients. In addition, hyperaesthesias, referring to increased sensation to a stimulus, were also observed. Thus both hyperalgesia (increased pain to noxious stimuli) and mechanical as well as thermal allodynia (pain evoked by innocuous stimuli) were found in patients suffering from central pain. Paraesthesias (tingling sensation) and numbness are also sometimes experienced by central pain patients.

3.3. Thalamic Mechanisms of Central Pain

The thalamus is believed to play a major role in most hypotheses dealing with the mechanisms of central pain. Based on careful inspection of patients with the Dejerine-Roussy syndrome (intractable pain following thalamic damage), Head and Holmes (1911) were the first to propose that lesions of the lateral thalamus were critical in the development of chronic pain. They believed that an infarct in the posterolateral thalamus resulted in the destruction of a specific sensory substrate for pain, which in turn released (or disinhibited) activity in the emotional centre of the medial thalamus that was experienced as pain.
More recently, a number of investigators have found evidence that most patients suffering from chronic pain of central origin have lesions somewhere along the spinothalamic system (for references see Boivie, 1994). The location of such lesions was deduced from the fact that central pain patients often exhibit abnormal pain and temperature sensibility, whereas their thresholds to touch, vibrations and joint movements may be normal. Bowsher (1959) proposed that the necessary lesion must affect the neospinothalamic projections terminating in the ventroposterior thalamic region.

A new version of the thalamic disinhibition hypothesis of Head and Holmes (1911) has been introduced by Craig (1998). Craig (1998) proposed that central pain results from a disruption of a part of the general homeostatic interaction between the thermosensory activity and polymodal nociceptive activity. The hypothesis predicted disruption of the thermoreceptive-specific cold activity due to damage of the lateral lamina I spinothalamo-cortical pathway to parieto-insular cortex. Since the 'thermosensory pathway' was said to inhibit the 'polymodal pain pathway', such a lesion would disinhibit the cold-evoked polymodal nociceptive activity in the medial lamina I spino-thalamo-cortical pathway to the anterior cingulate cortex. The functional consequence of a disruption of the inhibitory thermosensory pathway would then be the development of an ongoing burning pain that could be exacerbated by cold temperatures that are normally perceived as innocuous cool. Although the hypothesis eloquently combines functional and anatomical data to expand on the original Head and Holmes (1911) theory, many functional and anatomical details remain to be determined.
4. Microstimulation and Pain

The recent introduction of microstimulation in awake humans has allowed for studies to confirm and further explore the role of various thalamic nuclei (and cortical regions) in the processing of pain and temperature. Neuronal responses to noxious stimulation in animals do not necessarily prove that the neurons are involved in the perception of pain. The microstimulation technique in awake humans allows for the unique opportunity to directly ascertain the quality of the sensations evoked by stimulation of a specific nuclear structure. If a nucleus subserving a particular sensory modality is stimulated, the signals relayed to the cortex via efferent projections will result in the experience of a specific sensation. For example, stimulation of the auditory nucleus of the thalamus, medial geniculate (MG), results in the experience of auditory sensations (Dostrovsky et al., 1993). Similarly, tactile sensations known as paresthesia are generally evoked by stimulation of the principal sensory thalamic nucleus (Vc). Thus it is reasonable to assume that stimulation of a nucleus involved in the mediation of pain and/or temperature will produce painful and/or thermal sensations.

In the past only a handful of studies have employed microstimulation in awake humans to investigate thalamic mechanisms of pain and temperature. For example, Lenz et al. (1993b) studied the sensations evoked by microstimulation in the area of the human principal sensory nucleus of the thalamus in patients undergoing stereotactic surgery for relief of pain or tremor. They found that stimulation within VP most often evoked paresthetic sensations described by patients as tingling, vibration, or electric current. However, stimulation occasionally resulted in sensations of warm, cool, and pain.
Although, the study included both movement disorder and chronic pain patients, it failed to analyze the two groups separately. Thus it was not possible to comment on differences in pain and thermal sensations evoked in the two patient groups.

These findings were later confirmed and extended by Lenz et al. (1998a) who showed that pain and thermal sensations were occasionally evoked by stimulation in Vc and the region ventroposterior to Vc in chronic pain patients and in patients with movement disorders. They further found that microstimulation of both Vc and the posterior-inferior region produced sensations of pain more commonly and sensations of temperature less commonly in patients with chronic pain than in movement disorder patients.

The role of Vc in chronic pain was further investigated by Davis et al. (1996) who examined the effect of stimulation within the Vc nucleus of patients suffering from movement disorders and chronic pain. They demonstrated that pain sensations were rarely evoked by microstimulation within Vc of movement disorder patients. However, sensations of pain were more frequently elicited by stimulation of Vc in patients suffering from post-stroke pain. Interestingly, there was no difference in the incidence of pain evoked in Vc of movement disorder patients and patients with non-stroke chronic pain.

More recently, Davis et al. (1999) investigated the role of the thalamus in the perception of cold sensations. They microstimulated the thalamus of movement disorder and chronic pain patients and found such stimulation produced sensations of cold. The stimulation sites at which cold sensations were evoked were located posterior and inferior.
to Vc. This was the first study that also localized the stimulation sites in the medial-lateral plane. They found that the cold sensations were evoked by stimulation ventral and/or medial to the face/hand representation of Vc in a region that roughly corresponded to the presumed location of the VMpo nucleus.

The above microstimulation studies are subject to a number of limitations which need to be addressed and rectified if possible in future research. A difficulty common to all microstimulation studies dealing with human patients is the limited ability to precisely localize the sites where stimulation evoked pain or thermal sensations due to the lack of histological confirmation and the possibility that fibers of passage may be responsible for stimulation-evoked sensations. In order to try to deal with this issue the study by Davis et al. (1996) considered only stimulation sites delivered within the cutaneous core of Vc. Although this approach minimized the need for histological confirmation by using functional findings, it excluded data from the region posterior and inferior to Vc. On the other hand, the study by Lenz et al. (1998a) examined the effects of stimulation ventroposterior to Vc, which reintroduced the issue of accuracy of the stimulation site locations. In addition, the number of patients used in the study was quite low and there was a slight inconsistency with the findings of Davis et al. (1996). Finally, since the study by Davis et al. (1999) only examined stimulation-evoked cold sensations, its findings need to be expanded to include warm and pain sensations. Thus it is necessary to use a larger number of patients and an improved method of stimulation site localization in order to further explore the effects of microstimulation in Vc as well as in the region ventroposterior to Vc.
The present study was undertaken to address some of these issues. The incidence and locations of sites where pain and thermal sensations were evoked by microstimulation of the lateral thalamus were examined in awake patients with movement disorders as well as chronic pain. The chronic pain patients were separated according to pathology into two groups: non-stroke pain and post-stroke pain. The study examined the effects of stimulation in the posterior-inferior region as well as in Vc to allow for the extension of the findings of Davis et al. (1996) into the posterior-inferior region. To improve on some of the limitations of the study by Lenz et al. (1998a), a large number of patients was used and the method for the determination of Vc borders was improved to aid in the localization of stimulation sites within the thalamus. Also, a novel method of localizing the stimulation sites along the medial-lateral axis was developed by taking advantage of the functional microelectrode recording data showing the somatotopic organization of Vc.
Section 3. Aims and Objectives

The neural substrates and mechanisms responsible for normal physiologic perception of pain and chronic pain are still unclear. Due to the development of functional stereotactic neurosurgery it is possible to examine these issues in awake human patients to acquire unique data unavailable from animal studies. The general aim of this thesis was to examine the thalamic mechanisms responsible for perception of painful stimuli and chronic pain. More specifically, the following issues were addressed:

1) To examine the involvement of Vc in pain, the location and incidence of sites where painful or thermal sensations were evoked by stimulation of Vc was investigated.

2) To clarify the role of the region ventroposterior to Vc (i.e. VMpo) as a major thalamic pain and temperature relay nucleus, the location and incidence of sites where painful or thermal sensations were evoked by stimulation of the region ventroposterior to Vc was examined.

3) The location and incidence of the pain and temperature sites was compared between non-pain and chronic pain patients in an attempt to elucidate the thalamocortical mechanisms responsible for chronic pain.
4.1. Patient Population

The findings described in this thesis were obtained from 86 patients. These patients were undergoing stereotactic thalamotomy or insertion of thalamic deep brain stimulation (DBS) electrodes for tremor reduction (49 movement disorder patients) or control of pain (37 chronic pain patients). The chronic pain patients were further subdivided into non-stroke pain (NSP, n=26) and post-stroke pain (PSP, n=11) groups. The movement disorder group served as the non-pain control group and consisted mostly of patients with tremor as a result of Parkinson's disease or essential tremor (see Table 1 for details). The chronic pain group was comprised of patients suffering from chronic pain following primarily cerebrovascular accidents or deafferentation. The study comprised a retrospective analysis of patients operated on between the years 1990 and 1998 (see Appendix A for patient codes). Data collection was directed solely according to the requirements of the surgery with no specific hypotheses being tested during the operative mapping procedure. All patients consented to the procedures approved by the Human Experimentation Committee of the University of Toronto and Toronto Hospital.

4.2. Microelectrodes

The tungsten microelectrodes were constructed as previously described in Lenz et al. (1988a). Briefly, the length of the exposed tip of the microelectrodes ranged between 10 and 40-μm. The microelectrodes were constructed as follows: First, the connector that the manufacturer (Micro Probe Inc., Potomoc, MD) attached to the microelectrode was cut off and the shank of the microelectrode was carefully scraped with sandpaper to
TABLE 1. Patient population

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Pathology</th>
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<tbody>
<tr>
<td>Post-stroke pain</td>
<td>Undetermined lesion location (3)</td>
</tr>
<tr>
<td></td>
<td>Thalamic lesion (3)</td>
</tr>
<tr>
<td></td>
<td>Suprathalamic &amp; cortical lesion (2)</td>
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<tr>
<td></td>
<td>Cortical lesion (2)</td>
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<tr>
<td></td>
<td>Suprathalamic lesion (1)</td>
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<tr>
<td>Nonstroke pain</td>
<td>Anesthesia dolorosa (9)</td>
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<td></td>
<td>Peripheral deafferentation (5)</td>
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<tr>
<td></td>
<td>Back/spinal cord injury (3)</td>
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<tr>
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<td>Atypical facial pain (3)</td>
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<td>Essential tremor (11)</td>
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<td>Cerebellar tremor (1)</td>
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<tr>
<td></td>
<td>Shay-Drager syndrome (1)</td>
</tr>
<tr>
<td></td>
<td>Hepatolenticular degeneration tremor (1)</td>
</tr>
<tr>
<td></td>
<td>Myoclonus (1)</td>
</tr>
</tbody>
</table>

Number of patients shown in parenthesis
remove the insulation coating. This end of the microelectrode was bent to prevent
movement of the electrode and improve contact, and then inserted into a 30-cm long 25-
gauge stainless steel tube (Small Parts HTX-25-12) until about 2-cm of the electrode
remained exposed. The stainless steel tube was in turn inserted into polyamide Kapton
tubing (23 Micro ML). Epoxy glue was used to permanently fix and insulate the junction
between the microelectrode and the polyamide tubing (see Figure 1).

A customized apparatus consisting of a 3V DC battery, microelectrode clamp and a saline
bath was used to perform a "bubble test" in order to test the integrity of the insulation of
the microelectrode. The exposed end of the microelectrode shaft was connected to one
terminal of the DC battery, while the other terminal was connected to a lead. The
microelectrode and the lead were then lowered into the saline bath and the DC battery
was turned on. The microelectrode was visually inspected for the formation of oxygen
bubbles at the electrode tip. Formation of bubbles at any other place along the length of
the electrode was indicative of a break in the integrity of the electrode's insulation.
Electrodes in which the insulation was compromised were discarded or repaired if
possible.

The microelectrode was then electroplated with platinum to lower its impedance by
increasing the surface area of the tip. The microelectrode was first plated with gold to
improve the platinum plating. Each metal was plated for 5 s at 3 μA. A Microelectrode
Admittance Meter (V. Corti Elektronik Labor CH-8031, Zurich) was used to check the
impedance of the microelectrode following electroplating to ensure that the impedance of
Figure 1. Diagram depicting the construction of the microelectrode.
Figure is not drawn to scale.

- Epoxy Resin
- Polyamide Kapton Tubing
- 25-Gauge Stainless-Steel Shaft
- Tungsten Microelectrode
- Microelectrode Tip

10-40 μm
The microelectrode was less than 0.2M ohms. The electroplating procedure was repeated if the microelectrode impedance was > 0.2M ohms.

4.3. Intraoperative Setup

At the beginning of each surgical procedure the slave cylinder assembly of the hydraulic microdrive was sterilized by immersion in 2% gluteraldehyde solution followed by a sterile water rinse. The microelectrode was taken out of its protective carrier tube and inserted into a 19-gauge guide tube that was fixed to the Lexell frame adapter. The 25-gauge stainless-steel shaft located at the end of the microelectrode opposite to the tip was secured to a metal pin on the microdrive assembly to establish a connection between the electrode and the WPI DAM 80 preamplifier and the head stage by means of a coaxial cable. A ground lead was then connected to the guide tube. The microstimulation leads were attached to the Lexell adapter with sterile tape and switched with the recording leads whenever stimulation was desired. After 1988 the same leads were used for recording and microstimulation since a technique was developed that allowed stimulation and recording through the same microelectrode (Dostrovsky et al., 1993). For the most recent cases an Axon Guideline 3000 system was used that connected the microelectrode directly to the head stage.

The output from the preamplifier was amplified, isolated and filtered (highpass 300Hz, lowpass 5 kHz). The signals were then routed to a pair of oscilloscopes, a single window discriminator and an audio monitor. The oscilloscopes were used for visual inspection of multiunit neuronal activity, while the single window discriminator enabled the isolation
of single units. The activity of neurons (eg. during a receptive field search) was also monitored via the audio monitor. A CED 1401 was used to digitize neuronal activity which was stored on videocassettes for off-line analysis. A visual record of the recording and stimulating procedure was also obtained by means of a video camera and stored on videocassettes.

4.4. Stereotactic Procedures

The patients were fitted with a Leksell stereotactic frame following injection of a long acting local anesthetic at sites where the pins contact the scalp. The 3-dimensional stereotactic coordinates of each patient's anterior and posterior commissures (AC and PC) relative to the frame were then determined from high-resolution computerized tomography (CT) or magnetic resonance imaging (MRI) scans. The patients operated upon between the years 1987 and 1989 had the Leksell stereotactic frame fitted and AC-PC coordinates determined using ventriculography or CT scanning one day prior to surgery. After 1989 however, the frame application and the determination of AC-PC coordinates were performed in a single day. From 1995, the MRI was substituted for the CT scan with the rest of the operative procedure remaining unchanged. A set of sagittal thalamic maps based on the Schaltenbrand and Bailey (1959) or Schaltenbrand and Wahren atlas (1977) was generated with the use of a computer program (Hawrylyshyn et al., 1976) and stretched or shrunk as necessary to conform to each patient's intercommissural distance. These maps were then used to choose the initial target site at a distance of about 15-mm lateral to the midline, in the ventral third of the Vc (i.e. hand representation) since the Vc is the most reliable physiological landmark in the ventral
thalamus. An access burr or twist drill hole (for DBS electrode placement or lesion, respectively) was drilled in the skull of the patient following the subcutaneous injection of a long acting local anesthetic into the surrounding area of the scalp. The exposed dura matter was resected to allow stereotactic insertion of the guide tube. The Leksell adapter was then secured to the frame and the microelectrode was inserted through the guide tube. A hydraulic microdrive was used to stereotactically direct the electrode toward the chosen target in an anterodorsal to posteroventral direction so that its tip rested 10-mm short of the target. Single and multiunit recordings and microstimulation was performed as the microelectrode was driven through the thalamus to physiologically map the different nuclei (see below).

4.5. Recording and Stimulation Procedures

During each electrode trajectory the recorded activity of cells was subjected to visual and auditory inspection for any alteration in firing pattern in response to somatosensory stimulation. The predicted electrode trajectory passes through the posterior part of the ventral oral nucleus (Vop), ventral intermediate nucleus (Vim) and then the ventrocaudal nucleus. Therefore, typical receptive field search stimuli were as follows: At the top of the trajectory, the stimuli consisted of voluntary joint movements of the upper and lower limbs, and jaw. Cells responding to any of these stimuli were presumed to lie within Vop. Further along the trajectory, responses to passive movements of joints or deep stimuli (eg. brisk stroke, squeeze and pressure) were sought and responsive units were likely located within the kinesthetic/deep zone corresponding to Vim bordering on the posterior boundary of Vop (Dostrovsky et al., 1993). Next, cutaneous tactile stimulation
was administered by lightly brushing various body parts (e.g. face, hand, and arm). The receptive field (RF) of tactile cells was characterized by increased cellular activity in response to innocuous mechanical stimulation localized to an area on the body. The RFs were delineated by means of a fine paintbrush. A thermode was used to test the units within Vc or posterior-inferior to Vc for responses to innocuous and noxious thermal stimulation. The tactile relay region of Vc is located just posterior to Vim and was defined by the presence of cells responsive to cutaneous tactile stimulation of the appropriate body parts. The location of anterodorsal and posteroverentral Vc borders was carefully noted (see below for details).

The microelectrode was also used to deliver electrical stimuli at 0.5-1 mm intervals as it advanced along its trajectory. The stimuli typically consisted of 1 sec trains of monophasic pulses of 0.1-0.2 ms duration at 300 Hz. At each stimulation site the current was increased until a sensation or a motor response (e.g. tremor reduction in tremor patients) was evoked up to a maximum of 100 μA and the stimulation threshold was noted. If initial stimulation intensity evoked a sensation, the current was decreased until the sensation was no longer detected. Once the threshold was determined, stimulation at current intensities 2x or 4x threshold was sometimes delivered. After each stimulus, the patient was asked to describe the quality of any perceived sensation and comment whether it was painful or not painful. If the patient had difficulty describing the evoked sensation, a list of possible sensations that could be evoked by microstimulation (e.g. tingling, pins and needles, warm, cool, flashes, buzzing or pain) was verbally presented to the patient and the stimulation was repeated until the sensation was reliably described.
The location of the evoked sensation on the patient's body, projected field (PF), was also noted. Since the patients were awake and received no sedation they were able to reliably report any effects of microstimulation.

The location of subsequent electrode trajectories was chosen on the basis of physiologic findings from the first trajectory and specific surgical objectives. A variable number of electrode trajectories (typically 3-6) was needed to functionally establish the appropriate location for the placement of a chronic stimulating electrode or a radio-frequency lesion. In movement disorder patients, the chronic stimulating electrode or lesion was typically placed rostral to Vc in a region where cells whose firing was synchronized with the tremor (tremor cells) were encountered and stimulation resulted in cessation or reduction of the tremor. Conversely, the placement of the chronic stimulating electrode in patients experiencing chronic pain was directed to the Vc representation of the affected body part.

4.6. Data Collection

During the surgical procedure, the data collected along each trajectory (eg. electrode depth, any PFs or RFs encountered as a result of stimulation or recording, presence/absence of cells, and level of background neuronal activity) were manually recorded on individual pages with standardized figurines as well as on enlarged sagittal maps of the thalamus. These notes were later reconstructed for each trajectory with the aid of a graphical computer program (Corel Draw, Ottawa, Ont.).
4.7. Data Analysis

The Vc nucleus was defined as the region where cells responded to innocuous cutaneous mechanical stimulation (e.g. light brushing). Since each trajectory passed from anterodorsal to posteroventral, the dorsal-most cell responsive to tactile stimulation along each trajectory was taken to represent the anterior border of Vc, whereas the ventral-most tactile-responsive cell represented the posterior border of Vc. The delineation of the ventral border of Vc was also aided by the marked decrease in the background cellular activity evident during recording in regions below Vc. Only stimulation sites located within these strictly defined sections of trajectories were considered to be located within Vc. Patients must have had at least 1-mm of Vc to be included in the study. Stimulation sites located posterior and/or ventral to Vc borders defined on the sagittal plots (i.e. posterior to the vertical axis and/or ventral to the horizontal axis) were considered to lie within the ventroposterior region. Stimulation sites located on sagittal planes lacking Vc were localized within the ventroposterior region using Vc borders defined in the nearest adjacent sagittal plane.

The density of stimulation along an electrode trajectory was not constant throughout the surgical procedure. For example when stimulation resulted in reports of pain and/or thermal sensations there was often a tendency to stimulate more frequently to explore the area. To eliminate this sampling bias only pain and thermal sensations evoked at stimulation sites that were at least 1-mm apart were included in the analysis. A distance of 1-mm was chosen because it was the smallest distance along the trajectory at which stimulation was systematically delivered.
The pain and thermal sensations evoked by stimulation were divided into three categories: pain, warm, and cold. Sensations that the patients described as painful or as pain with a thermal component (i.e. burning pain, hot/cold pain) were placed in the pain category. Warm and cold categories consisted of sensations respectively described as innocuous warm or cold. Only sites at which threshold stimulation evoked pain or temperature sensations were analyzed in this study.

The method used to reconstruct the locations of the stimulation sites in the thalamus was similar to the approach used by Lenz et al (1993b, 1998a). Trajectories containing sites from which microstimulation evoked pain/thermal sensations (sometimes referred to as 'pain and temperature sites' in this thesis) and/or recording sites with cells responsive to cutaneous tactile stimulation were reconstructed on computer-generated sagittal maps. The x and y coordinates of each pain/thermal site and/or the most dorsal and ventral tactile sites on a trajectory were measured with respect to the posterior commissure (PC) and the AC-PC line respectively (see Figure 2). The coordinates for the ventral- and dorsal-most tactile sites were then subtracted from the respective x and y coordinates of the pain/thermal sites. The coordinates were normalized for differences in patients' brain size by multiplying them by a normalization ratio (patient's AC-PC length/standard AC-PC length of 23-mm). The pain/thermal sites were then plotted on a sagittal plane where a line drawn parallel to the AC-PC line and traversing through the ventral-most tactile RF was chosen to represent the ventral Vc border. A line perpendicular to the AC-PC line and passing through the most posterior site depicted the posterior Vc border with a tactile RF within that sagittal plane. The pain/temperature sites were also plotted in a coronal
Figure 2. Method used to reconstruct the locations of stimulation sites in the thalamus. The x- and y-coordinate of each stimulation site was determined to localize the site in a sagittal plane. The shortest distance between the site and a line drawn through the posterior commissure (PC) perpendicular to the AC-PC line depicted the x-coordinate. The y-coordinate was obtained by measuring the perpendicular distance between the site and the AC-PC line. A line parallel to the AC-PC line and traversing the ventral-most tactile cell represented the ventral Vc border. A line perpendicular to the AC-PC line and traversing the posterior-most tactile cell represented the posterior Vc border. The x- and y-coordinates obtained for each stimulation site were then adjusted for the posterior and ventral borders of Vc by subtracting them from the respective dorsal- and ventral-most tactile site coordinates.
plane in which the stereotactic medial-lateral coordinates of each trajectory were adjusted according to the functional somatotopy of Vc, which is known to shift from face to hand to leg as one moves laterally (Jones 1985). This medial-lateral adjustment was necessary because of the inconsistency between the estimate of the laterality based on MRI-based stereotactic coordinates and the estimate based on functional physiologic findings. Since the physiologically determined "landmarks" of each patient provide a more accurate estimate of the actual nuclear boundaries of the patient's thalamus, physiological findings were used to adjust the medial-lateral location of each trajectory. Thus the trajectories of each patient were adjusted along the medial-lateral axis in order to align the tactile representation of face/hand in all patients. The trajectories containing sites with RFs on both face and hand were presumed to correspond to the border between the face and hand representations of Vc. This border was chosen as the reference point because it was the region with the highest concentration of trajectories. In addition, the border allowed for differentiation between the medial and lateral regions of Vc that could be extrapolated to the posterior-inferior region for the estimation of the location of VMpo. The laterality of electrode trajectories in patients lacking a trajectory traversing the face/hand representation in Vc was estimated according to the RFs on other trajectories passing through Vc which were used to interpolate the most likely position of the tactile face/hand region in the unexplored region. For example, if a trajectory with RFs located on the hand was located lateral to a trajectory with face RFs, the face/hand border was estimated to lie at the medial-lateral mid-point of the two trajectories. If no face RFs were available, the trajectory with body RFs was aligned with the corresponding RF
locations on other trajectories according to best fit. The adjusted medial-lateral
coordinates were then plotted versus the dorsal-ventral coordinates of the
pain/temperature sites to construct a coronal plot. The location of the ventral Vc border
was determined in the same manner as in the sagittal plot.

Percent-density plots in both the sagittal and coronal sections were constructed to
normalize the non-uniform distribution of trajectories throughout the thalamus (eg. initial
trajectories were directed along the 14-mm lateral stereotactic coordinates and thus were
over represented). The sagittal plot of the pain/temperature sites was divided into a 21-
mm x 21-mm matrix consisting of 441 bins of 1-mm x 1-mm dimensions. The vertical
axis representing the posterior Vc border as well as the horizontal axis that represented
the ventral Vc border were defined as above and crossed at the midpoint of the matrix.
The total number of stimulation sites - including ones from which paresthesia, no-
response, pain, temperature and other sensations could be evoked - were totaled in each
bin to construct a density plot of the sampling distribution. If a bin contained less than
two stimulation sites it was considered inadequately explored and was not included as
part of the stimulation-density matrix. The number of sites where pain, warm or cold
sensations were evoked was also totaled separately per bin. Normalization was
performed by dividing the corresponding bins in each pain/temperature matrix by ones in
the matrix containing totals of all stimulation sites delivered, thus yielding a percent-
density plot of pain and temperature sites relative to the posterior-ventral borders of Vc.
A percent-density plot in the coronal plane was constructed in an identical fashion.
However, the vertical axis of the coronal percent-density plot represented the face/hand border of Vc.

To examine the relationship between RFs and PFs, the PF at sites where pain or thermal sensations were evoked was compared with the RF of cells recorded at these sites in Vc or with the PF of paresthesia sensations at adjacent sites in the posterior-inferior region. If no cells or RFs were found at the site of stimulation-evoked pain or thermal sensations in Vc, the nearest recording site with a cell RF was chosen. Similarly, in the posterior-inferior region, the paresthesia PF closest to the pain or temperature stimulation site was used for comparison. If two RFs/PFs were at an equal distance from the stimulation site where pain or thermal sensations were evoked, the dorsal comparison site was arbitrarily selected.

4.8. Statistical Analysis

The Kolmogorov-Smirnov test was first used to determine whether the parametric data were normally distributed. All parametric data tested failed the normality test and were subsequently analyzed using the analysis of variance (ANOVA) on ranks. These data were represented in median values ± 25% and 75% quartiles. Nonparametric data consisting of proportions were tested by means of a Chi-square test. A Fisher-exact test was used for data that had five or less expected values in one or more cells of the contingency table. The level of statistical significance for all tests was set at P<0.05.
Section 5. Results

5.1. Effects of Microstimulation

The results described in this study were obtained from 537 electrode trajectories in 86 movement disorder and chronic pain patients undergoing stereotactic exploration of the thalamus for treatment of tremor or pain control. Pain or thermal sensations were reported at 383 (6.6%) of the 5842 sites stimulated. Of these sites, 3581 were in the movement disorder group, 1577 in the NSP group and 684 in the PSP group. The sensation of innocuous warmth was evoked by stimulation at 3.3% (193/5842) of the sites, innocuous cold was evoked at 0.7% (38/5842) of the sites, and pain was evoked at 2.6% (152/5842) of the sites. Stimulation at the remainder of the sites resulted in no response, paresthesia or other sensations (e.g. shock, tightness, and pulling).

Examples of the effects of microstimulation are shown in figures 3-5. The results of microstimulation and recording along a trajectory traversing the thalamus of a movement disorder patient (#225, S5) are shown in Figure 3. The patient was undergoing thalamotomy for relief of tremor due to a multi-system dysfunction caused by Shay-Drager Disease. Cells responding to passive movement of the elbow and wrist were encountered at the top of the trajectory. Stimulation in this region reduced the patient's tremor, but did not produce any sensation. Neuronal responses to light brushing of the first and second digits, and the face were found further along the trajectory and were indicative of Vc. A sensation of pain accompanied by an innocuous warm sensation was elicited by stimulation at a site at the ventral edge of the tactile response, presumed to be
Figure 3. An example of an electrode trajectory reconstructed from data obtained during thalamic exploration of a Shay-Drager Disease patient. Receptive field (RF) locations and the depth (in millimeters) of the electrode tip are represented to the left of the vertical line. Stimulation intensity (in microamperes), and the locations of projected fields (PF) are shown to the right of the vertical line. Inset: location of the electrode trajectory within the thalamus based on the patient's anterior and posterior commissures and stereotactic coordinates.
Patient # 225, S5

RF depth (mm) | Int. (μA) | PF
---|---|---
9.0 | 100 |  
8.0 | TR 80 |  
7.5 |  
7.0 | TR 40 |  
6.8 |  
6.0 | PTR 20 |  
5.8 |  
5.0 | P 5 |  
4.7 |  
4.0 | P 5 |  
3.6 |  
3.3 |  
2.5 |  
2.3 |  
2.0 | P 10 |  
1.7 |  
1.4 |  
1.0 | N.W 10 |  

 Blink, responds to air on cornea

BC = bursting cell
Ki = kinesthetic cell
Ta = tactile cell
TA = tremor arrest
TR = tremor reduction
NR = no response

P = paraesthesia
O = other sensation
N = pain
W = warm
H = hot

quieter cell responds to deep breaths, no RF in chest

sparse cells

0.95
0.8
0.5
0.4

0 P 10

-1.0 H 10

-2.0 W 10

-4.0 100

0.5 mm

P = paraesthesia
O = other sensation
N = pain
W = warm
H = hot
BC = bursting cell
Ki = kinesthetic cell
Ta = tactile cell
TA = tremor arrest
TR = tremor reduction
NR = no response
near the ventral edge of Vc. Few cellular recordings were obtained posterior-inferior to
the Vc border and stimulation in this region resulted in innocuous hot and warm
sensations being reported by the patient. The hot sensation changed to hot pain when
suprathreshold stimulation was delivered at the site. Cold sensations were not evoked by
stimulation along this trajectory.

Figure 4 illustrates the recordings and microstimulation effects in a non-stroke pain
patient (S271, S1) suffering from anesthesia dolorosa secondary to the surgical removal
of a skull base tumor. The chronic pain experienced by the patient was described as
steady, sharp and/or dull aching and was localized to the V1, V2, and V3 divisions of the
trigeminal nerve. Sensory clinical testing of the patient revealed total loss of sensibility
to touch and pin prick in the right maxillary trigeminal zone. A cell firing in a
spontaneous bursting pattern (BC) was recorded at the top of the trajectory. Cells
responding to voluntary and/or passive movements of the joints, and deep pressure
stimulation were encountered anterior and dorsal to the Vc nucleus. Within Vc,
responses to cutaneous mechanical stimulation of the digits, and face were recorded from
many cells. Stimulation within the Vc resulted in paresthesia of the hand and face at
stimulation intensities of 10 μA or lower. Stimulation below Vc evoked a painful
burning sensation projected to the entire lower right extremity. An auditory sensation
described as "ringing" was evoked by stimulation ventroposterior to the site where the
burning pain sensation was obtained.
Figure 4. An example of an electrode trajectory reconstructed from data obtained during thalamic exploration of a non-stroke pain patient. Receptive field (RF) locations and the depth (in millimeters) of the electrode tip are represented to the left of the vertical line. Stimulation intensity (in microamperes), and the locations of projected fields (PF) are shown to the right of the vertical line. Inset: location of the electrode trajectory within the thalamus based on the patient's anterior and posterior commissures and stereotactic coordinates.
In Figure 5, the results of microstimulation and recording are shown for a post-stroke pain patient (#221, S1) suffering from chronic pain following an infarct involving the thalamus. The patient also exhibited mechanical and cold hyperalgesia. A small length of Vc was found on this trajectory with cells responding to cutaneous mechanical stimulation of the face and thigh. Stimulation at a site near the top of the trajectory elicited paresthesia projected to the face. Pain that was similar in quality to the patient's chronic pain was evoked at all other stimulation sites above, within, and below Vc. No warm or cold sensations were elicited at any of the stimulation sites. Stimulation beyond 0.6mm of the ventral Vc border failed to produce any responses.

5.2. Multiple Sclerosis Patients

The movement disorder group in the present study included nine patients with multiple sclerosis (MS) that were being treated for MS-related tremor. A number of clinical studies noted the occurrence of persistent pain in a percentage of MS patients (Stenager et al., 1991; Tasker 1984), although none of the MS patients included in the present study complained of pain. In view of these reports, the MS patients were separated from the movement disorder patient population and their incidence of pain and temperature sites was compared to those of the remainder of the movement disorder patients (n=40) (see Table 2). It was found that the incidence of pain sites in the thalamus, Vc and the posterior-inferior region of MS patients was not significantly different from the rest of the movement disorder patients (P>0.05, One Way ANOVA on Ranks). There was also no significant difference in the proportions of pain and thermal, thermal, warm, or cold sites between the two groups (P>0.05, One Way ANOVA on Ranks). As a result of these
Figure 5. An example of an electrode trajectory reconstructed from data obtained during thalamic exploration of a post-stroke pain patient. Receptive field (RF) locations and the depth (in millimeters) of the electrode tip are represented to the left of the vertical line. Stimulation intensity (in microamperes), and the locations of projected fields (PF) are shown to the right of the vertical line. Inset: location of the electrode trajectory within the thalamus based on the patient's anterior and posterior commissures and stereotactic coordinates.
TABLE 2. Percent of sites where stimulation evoked pain and thermal sensations in the thalamus of movement disorder & multiple sclerosis-tremor patients

<table>
<thead>
<tr>
<th>Thalamic Region</th>
<th>Movement Disorder Patients</th>
<th></th>
<th>MS-Tremor Patients</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>25%</td>
<td>Median</td>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>Thalamus (AVc, Vc, PI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>0.00</td>
<td>0.00</td>
<td>1.56</td>
<td>0.00</td>
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<tr>
<td>Warm</td>
<td>1.02</td>
<td>2.32</td>
<td>4.76</td>
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<tr>
<td>Cold</td>
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<td>0.00</td>
<td>0.53</td>
<td>0.00</td>
</tr>
<tr>
<td>Vc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Warm</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Cold</td>
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</tr>
<tr>
<td>Posterior-Inferior Region</td>
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<td>0.00</td>
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<tr>
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<td>0.04</td>
<td>0.08</td>
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<tr>
<td>Cold</td>
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</tr>
</tbody>
</table>

Median of average percent of pain and/or thermal sensations evoked per patient
25% and 75% refer to the 25th and 75th percentiles of the median
AVc anterior and/or medial/lateral to Vc; Vc nucleus ventralis caudalis
Pl posterior-inferior region; MS multiple sclerosis
findings, the MS patients were included in the movement disorder group for subsequent analysis. A comparison of the incidence of pain and thermal sensations in PSP, NSP, and movement disorder patients is presented below.

5.3. Incidence of Pain and Thermal Sites

5.3.1. Pooled-Data Method

The incidence of sites at which warm, cold, or pain sensations were evoked by threshold stimulation of the thalamus was investigated in the movement disorder, NSP and PSP patient groups. The total area of the thalamus explored was examined, including the tactile Vc and the posterior-inferior region. The number of sites where stimulation evoked pain and thermal (warm or cold) across all patients in each group was divided by the total number of stimulations delivered in the group to obtain the percent incidence.

The percentages of pain and thermal sites in the entire region of the thalamus investigated during surgery are shown in Figure 6A. The incidence of sites where pain or thermal sensations were evoked by threshold stimulation was found to be significantly higher in the PSP group than in the movement disorder (P<0.001, Chi-square test) or the NSP group (P<0.005, Chi-square test). Pain sensations were more commonly evoked in the PSP patients than in the NSP (P<0.0001, Chi-square test) or movement disorder patients (P<0.0001, Chi-square test). In contrast, the incidence of stimulation-evoked thermal sensations in PSP patients was significantly lower than in movement disorder (P<0.0005, Chi-square test) or NSP patients (P<0.005, Chi-square test). Sites where stimulation
Figure 6. Percentages of pain, warm, and cold sensations evoked by stimulation within the entire region of the explored thalamus (A), Vc nucleus (B) and posterior inferior region (C). 'Thermal' group consists of warm plus cold sites. 'Pain or thermal' group includes pain plus thermal groups.  *** P<0.0001; ** P<0.01; * P<0.05 (Chi-square test)
Thalamus

% of Total Stimulation Sites in Thalamus

Pain or Thermal

Pain

Thermal

Warm

Cold

Ventral Caudal Nucleus

% of Total Stimulation Sites in Vc nucleus

Pain or Thermal

Pain

Thermal

Warm

Cold

Posterior-Inferior Region

% of Total Stimulation Sites in Post-Inferior Region

Pain or Thermal

Pain

Thermal

Warm

Cold
evoked warm were much less common in the PSP group than in the movement disorder (P<0.005, Chi-square test) or the NSP group (P<0.05, Chi-square test) although this effect was not significant for the cold sensations. However, there was no statistically significant difference between the percentage of stimulation-evoked warm, cold, or pain sensations between the NSP and movement disorder patients.

The incidence of pain and thermal sensations evoked by threshold stimulation within the Vc borders defined for each trajectory by the most anterior and most posterior cell responding to cutaneous tactile stimulation was determined for the movement disorder, NSP, and PSP groups (see Figure 6B). Sensations of pain/temperature were more commonly evoked in the PSP patients than in either the NSP (P<0.0001, Chi-square test) or movement disorder patients (P<0.0001, Chi-square test). The incidence of pain and thermal sites was analyzed separately to determine which could account for the increase of pain/temperature sensations in the PSP group. It was found that PSP patients had significantly higher percentages of pain sensations evoked in Vc when compared to NSP (P<0.0001, Chi-square test) and movement disorder patients (P<0.0001, Chi-square test). There was no significant difference in the percentage of pain evoked in NSP and movement disorder patients. Furthermore, the incidence of thermal sites (warm or cold, warm, and cold) was not significantly different between the movement disorder, NSP, and PSP groups.

The proportions of sensations of pain and temperature evoked by stimulation within the region posterior-inferior to Vc were also compared among the three patient groups (see
Figure 6C). No significant difference was found in the incidence of sites where PSP, NSP or movement disorder patients reported pain or thermal sensations. However, analysis of pain and thermal sites separately, revealed that pain sensations were more commonly evoked in the PSP patients than in the movement disorder (P<0.0001, Chi-square test) or the NSP patients (P<0.0001, Chi-square test). Conversely, the percentage of thermal sensations in PSP patients was found to be significantly lower than in movement disorder (P<0.0001, Chi-square test) or NSP (P<0.001, Chi-square test) groups. More specifically, the warm sensations were found to be evoked significantly less frequently in PSP patients than in movement (P<0.0005, Chi-square test) and NSP patients (P<0.005, Chi-square test). The incidence of cold sensations in the PSP patient group exhibited a similar trend although it failed to reach statistical significance. The percentages of pain and thermal sensations did not significantly differ for the movement disorder and NSP patient groups.

5.3.2. Conservative Statistical Method

Due to the inherent problems of the above statistical method (see DISCUSSION), a more conservative statistical approach was also used to examine the incidence of pain and temperature sensations evoked in the different patient groups. For each region, the percent of sites at which either pain, warm, or cold sensations were evoked were first calculated per patient. The medians of these percentages were then calculated and statistically compared across the different groups of patients.
Figure 7. Medians of percentage of pain, warm, or cold sensations evoked per patient by stimulation of the thalamus. The median is represented by the line within the box plot. The 75th and 25th percentiles of the median are represented by the respective top and bottom edges of the box plot. The top and bottom error bars represent the highest and lowest percentage value respectively. 'Thermal' sites consist of warm plus cold sites. 'Pain or thermal' sites consist of pain plus thermal sites.
Thalamus

Median Percent Pain & Thermal Sites

Motor Patients | NSP Patients | PSP Patients

Median Percent Thermal Sites

Motor Patients | NSP Patients | PSP Patients

Median Percent Pain Sites

Motor Patients | NSP Patients | PSP Patients

Median Percent Warm Sites

Motor Patients | NSP Patients | PSP Patients

Median Percent Cold Sites

Motor Patients | NSP Patients | PSP Patients

* P<0.05 (One Way ANOVA on Ranks)
The median percentages of sites where pain and thermal sensations were evoked in the entire region of the thalamus investigated during surgery are shown in Figure 7. No significant difference was found in the incidence of sites where pain/thermal sensations were evoked by threshold stimulation in any of the patient groups. However, pain sensations alone were more commonly evoked in the PSP patients than in the movement disorder patients ($P<0.005$, One Way ANOVA on Ranks), but were not significantly different from the NSP patients. The incidence of pain evoked in NSP patients was also not significantly different from the movement disorder group, although there appears to be a trend toward an increased incidence of pain in NSP patients compared to the movement patients. There was no statistically significant difference between the percentage of thermal sites evoked in any of the groups. Similarly, no significant differences were found in the proportions of warm or cold sites when tested separately in the three groups of patients. Again, a non-significant trend of decreased incidence of warm and cold sites was seen in the PSP group when compared to the movement disorder control group.

The incidence of stimulation-evoked pain and thermal sensations in Vc was examined for the movement disorder, NSP, and PSP groups (see Figure 8). The incidence of sensations of pain/temperature was not significantly different between the three patient groups. When the percent incidence of pain and thermal sites was analyzed separately, it was found that PSP patients had significantly higher percentages of pain sensations evoked in Vc when compared to movement disorder patients ($P<0.05$, One Way ANOVA on Ranks). The percent pain evoked in NSP patients was not significantly different from
Figure 8. Medians of percentage of pain, warm, or cold sensations evoked per patient by stimulation of the Vc. The median is represented by the line within the box plot. The 75th and 25th percentiles of the median are represented by the respective top and bottom edges of the box plot. The top and bottom error bars represent the highest and lowest percentage value respectively. 'Thermal' sites consist of warm plus cold sites. 'Pain or thermal' sites consist of pain plus thermal sites.
Ventral Caudal Nucleus

- Median - dark line in box plot
- 75th percentile - top of box plot
- 25th percentile - bottom of box plot
- Top value - top error bar
- Bottom value - bottom error bar

* P<0.05 (One Way ANOVA on Ranks)
Figure 9. Medians of percentage of pain, warm, or cold sensations evoked per patient by stimulation of the posterior-inferior region. The median is represented by the line within the box plot. The 75th and 25th percentiles of the median are represented by the respective top and bottom edges of the box plot. The top and bottom error bars represent the highest and lowest percentage value respectively. 'Thermal' sites consist of warm plus cold sites. 'Pain or thermal' sites consist of pain plus thermal sites.
Posterior-Inferior Region

- Median Pain Sites
- 75th percentile
- 25th percentile
- Top value
- Bottom value

* P<0.005 (One Way ANOVA on Ranks)
the rest of the groups. Furthermore, the incidence of thermal (warm or cold), warm, or cold sites was not significantly different between the movement disorder, NSP, and PSP groups.

The proportion of pain and temperature sensations evoked by stimulation within the posterior-inferior region was also compared among the PSP, NSP and movement disorder groups (see Figure 9). Pain/thermal sensations evoked in the PSP, NSP or movement disorder patients were not significantly different between the groups. However, analysis of pain and thermal sites separately revealed that pain sites were more commonly evoked in the PSP patients than in patients with movement disorders (P<0.05, One Way ANOVA on Ranks). Conversely, the percentage of warm sites in PSP patients was found to be significantly lower than in the movement disorder group (P<0.05, One Way ANOVA on Ranks). No significant differences were found in the proportions of cold sites in the movement disorder and PSP groups although the same trend as observed for warm sensations was seen. Finally, the incidence of pain, warm, or cold sensations evoked in the NSP patients was not significantly different from the other patient groups.

5.4. Location of Pain and Temperature Sensations

5.4.1. Distribution of Unadjusted Pain and Thermal Sites in the Thalamus

The locations of sites where pain, warm and cold sensations were evoked in all patients were reconstructed in sagittal and coronal planes as shown in Figures 10 and 11 (see Methods). The vertical and horizontal axes in the sagittal plane represent the posterior and inferior Vc borders, respectively. The locations of sites where stimulation evoked
Figure 10. Sagittal reconstructions of thalamic stimulation-evoked pain and thermal sensations in all patients. Sites where stimulation produced pain (A), warm (B) and cold (C) are shown separately. The vertical and horizontal axes represent the posterior and inferior borders of Vc respectively and are respectively perpendicular and parallel to the AC-PC line. Open circles designate pain and thermal sites located in Vc, whereas filled circles designate those outside of Vc. D dorsal; V ventral; A anterior; P posterior.
A: Pain Sites

B: Warm Sites

C: Cold Sites

D: Sites not in Vc

E: Sites in Vc

Inf. Vc Border (mm)
painful or thermal sensations were collapsed across all lateralities onto a single sagittal plane. Figure 10 shows that the pain and thermal sensations evoked in Vc (7.8% of all pain/thermal sites, open circles) were located in the anterior-dorsal quadrant of the sagittal plot and extended up to about 2-mm dorsal and 4-mm anterior to the respective inferior and posterior borders of the Vc. The majority (83.9%) of the pain and temperature sites outside of Vc (full circles) were located posterior and/or inferior to Vc.

Figure 11 shows the locations of the sites plotted in a coronal plane. The placement of the vertical axis along the x-axis in these plots represents the face/hand representation Vc border and the horizontal axis is the same as in the sagittal plot. The majority of the sites located within Vc extended about 2-mm medial or lateral to the face/hand border. The extent of Vc sites in the dorsal-ventral direction was about 2-mm dorsal to the ventral border of Vc. There was no apparent tendency for the pain sites to cluster in any region of the plot (P>0.05, Chi-square test). In contrast, most of the warm sites were located in the medial-ventral quadrant (P<0.0001, Chi-square test). The same trend was observed for the cold sites although it failed to reach statistical significance (P=0.0593, Fisher-exact test).

The distribution of the pain and temperature sites in the different regions of the thalamus explored during the surgical procedure is shown in Figure 12. The sites located in anterior-dorsal quadrant of the sagittal plot (see bellow), but which were outside of Vc (full circles), were combined into the quadrant 2 group. The presumed anatomical locations of these sites were in areas anterior-dorsal, medial or lateral to Vc. The
Figure 11. Coronal reconstructions of thalamic stimulation-evoked pain and thermal sensations in all patients. Sites where stimulation produced pain (A), warm (B) and cold (C) are shown separately. The vertical and horizontal axes represent the face/hand and inferior borders of Vc respectively and are respectively perpendicular and parallel to the AC-PC line. Open circles designate pain and thermal sites located in Vc, whereas filled circles designate those outside of Vc. D dorsal; V ventral; A anterior; P posterior.
Figure 12. Segregation of sites within the human thalamus where stimulation evoked painful and/or thermal sensations. AVc region anterior and/or medial/lateral to Vc; Vc Ventralis caudalis; PI posterior-inferior region.

*** P<0.001; ** P<0.005; * P<0.05 (Chi-square test)
Distribution of Pain & Thermal Sites in Thalamus

Motor
NSP
PSP

% of Total Stim. Sites within Patient Group

n=1594  n=345  n=1642
n=631  n=156  n=790
n=222  n=73  n=389

AVc
VC
PI

***
**
***
remaining sites were grouped into either Vc or the posterior-inferior region as described in the methods section. The percent of pain and temperature sensations evoked in the posterior-inferior region of NSP and movement disorder patients was significantly greater than in either Vc (P<0.005 and P<0.0001, respectively, Chi-square) or in quadrant 2 (P<0.0001 and P<0.0001, respectively, Chi-square). In contrast, the percentage of pain and temperature sites in PSP patients was found to be significantly higher in Vc than in quadrant 2 (P<0.05, Chi-square). The percent pain and thermal sensations evoked in the posterior-inferior region and quadrant 2 of PSP patients was also combined and compared to Vc. It was found that pain and thermal sensations tended to be more commonly evoked in Vc of PSP patients than in the ventroposterior and quadrant 2 regions combined, although this trend did not reach statistical significance (P=0.055, Chi-square test).

5.4.2. Sampling Distribution of Stimulation Sites
The sampling distribution of all the stimulations delivered during the surgical procedure was also investigated. Figure 13 shows the locations of the 5848 stimulation sites plotted on density graphs in both the sagittal and coronal planes. The density plots were constructed by obtaining the total number of stimulations within each 1-mm² bin on a 11-mm x 11-mm grid in the two planes (see Methods). It was found that the sites were not located uniformly across the sagittal and coronal planes but that they clustered in specific regions of the thalamus. Most stimulation sites in the coronal plane were located about 1-mm lateral to the face/hand representation border of Vc in a parasagittal plane to the tactile representation of the hand (see Figure 13A). In the sagittal plane the majority of
Figure 13. Coronal (A) and sagittal (B) reconstructions of location and density of all sites stimulated during functional stereotactic surgery on patients undergoing treatment for tremor or chronic pain. In the coronal section, the vertical and horizontal axes represent the face/hand and inferior borders of Vc respectively. In the sagittal section, the vertical and horizontal axes represent the posterior and inferior borders of Vc respectively. D dorsal; V ventral; A anterior; P posterior.
Coronal Plane

Sagittal Plane

Legend:

- >200
- ≤150
- ≤50
- ≤10
- 0
the sites were located along a 50° trajectory passing through the origin of the plot (see Figure 13B).

5.4.3. Distribution of Pain and Thermal Sites Adjusted for Sampling Density

To account for the non-uniform sampling, percent-density plots were constructed by dividing the total pain, warm, and cold sites by the total number of stimulations in each bin of the 11-mm x 11-mm density matrix (see METHODS). This method yielded a percent-density distribution of sites where pain, warm, or cold sensations were evoked, normalized for sampling bias (see Figures 14-16).

Figure 14 shows the percent-density distribution of pain and thermal sites in movement disorder patients. In the coronal plane, the pain sensations evoked in movement disorder patients were densely localized near the center of the plot. In contrast, the majority of the warm and cold sites on the coronal plot were located in the medial part of the region ventral to the horizontal axis (see medial-ventral quadrant). In the sagittal plane, the pain sites were also centrally located, whereas the highest density of warm and cold sites was seen more ventroposteriorly (see posterior-ventral quadrant). It was also quite evident from visual inspection of the plots that the density of the thermal sites (warm especially) dominated over the pain sites.

The percent-density plots for pain and thermal sensations evoked in NSP patients are shown in Figure 15. The distribution of the sites was very similar to that of the movement disorder group. In the coronal plane, the pain sites were located near the
Figure 14. Sagittal and coronal density plots of stimulation-evoked pain (top), warm (middle), and cold (bottom) sensations in the human thalamus of movement disorder patients. In the sagittal plane, the sites were plotted with respect to posterior (vertical line) and inferior (horizontal line) Vc borders. In the coronal plane, sites were plotted with respect to face/hand RF (vertical line) and inferior (horizontal line) Vc borders. D dorsal; V ventral; A anterior; P posterior; Nx non-explored region.
Figure 15. Sagittal and coronal density plots of stimulation-evoked pain (top), warm (middle), and cold (bottom) sensations in the human thalamus of non-stroke pain patients.

In the sagittal plane, the sites were plotted with respect to posterior (vertical line) and inferior (horizontal line) Vc borders. In the coronal plane, sites were plotted with respect to face/hand RF (vertical line) and inferior (horizontal line) Vc borders. D dorsal; V ventral; A anterior; P posterior; Nx non-explored region.
center of the plot, although there was a tendency for these sites to extend somewhat more laterally. The highest concentration of warm and cold sites was located within medial-ventral quadrant of the coronal plot. The pain sites were also located about the center of the sagittal plot, whereas most of the thermal sites (warm and cold) were located in the region ventroposterior to Vc (see posterior-ventral quadrant). Similar to the movement disorder patients, the intensity of the density of warm sites in the NSP group seemed markedly greater than that of the pain sites, although this effect was not as dramatic as in the movement disorder group.

The percent-density of pain and temperature sites in PSP patients can be seen in figure 16. The density of pain sites in the PSP group was higher in intensity and more diffusely spread from the center of the plot than in the other patient groups. This trend was seen in both the coronal and sagittal views. No prevalence of warm or cold sites in any particular location was seen in either of the two plots. This was perhaps due to the scarcity of warm and cold sensations evoked in the PSP patients (i.e. thalamic stimulation evoked far less thermal sensations in PSP patients than in the others).

5.4.4. Statistical Analysis of Medial-Lateral Distribution of Pain and Thermal sites

The locations of sites where pain or thermal sensations were evoked by threshold microstimulation of the thalamus were also analyzed statistically along the medial-lateral axis (see Figure 17). The sites were divided into three separate groups according to their location: medial region (sites medial to face/hand border), border region (sites along
Figure 16. Sagittal and coronal density plots of stimulation-evoked pain (top), warm (middle), and cold (bottom) sensations in the human thalamus of post-stroke pain patients. In the sagittal plane, the sites were plotted with respect to posterior (vertical line) and inferior (horizontal line) Vc borders. In the coronal plane, sites were plotted with respect to face/hand RF (vertical line) and inferior (horizontal line) Vc borders. D dorsal; V ventral; A anterior; P posterior; Nx non-explored region.
Figure 17. Medial-lateral distribution of sites where pain (A) and thermal (B) sensations were evoked by stimulation in the thalamus. Medial, sites located medial to the face/hand representation; Border, sites located along the face/hand representation; Lateral, sites located lateral to the face/hand representation. 'Cold' refers to % cold sites of total stimulation sites. * P<0.05 (Chi-square test)
A: Thalamus

% Pain of Total Stim. Sites per Region

Medial | Border | Lateral
---|---|---

B: Thalamus

% Thermal of Total Stim. Sites per Region

Medial | Border | Lateral

Motor Sites
B=1372
M=569
L=1640

NSP Sites
B=681
M=251
L=645

PSP Sites
B=348
M=160
L=176
face/hand border), and lateral region (sites lateral to face/hand border). The proportions of pain and thermal sites for each group were calculated by dividing the number of pain/thermal sites by the total number of stimulation sites in each of the three regions.

The incidence of pain sites in the medial, border, and lateral regions is shown in figure 17A for the movement disorder, NSP, and PSP patients. Pain sensations evoked in the movement disorder patients tended to be located along the medial-lateral Vc border. The incidence of pain in the border region was significantly higher than in the medial (P<0.05, Chi-square test) and lateral parts of the thalamus (P<0.01, Chi-square test) for the movement patients. In the NSP patient group, pain sensations were more commonly evoked in the lateral than in the medial region (P<0.05, Chi-square test). No significant difference was found in the medial-lateral location of pain sites in the PSP patients.

The incidence of sites where warm or cold sensations were evoked was also analyzed along the medial-lateral axis (see Figure 17B). It was found that thermal sensations in the movement disorder patient group were evoked more frequently in the medial part of the thalamus than in either the border (P<0.001, Chi-square test) or lateral region (P<0.0001, Chi-square test). The medial-lateral locations of thermal sites did not significantly differ in the NSP and PSP patient groups. The incidence of warm and cold sites was also analyzed separately. Warm sensations evoked in movement disorder patients were found to be more concentrated in the medial region of the thalamus than the lateral (P<0.005, Chi-square test) or border region (P<0.005, Chi-square test). Similarly, the cold sites obtained in the movement disorder patients were also more common in the medial than in
the lateral region (P<0.0001, Chi-square test). No difference among the three medial-lateral areas was found for thermal or warm sites in the NSP patients. However, cold sensations in the NSP patients were evoked more frequently in the border region than in the lateral region (P<0.05, Chi-square test). There was no difference in the incidence of thermal, warm, or cold sites along the medial-lateral axis in the PSP patient group.

5.5. Quality of Stimulation-Evoked Pain
The quality of the stimulation-evoked pain was examined for the different groups of patients and thalamic regions. Table 3 shows the various descriptors volunteered by patients to describe the microstimulation-evoked sensation of pain. A sensation of nondescript pain was the most common type reported by patients in all groups. A sensation of pain described as burning or accompanied by an innocuous warm sensation was also commonly evoked by stimulation in all patients. There were no significant differences in the quality of stimulation-evoked pain between the movement disorder, NSP, and PSP patient groups. Similarly, no significant difference in pain quality was found when compared across the thalamus, Vc and ventroposterior regions (see Table 4). Interestingly, stimulation within Vc of one PSP patient evoked a sensation of pain described as identical to the chronic pain experienced by the patient.

5.6. Mismatches Between Receptive Fields and Projected Fields
The incidence of mismatches between the PFs of stimulation-evoked pain and thermal sensations and the RFs of neurons located at or adjacent to the stimulation site was
TABLE 3. Quality of stimulation-evoked pain sensations in different patient groups

<table>
<thead>
<tr>
<th>Quality of Evoked Pain</th>
<th>Movement Disorder</th>
<th>Nonstroke Pain</th>
<th>Post-stroke Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning</td>
<td>6 (16%)</td>
<td>7 (25%)</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Shock</td>
<td>3 (8%)</td>
<td>4 (14%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Sharp</td>
<td>2 (5%)</td>
<td>3 (11%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Stabbing/shooting</td>
<td>5 (13%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chronic-pain-like</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Hot/cold pain</td>
<td>7 (18%)</td>
<td>4 (14%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (11%)</td>
<td>5 (18%)</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Pain (nondescript)</td>
<td>11 (29%)</td>
<td>5 (18%)</td>
<td>5 (19%)</td>
</tr>
</tbody>
</table>

Percent of patients in each group is shown in parentheses.
Other: deep, dull/blunt, numb, pressure, gnawing, pulling, birth pain, spasm
<table>
<thead>
<tr>
<th>Quality of Evoked Pain</th>
<th>Thalamus</th>
<th>Vc</th>
<th>Posterior-Inferior Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning</td>
<td>19 (21%)</td>
<td>3 (21%)</td>
<td>7 (27%)</td>
</tr>
<tr>
<td>Shock</td>
<td>11 (12%)</td>
<td>1 (7%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Sharp</td>
<td>7 (8%)</td>
<td>0</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Stabbing/shooting</td>
<td>4 (4%)</td>
<td>2 (14%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Chronic-pain-like</td>
<td>0</td>
<td>1 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Hot/cold pain</td>
<td>15 (17%)</td>
<td>3 (21%)</td>
<td>12 (19%)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (13%)</td>
<td>0</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Pain (nondescript)</td>
<td>21 (23%)</td>
<td>4 (29%)</td>
<td>15 (24%)</td>
</tr>
</tbody>
</table>

Percent of patients in each region is shown in parentheses.
Other: deep, dull/blunt, numb, pressure, gnawing, pulling, birth pain, spasm
examined in the Vc nucleus. The classification scheme used to identify the magnitude of the RF/PF mismatch was similar to the method employed in Davis et al. (1996). If a PF included the RF but was much larger in size within the same extremity (e.g. foot vs. toe) the mismatch was classified as a 'size' mismatch. PFs not located within the RF but adjacent to the RF within the same extremity (e.g. hand vs. forearm) were considered 'minor' mismatches. Mismatches were classified as 'gross' when the PF did not include the RF and the two fields were not adjacent (e.g. hand vs. trunk). The three types of mismatches were combined to give an overall incidence of RF/PF mismatch, which was then compared between the different patient groups (see Table 5). It was found that the total incidence of RF/PF mismatch was significantly higher in the PSP patient group than in the movement disorder group (P<0.05, Chi-square). There was no significant difference in the RF/PF mismatch incidence between the NSP patients and the rest of the groups.

Since neurons were only infrequently encountered in the ventroposterior region it was not possible to examine the incidence of RF/PF mismatch in this area. Instead, the incidence of mismatch between the stimulation-evoked pain/thermal PFs and the PFs of paresthesias evoked at adjacent sites was investigated (see Table 6). The same classification scheme discussed above was also used for this analysis. The incidence of PF/PF mismatch in the ventroposterior region was significantly greater than the incidence of RF/PF mismatch in Vc for all patient groups (P<0.05. Chi-square test; see Tables 5 and 6). However, the incidence of PF/PF mismatch in the ventroposterior region did not vary among the different patient groups.
<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Size</th>
<th>Minor</th>
<th>Gross</th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Movement disorder</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
<td>3 (24%)*</td>
<td></td>
</tr>
<tr>
<td>Nonstroke pain</td>
<td>1 (33%)</td>
<td>0</td>
<td>0</td>
<td>1 (33%)</td>
<td></td>
</tr>
<tr>
<td>Post-stroke pain</td>
<td>2 (14%)</td>
<td>2 (14%)</td>
<td>6 (43%)</td>
<td>10 (71%)*</td>
<td></td>
</tr>
</tbody>
</table>

Percent of RFPF mismatches in each group is shown in parentheses.
* Statistically significant difference between movement disorder and PSP groups
P<0.05, Chi-square test
<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Size</th>
<th>Minor</th>
<th>Gross</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17 (16%)</td>
<td>13 (12%)</td>
<td>43 (41%)</td>
<td>73 (69%)</td>
</tr>
<tr>
<td>Movement disorder</td>
<td>10 (21%)</td>
<td>5 (11%)</td>
<td>18 (38%)</td>
<td>33 (70%)</td>
</tr>
<tr>
<td>Nonstroke pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Movement disorder</td>
<td>0</td>
<td>2 (18%)</td>
<td>6 (55%)</td>
<td>8 (73%)</td>
</tr>
</tbody>
</table>

Percent of sites in each group is shown in parentheses.
5.7. Projected Field Location and Size of Pain and Thermal Sensations

The locations of the PFs of pain and thermal sensations evoked by stimulation of the thalamus were investigated in the three patient groups. The proportions of pain and thermal sensations with PFs located on the face, hand, trunk, and leg are shown in Table 7. There were significantly more pain and thermal sensations with PFs in the area of the hand in the movement disorder group than in the NSP (P<0.05, Chi-square test) or PSP (P<0.005, Chi-square test) groups of patients. In contrast, PFs located on the trunk were significantly more common in the PSP patient group than in the movement disorder (P<0.001, Chi-square test) or NSP patients (P<0.05, Chi-square test). Finally, the incidence of pain and thermal sensations with PFs located on the leg was significantly greater in NSP patients than in patients with movement disorders (P<0.01, Chi-square test). There were no significant differences in the incidence of sensations with PFs on the face among the different groups of patients.

The PF size of the pain and thermal sensations was also examined within the different patient groups (see Table 8). The classification of the size of the PFs was based on the method used by Lenz et al. (1993b). PFs were classified as 'large' if the PF crossed any of the major joints of the body (eg. wrist, elbow, shoulder, ankle, knee or hip). If the PF did not cross any joints it was classified as 'small'. The size of the PFs for pain, warm and cold sensations was compared within each patient group. In the movement disorder group, the proportion of large warm PFs was found to be significantly greater than large pain PFs (P<0.01, Chi-square test). Conversely, the proportion of large pain PFs evoked in the PSP patients was significantly greater than the large PFs of the warm sensations.
<table>
<thead>
<tr>
<th>PF Location</th>
<th>Movement Disorder</th>
<th>Nonstroke Pain</th>
<th>Post-stroke Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>33 (15%)</td>
<td>19 (20%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Face+Body Part</td>
<td>10 (5%)</td>
<td>2 (2%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Hand</td>
<td>66 (31%)</td>
<td>17 (18%)*</td>
<td>11 (13%)*</td>
</tr>
<tr>
<td>Hand+Body Part</td>
<td>7 (3%)</td>
<td>3 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Trunk</td>
<td>24 (11%)†</td>
<td>13 (14%)*</td>
<td>23 (28%)</td>
</tr>
<tr>
<td>Trunk+Leg</td>
<td>2 (1%)</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Leg</td>
<td>49 (23%)</td>
<td>37 (39%)*</td>
<td>23 (28%)</td>
</tr>
<tr>
<td>Hemibody</td>
<td>23 (11%)</td>
<td>3 (3%)</td>
<td>11 (13%)</td>
</tr>
</tbody>
</table>

Percent of sites in each group is shown in parentheses.
* Statistically significant difference from movement disorder group.
† Statistically significant difference from PSP group. P<0.05 (Chi-square test)
TABLE 8. Projected field size of stimulation-evoked sensations in movement disorder, nonstroke pain & post-stroke pain patients

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Pain Sensations PF Size</th>
<th>Warm Sensations PF Size</th>
<th>Cold Sensations PF Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small</td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Movement disorder</td>
<td>44 (79%)</td>
<td>12 (21%)</td>
<td>76 (57%)</td>
</tr>
<tr>
<td>Nonstroke pain</td>
<td>24 (67%)</td>
<td>12 (33%)</td>
<td>35 (71%)</td>
</tr>
<tr>
<td>Post-stroke pain</td>
<td>35 (61%)</td>
<td>22 (39%)</td>
<td>9 (100%)</td>
</tr>
</tbody>
</table>

Percent of sites in each group is shown in parentheses.
† Statistically significant difference within column. * Statistically significant difference within a row.
P<0.05 (Chi-square or Fisher-exact test)
(P<0.05, Fisher-exact test). The PFs of the cold sensations evoked in movement disorder and PSP patients were not significantly different from the other modalities. No significant differences were found in the size of PFs of the pain, warm, and cold sensations evoked in NSP patients.

Differences in PF size of the pain, warm, and cold sensations evoked in the thalamus were also investigated between the different patient groups. The proportion of large warm PFs was found to be significantly smaller in the PSP patients than in the movement disorder patients (P<0.05, Fisher-exact test), but not different from the NSP patients. There were no differences in the size of the PF at sites where pain or cold was evoked in the three groups of patients.

Finally, the size of the PF of pain and thermal sensations was analyzed by region. The distribution of the size of the PFs in the thalamus, Vc and ventroposterior region is shown in Table 9. However, the PF size of pain, warm, and cold sensations did not significantly differ either within or between the different thalamic regions.
<table>
<thead>
<tr>
<th>Thalamic Region</th>
<th>Pain Sensations PF Size</th>
<th>Warm Sensations PF Size</th>
<th>Cold Sensations PF Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small</td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Thalamus</td>
<td>103 (69%)</td>
<td>46 (31%)</td>
<td>120 (63%)</td>
</tr>
<tr>
<td>Vc</td>
<td>15 (71%)</td>
<td>6 (29%)</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>Posterior-Inferior Region</td>
<td>71 (67%)</td>
<td>35 (33%)</td>
<td>94 (61%)</td>
</tr>
</tbody>
</table>

Percent of sites in each group is shown in parentheses.
**Section 6. Discussion**

This study demonstrates that stimulation within and posterior-inferior to Vc can produce pain or temperature sensations. In pain (PSP, NSP) and movement disorder patient groups the incidence of sites evoking pain and temperature sensations was higher in the posterior-inferior region than in Vc. The incidence of stimulation-evoked pain was more common in Vc and the posterior-inferior region of PSP than in non-PSP patients, whereas the proportion of thermal sensations evoked by stimulation of the posterior-inferior region was significantly decreased in PSP patients. The degree of mismatch between sites where stimulation evoked painful and/or thermal sensations was greater in PSP than in movement disorder patients. A greater proportion of tactile RF and pain/temperature PF mismatches was also observed in the posterior-inferior region than in Vc. There was a higher proportion of warm PFs defined as large (see METHODS) than pain PFs in movement disorder patients. An opposite trend was observed in PSP patients. The size of the cold PFs was generally small and did not vary between patient groups. These results suggest that Vc and the posterior-inferior region are likely involved in the perception of pain and temperature, and that alterations in the physiology of these structures or their projection targets may be involved in the mediation of central pain.

**6.1. Methodological Issues**

The present study was possible because of the unique opportunity to investigate the representation of pain and temperature in the thalamus of awake human patients. One advantage of human studies is that the subjects can provide the experimenter with a verbal report of the perceptual effects of microstimulation. It is assumed that stimulation
of neurons involved in mediation of pain or temperature sensations will give rise to these sensations. This direct measure of pain elicited by stimulation is not possible in animal studies of a similar design. However, this approach does have several limitations. One of the major limitations of the present study is the lack of histological confirmation of the location of microelectrode stimulation sites. As a result it was necessary to estimate the electrode location via other means. Stereotactic coordinates can be imprecise due to interpatient anatomical and functional differences. Therefore, the physiologic findings of each patient were used to approximate the electrode locations. The Vc nucleus was used as a reference point since it is one of the most reliable physiologic landmarks in the thalamus. The posterior Vc border and the tactile somatotopy of Vc were used to adjust the electrode trajectories in the anterior-posterior and medial-lateral direction respectively. A line parallel to the AC-PC line and traversing through the ventral-most tactile cell was used to estimate the ventral border of Vc. Although, the angle of the AC-PC line does not correspond perfectly to the actual anatomical border of Vc, it does make a reasonable approximation in view of the constraints of the present study. In this way it was possible to approximate the location of the stimulation sites within the various regions surrounding the tactile Vc. However, since correlation of the sites with actual nuclear structures was not possible without histological verification of the electrode trajectories, the location of pain and temperature sites is suggestive rather than conclusive.

In contrast to animal experiments where the nuclear region under study can be systematically explored, the number and location of electrode trajectories performed
during the surgical procedure was quite limited due to ethical constraints. As a result, the area of the thalamus explored and the number of electrode trajectories performed were relatively small and quite variable between patients. Thus the data were pooled across subjects to collectively cover a large area of thalamus. The regions of the thalamus where stimulation failed to evoke any pain or thermal sensations were also noted to indicate the overall area of the thalamus explored in the study. However, the pooling of data also served to artificially inflate the data sample. Although it is unlikely that this significantly altered the present findings due to the large number of patients used in the study, a more conservative statistical test (see RESULTS) was used to test the incidence of pain and temperature sites. In general the results of the conservative statistical test did not differ from the pooled data indicative of the validity of the present findings.

Another major limitation of the present study is that it can not distinguish whether the high proportion of pain and thermal sensations reported by patients in the posterior-inferior region (see below) was evoked by stimulation of cells or by stimulation of fibers of passage. The high incidence of stimulation-evoked pain and thermal sensations in the posterior-inferior region (as opposed to in Vc) maybe due to a higher density of STT fibers in this region. Furthermore, the much lower incidence of pain/thermal sensations evoked in Vc could be explained by the tendency of the STT fibers to spread out upon entering Vc. However, data from animal studies (see below) suggest that nociceptive and thermoreceptive cells exist in the posterior region and that their stimulation rather than stimulation of the STT fibers is responsible for the evoked pain and temperature sensations. For example, many of the pain sites and most of the warm and cold sites
were localized to the medial part of the posterior-inferior region. This region roughly corresponds to the anatomical location of VPI and VMpo where cells responding to noxious and thermal stimulation were identified in animals (Apkarian et al., 1991; Craig et al., 1994) and humans (Davis et al., 1999). Thus it is reasonable to assume that these nuclei are likely activated by stimulation, resulting in sensations of pain and temperature.

Finally, it is necessary to address the issue of stimulation current spread. The sensations reported in the present study were evoked by stimulation at different current intensities. Thus, the distance of the affected neural elements from the microelectrode varied according to the current strength used. This variability in current spread might impact on the accuracy of stimulation site localization. A report by Ranck (1975) described the current-distance relations for stimulation of myelinated fibers and cell bodies with monopolar electrodes. According to Ranck (1975) 25µA and 50µA currents will stimulate neural elements up to distances of 120µm and 200-500µm away, respectively. The highest current intensity used in the present study (100µA) would likely stimulate up to 1200µm away from the tip of the electrode. Since the majority of the pain/thermal sensations reported in the present study were evoked by stimulation below 20µA, it is unlikely that current spread significantly affected the accuracy of localization of the stimulation sites.
6.2. Involvement of Vc and Posterior-Inferior Region in Perception of Thermal Sensations

In the present study, innocuous thermal sensations were evoked by stimulation at sites located in Vc and the posterior-inferior region. Warm sensations comprised the majority (84%) of the thermal sensations in all patients. These results are generally consistent with Lenz et al. (1993b) who reported that warm sensations comprised the majority (69%) of thermal sensations evoked at sites in Vc and the posterior-inferior region. Lenz et al. (1993b) also reported that warm sensations were evoked at 11% of the sites and cold at 4% of the sites stimulated, somewhat higher proportions than those of the present study, where warm and cold sensations were evoked respectively at 3.4% and 0.7% of the sites. This discrepancy might be due to the difference in sample size between the two studies. It is possible that the study by Lenz et al. (1993b) overestimated the actual percentages due to the fairly small sample size (n=216 sites) in comparison to the present study (n=5848 sites). Alternatively, since the present study explored a larger area of the thalamus, the percentages of stimulation-evoked thermal sensations might be underrepresented due to the increase in ‘negative space’. A more recent study by Lenz et al. (1998a) found that innocuous warm and cold sensations were evoked with microstimulation of the Vc/posteroinferior region at 10% and 3% of the 384 stimulation sites, respectively. Although the exact proportions of the microstimulation-evoked thermal sites are somewhat different from those of the present study, the general findings are consistent. Furthermore, the location of the thermal sites evoked by microstimulation in the study by Lenz et al. (1993b) was found to be consistent with the present study. They found that innocuous thermal sensations were evoked more commonly by
stimulation in the posterior-inferior region (25% of 118 sites) than in Vc (4% of 98 sites). The incidence of stimulation-evoked innocuous thermal sensations in the present study was also found to be higher in the posterior-inferior region (7.4%) of movement disorder and non-stroke pain patients than in Vc (1.6%). Similar findings were reported by Dostrovsky et al. (1993) who found that the cold and warm sensations that were occasionally evoked by stimulation of the thalamus were usually located below Vc. The results of the present study along with the previous studies suggest that Vc and the posterior-inferior regions are involved in the pathways mediating the perception of thermal sensations.

It is interesting to note that the sensations of warm and cold were not reported simultaneously by patients in the present study even though it might be assumed that warm and cold are co-represented in the CNS. Other studies have found very similar results. For example, Lenz et al. (1998a) found that stimulation did not evoke co-existent warm and cold sensations, and such sensations were reported at only 1% of the total stimulation sites in the tactile Vc core in a study by Lenz et al. (1993b). It is possible that the brain can not interpret simultaneous signals from the opposite ends of the thermal spectrum as two distinct sensations. Instead, such signals may be perceived in terms of the dominant sensation, warm, or cold, or even pain. Alternatively, the data might suggest that thermal cells giving rise to warm and cold sensations are physically separated and therefore are very rarely stimulated simultaneously.
Finally, the data of the present study demonstrated an inconsistency between the stimulation data and the data from animal recording studies. The incidence of cells in the spinal cord, the trigeminal nucleus, and the thalamus that respond specifically to innocuous warm stimuli is very low, whereas the incidence of COLD-specific cells is significantly higher (Auen et al., 1980). These observations are consistent with the small size of the cold cell receptive fields documented by Auen et al. (1980) since more cells would be needed to represent the entire body surface. Even though there are no relevant data pertaining to the size of RFs of warm cells, based on psychophysical studies showing a poor localization of warm stimuli (Nathan and Rice, 1966; Simmel and Shapiro, 1969), it might be expected that their RFs would be rather large. Thus it seems that in the central nervous system, warm is under-represented with respect to cold. However, the present findings – together with other microstimulation studies (Lenz et al., 1993b, 1998a) – showed that warmth is the most common sensation of the spinothalamic-type evoked in non-chronic pain patients. In contrast, the incidence of stimulation-evoked cold was quite rare. These results are puzzling since one would expect that due to the low incidence of warm cells in the thalamus and rest of the central nervous system – it would be quite difficult to evoke sensations of warm by microstimulation. At present time, it is difficult to adequately explain this discrepancy.

6.3. Involvement of Vc and Posterior-Inferior Region in Perception of Pain

Sensations

Pain sensations were reported by patients in the present study following stimulation of Vc and the posterior-inferior region. The incidence of stimulation-evoked pain in the
posterior-inferior region (2.8%) was higher than in Vc (1.6%) of movement disorder and non-stroke pain patients. Sensations of burning pain evoked by stimulation ventroposterior to Vc were also reported by Hassler and Riechert (1959) in patients undergoing stereotactic surgery. Furthermore, the findings of Halliday and Logue (1972) although not directly comparable to the present study note that macrostimulation of the posterior-inferior aspect to Vc, which they believed corresponded to Vcpc, resulted in pain sensations in 16% of patients with Parkinson’s disorder. The low number of patients used in their study and the limited anatomical accuracy may explain the rather low percentage of patients in which stimulation evoked pain. Their report was later confirmed by others who also observed that stimulation in Vc, especially near its inferior-posterior boundary, evoked painful or unpleasant sensations in both movement disorder and chronic pain patients (Davis et al., 1996; Dostrovsky et al., 1993). Finally, studies by Lenz et al. (1993b, 1998a) demonstrated that threshold stimulation of Vc and the region ventroposterior to Vc resulted in sensations of pain. For example Lenz et al. (1993b) noted that pain was evoked by stimulation at 1% of the sites in Vc and that microstimulation at 4% of the sites posterior and inferior to Vc resulted in pain. The present findings, along with the above studies, provide evidence for the role of the Vc and posterior-inferior thalamic regions in the processing of pain.

It is surprising that the overall incidence of stimulation-evoked pain in Vc is so low. Extensive anatomical, physiological, and clinical evidence points to the involvement of Vc in the processing of pain (see below). Yet microstimulation in this region only rarely evokes pain sensations (except in chronic pain patients, see below). It is tempting to
speculate that perhaps the numerous cells signaling tactile information that are present in Vc, somehow mask the activity of the nociceptive cells within Vc. Alternatively, it is possible that for the most part, stimulation of nociceptive cells within Vc is inadequate to produce a conscious sensation of pain and it may be necessary to co-stimulate another region of the thalamus (i.e. posterior-inferior region). Also, it may be that the stimulation parameters chosen were insufficient to evoke pain in Vc. For example, the maximum current used in the present study (100μA) may have been insufficient to recruit enough cells needed for the perception of pain. However, this is unlikely since macrostimulation, which used far greater currents, also only rarely evoked pain in Vc (Tasker et al., 1987). Finally, it is possible that Vc may have a role in the modulation of pain rather than in its perception (Craig 1998).

6.4. Neural Substrates of Stimulation-Evoked Pain and Thermal Sensations

The present findings of pain and thermal sensations being evoked by stimulation of Vc and posterior-inferior regions fit well within the current context of our understanding of the anatomy and physiology of these areas. It is likely that the painful and thermal sensations observed in the present study were evoked by stimulation of STT fibers or neural elements to which they project. Much evidence implicates the spinothalamic tract in the mediation of pain and temperature sensations to higher levels of the CNS. The activity of STT cells within the spinal cord has been found to correlate with pain behavior in animals (Dubner et al., 1989; Simone et al., 1991). In addition, stimulation of the anterolateral tract has been shown to evoke painful sensations in patients undergoing percutaneous anterolateral cordotomy (Mayer et al., 1975), whereas lesions of the
anterolateral quadrant were shown to impair nociception and thermosensitivity (Norrsell 1989; Vierck et al., 1990). Studies involving silver stains for degenerating fibers following STT lesions in human autopsies showed that STT fibers terminate in dense clusters in the region of Vc as well as in a region posterior inferior to Vc which is roughly consistent with the location of VMpo/Vcpc (Craig 1994; Holliday and Logue, 1972; Mehler, 1962; Mehler, 1966). More specifically, Vc has been shown to receive STT projections mostly from the deeper layers of the spinal cord (i.e. lamina V), whereas VMpo is predominantly innervated by fibers originating in lamina I (Craig and Dostrovsky, 1997). Sparse lamina I STT projections to VPI located ventral to VPM were also noted by Ralston and Ralston (1992).

Cells responding to noxious and thermal stimulation have been identified in both Vc and in the region posterior and inferior to Vc. For example, Lenz et al. (1994) identified a population of neurons located within the Vc nucleus of human patients undergoing functional neurosurgery for tremor or chronic pain that responded in a graded manner to mechanical stimuli extending into the noxious range. Neurons responding to innocuous cool and mechanical or painful heat stimuli were also observed in the cutaneous core of the human Vc (Lenz et al., 1993a; Lenz and Dougherty, 1998). Cells within the posterior-inferior region were found to respond exclusively to noxious heat stimulation (Lenz et al., 1993a). Recently, Davis et al. (1999) used microelectrode recording in human neurosurgical patients to identify neurons responsive to innocuous cooling. Electrical stimulation delivered at these sites also produced sensations of innocuous cold. The location of these neurons was determined to lie ventroposterior to the face.
representation of Vc in a region corresponding to VMpo, which has been identified as a thalamic substrate specific for pain and temperature (Craig et al., 1994). Interestingly, most of the cool sensations and many of the warm sensations reported in the present study were obtained by stimulation approximately within this area. The VPI was also found to contain neurons responding to innocuous and noxious mechanical stimuli (Apkarian et al., 1991). The location of these neurons is consistent with the pattern of STT terminations, which suggests that they receive direct input from the spinothalamic pain and temperature pathway. These reports along with the results of the present study suggest that Vc and posterior inferior region - specifically VMpo - are involved in the mediation and processing of pain and thermal sensations.

At this point it should be noted that the actual nuclear composition of the posterior-inferior region is unclear due to the different nomenclature used by various investigators and interspecies differences. A number of nuclei have been reported to lie roughly within the posterior-inferior region, including suprageniculate/posterior complex (Jones 1985; Olszewski 1952), posterior VP (Mehler 1966), limitans portae/Vc portae (Hassler 1970), Vcpc (Hassler and Riechert, 1959). The recently identified VMpo nucleus (Craig et al., 1994) is also located roughly in this region. The extent to which these nuclei represent analogous nuclear substrates is largely unknown, although it is likely that a fair degree of overlap exists between them.
6.5. Incidence of Stimulation-Evoked Pain and Temperature in Posterior-Inferior Region of Chronic Pain Patients

A difference was found between the incidence of pain and thermal sensations evoked by threshold stimulation of the posterior-inferior region in PSP patients. Microstimulation within the posterior-inferior region was frequently (10%) found to result in sensations of pain in the PSP patients. In contrast, innocuous thermal sensations were evoked only infrequently (1.8%) by stimulation in this region. A similar relationship was found in a study by Lenz et al. (1998a) who noted that in pain affected areas of chronic pain patients, there was an increase in the number of sites (16%) in the posterior-inferior region where pain was evoked by stimulation relative to the control sites (2%). However, a decrease in the number of sites (≈12%, Figure 5B; Lenz et al. (1998a)) where stimulation evoked thermal sensations was observed in the pain affected areas of chronic pain patients when compared to the control (≈28%). They proposed that reorganization occurred in the thalamus of chronic pain patients whereby STT or elements to which the STT projects signaled pain rather than thermal sensations. The incidence of pain and thermal sensations evoked by stimulation of the posterior-inferior region in the NSP patients was not different from the control movement disorder group, suggesting that the mechanism of their chronic pain is likely different from that of the PSP patients.

This relationship between pain and temperature sites in PSP patients suffering from central pain may have a clinical correlate. For example, Boivie et al. (1989) found that post-stroke pain patients had impaired temperature and pain sensibility. Bowsher (1996) observed that the pain experienced within the hypoaesthetic zone is most closely
correlated with the zone of decreased thermal sensibility. Furthermore, the pain experienced by the patients seemed to be proportional to the degree of the thermal impairment, so that the thermal deficit was more pronounced in areas of greatest pain.

These observations were critical for a new mechanism of central pain recently proposed by Craig (1998) who hypothesized that central pain results from a disruption of thermosensory integration which normally inhibits pain. The hypothesis involved two pathways: thermosensory and polymodal nociceptive. Under normal conditions, the lateral lamina I spino-thalamo-cortical thermosensory pathway to the parieto-insular cortex inhibits the medial lamina I spino-thalamo-cortical polymodal nociceptive pathway to the anterior cingulate cortex. Central pain was said to occur when a lesion to the lateral thermosensory pathway results in disinhibition of the polymodal nociceptive activity in the medial pathway.

The results of the present study provide further support for the existence of a thermosensory disruption along the lamina I-thalamo-cortical pathway to the parieto-insular cortex. In the present study, the decreased frequency of sites where thermal sensations were evoked in PSP patients was localized to the medial part of the posterior-inferior region of the thalamus. It is likely that this region roughly corresponds to the calbindin-staining VMpo nucleus identified by Craig et al. (1994) as the thalamic nucleus specific for pain and temperature. The VMpo nucleus has been shown to contain thermospecific (COLD) neurons and nociceptive-specific neurons (Craig et al., 1994; Dostrovsky and Craig, 1996a). VMpo is also the thalamic substrate in the lateral lamina I
spino-thalamo-cortical pathway to parieto-insular cortex referred to in Craig's (1998) hypothesis. Thus the decreased ability to evoke thermal sensations in VMpo by stimulation in PSP, but not NSP patients, may be indicative of the changes in thalamic representation that may parallel the impairment in thermal sensibility. This decrease in stimulation-evoked thermal sites in the area of VMpo could be explained by retrograde degeneration of the appropriate neural elements within this region, subsequent to lesions of thalamic and extrathalamic areas. In order to confirm this notion, future study should examine if these lesions included the internal capsule and/or parts of the insula.

The disinhibition hypothesis predicted that a lesion to the thermosensory pathway projecting from VMpo to the insula would result in release of inhibition of pain in the lamina I-medial dorsal nucleus pathway terminating in the anterior cingulate cortex. The present study found an increase in the incidence of stimulation-evoked pain in Vc (see below) and the posterior-inferior region (i.e. VMpo), although such an increase would not be expected on the basis of the thermal disinhibition hypothesis. However, these findings could be accounted for by the loss of inhibitory collateral projections from the lamina I-VMpo-insula thermosensory pathway that may terminate directly or indirectly on pain signaling cells in these areas. At the present time however, this conjecture is purely speculative as no evidence exists of inhibitory connections between the thermosensory pathway and other thalamic or suprathalamic regions.
6.6. Incidence of Stimulation-Evoked Pain and Temperature in Vc of Chronic Pain Patients

Microstimulation at sites in the Vc of PSP patients frequently produced painful sensations. In contrast, stimulation in the Vc of movement disorder or NSP patients only rarely resulted in pain. These findings are in agreement with a similar study by Davis et al. (1996) that investigated the incidence of painful sensations evoked by thalamic stimulation in patients with and without chronic pain. They found that threshold stimulation in the tactile Vc region never evoked pain in the NSP patients and evoked pain at only 2% of Vc sites in the movement disorder patients. However, in the PSP patients, threshold stimulation at 28% of the sites in Vc resulted in painful sensations.

Others have also demonstrated an increase in the proportion of stimulation-evoked pain in patients with chronic pain, especially those with PSP (Lenz et al., 1988b; Obrador and Dierssen, 1966).

A recent study by Lenz et al. (1998a) examined the incidence of threshold microstimulation-evoked pain and thermal sensations in movement disorder and chronic pain patients. They found that painful sensations were more frequently evoked in the Vc core of chronic pain (and a subset of central pain) patients than in the movement disorder group. By contrast, they found that the incidence of stimulation-evoked thermal sensations in the chronic pain patients was reciprocally reduced. The present study failed to confirm this reciprocal relationship between the pain and thermal stimulation-induced sensations in the Vc nucleus, as there appeared to be no difference in the incidence of thermal sites between the control and chronic pain groups of this study. A possible
explanation for the differing findings of the present study and the study by Lenz et al. (1998a) is the difference in the precise definition of Vc. The present study defined Vc as the region where neurons responded to cutaneous innocuous mechanical stimulation (i.e. light brushing with a paintbrush). In contrast, Lenz et al. (1998a) defined the tactile region of Vc as “the cellular region where the majority of cells responded to innocuous somatosensory stimulation”. This latter definition allowed the inclusion of not only tactile units, but also cells responding to deep stimulation including brisk stroking, tapping, and pressure. As a result, the area designated as Vc by Lenz et al. (1998a), would likely have been somewhat larger than Vc of the present study and may have included cells from the region posterior and inferior to Vc. Also, the ventral border of Vc on the sagittal thalamic reconstructions used in the study by Lenz et al. (1998a) was approximated by the intercommisural line, whereas the present study defined the ventral Vc border by a line parallel to the AC-PC line and passing through the ventral-most tactile cell.

6.7. Quality of Stimulation-Evoked Pain

A number of different descriptors were volunteered by the patients to describe the pain sensations evoked by stimulation of the thalamus. The most common of these descriptors included burning, shock, sharp, stabbing/shooting, and hot/cold pain, although in the majority of the cases patients did not volunteer or could not accurately describe the quality of the evoked pain. It may have been expected that if the thalamus of the chronic pain patients was acting as their chronic pain generator, then stimulation of the thalamus would evoke pain similar in quality to the chronic pain. However, the study failed to
show any difference in the quality of the pain evoked by stimulation between the pain and non-pain patients. Although these results are not directly comparable with the study by Davis et al. (1996), they are generally inconsistent with their findings. Davis et al. (1996) compared the quality of stimulation-evoked pain in Vc of movement disorder and chronic pain patients. They found that the PSP patients most often described the stimulation-evoked pain as nondescript pain (33% of sites) or burning pain (43%). In contrast, movement disorder patients never reported a burning pain sensation and in NSP patients such a sensation was evoked at only two sites. It is possible that the difference between the findings of the present study and those of Davis et al. (1996) are due to the different regions included in the analysis. The study by Davis et al. (1996) examined only sites in the tactile region of Vc, whereas the sites analyzed in the present study were not limited to Vc but included regions anterior and posterior to Vc. However, neither the present study nor the study by Davis et al. (1996) required the patients to describe the quality of the stimulation-evoked pain sensations in a strictly systematic fashion. For example, although the patients were usually asked to describe the stimulation-evoked pain, this was not done consistently. Thus it is also possible that the present study did not find a preponderance of burning pain in PSP patients simply because the information was not volunteered by the patients in the absence of inquiry. The use of a standardized list of descriptors (i.e. McGill pain questionnaire) referred to at every site where a pain sensation is evoked would perhaps be useful to reexamine this issue in the future.
6.8. Mismatches Between Receptive and Projected Fields

The present study found an increased incidence of mismatches between the tactile RFs and pain/temperature PFs in PSP patients at Vc sites where pain or thermal sensations were evoked. Comparison of RFs/PFs in the movement disorder or NSP groups of patients failed to show any significant inconsistencies. Although the findings of this study are not directly comparable to those of Dostrovsky et al. (1993), it is interesting to note that they found a generally good correspondence between the location of the tactile RFs of neurons recorded at stimulation sites within Vc and the location of paresthesia sensations evoked by the stimulation. In some cases, they observed that the PFs were located in a totally different part of the body than the RFs of the neurons recorded at that site. Davis et al. (1996) performed a similar study where they examined the incidence of mismatches between RFs and microstimulation-evoked PFs in the Vc of pain and non-pain patients. They found that the total number of RF/PF mismatches was significantly greater in each group of pain patients (NSP and PSP) compared with the movement disorder patients. Furthermore, this difference seemed to be due to an increase in the 'gross' mismatches rather than 'minor' or 'size' mismatches (defined in METHODS).

The tactile RFs and pain/thermal PFs in the movement disorder and NSP patients were well matched and are consistent with the known organization of the thalamus. For example, the tactile RF of a low threshold neuron is determined by the medial lemniscal projections it receives from the spinal cord. Interspersed between the medial-lemniscal receptive cells are thalamic neurons receiving projections from the STT. Both units then relay the received signals to the cortex through appropriate efferent projections. Under
normal physiologic conditions it is to be expected that afferent and efferent signals should coincide as is evident by the match in the receptive and projected fields (Davis et al., 1996; Dostrovsky et al., 1993). It should be noted that the pain and thermal sensations evoked by microstimulation in the present study were often accompanied by paresthesia. This suggests that both pain/thermal and tactile elements were being stimulated since paresthesiae seem to be evoked by stimulation of tactile Vc cells (Davis et al., 1996; Dostrovsky et al., 1993). The findings that the location of stimulation-evoked pain/thermal sensations corresponded to the RF location of a tactile neuron at the stimulation site suggest that the somatotopic organization of thalamic pain/thermal units coincides with units receiving lemniscal input. This notion is in agreement with physiological findings, which show that the receptive fields of nociceptive neurons are generally consistent with the lemniscal somatotopography of VP (Kenshalo et al., 1980).

The rare occurrence of tactile RF and pain/thermal PF mismatches in the movement disorder group may be due to the spread of the stimulation current to nearby fibers of passage. On the other hand, the increase in frequency of the tactile RF and pain/thermal PF mismatch observed in the PSP patients seems to indicate some degree of reorganization at the level of the thalamus. It is likely that such changes may be attributed to thalamic or extrathalamic lesions resulting in antidromic as well as orthodromic neuronal degeneration. Whether such changes could play a role in the mediation of central pain remains to be determined.

The present study also showed that the incidence of mismatch between PFs of stimulation-evoked paresthesia and pain/temperature at adjacent sites in the posterior-
The inferior region was significantly greater than incidence of RF/PF mismatch in Vc. Thus there does not appear to be a similarity in the somatotopography of the neural elements giving rise to the paresthesia and pain/temperature sensations. This finding may also be explained on the bases of anatomy. The paresthesia sensations are likely the result of stimulation of the medial lemniscal fibers that traverse posterior to the posterior-inferior region or neural elements onto which they terminate. By contrast, the pain/thermal sensations were likely produced by the stimulation of STT fibers or nociceptive and/or thermoceptive neurons located in the posterior-inferior region. The present findings are consistent with the lack of anatomical or physiological evidence to suggest that the somatotopic organization of these neuronal substrates is related. Furthermore, these findings provide support for the presence of a specific pain and temperature substrate located posterior-inferior to Vc that is distinct from the medial lemniscal pathway and its terminations.

6.9. Projected Field Location and Size of Pain and Thermal Sensations
Differences in the location of the PFs of stimulation-evoked pain and thermal sensations were observed in the present study among the different patient groups. Pain and thermal sensations evoked by stimulation were located more frequently on the hand in the movement disorder patients than in the patients being treated for chronic pain. By contrast, more pain and thermal sensations were located on the trunk and leg in the chronic pain patients than in the movement disorder patients. This difference might be explained by the different stereotactic targets required for the surgical treatment of the two patient groups. The movement disorder patients are usually being treated for tremor...
of the hand and thus the radio-frequency lesion or DBS electrode is placed in the physiologically determined hand representation of the Vc core. Conversely, the pain experienced by chronic pain patients is often localized to the body and/or the extremities. Thus in the chronic pain patients the DBS electrode is placed more laterally in the body regions, whereas these areas are explored less frequently in the movement disorder patients. These results might be taken to suggest a certain degree of somatotopic organization of pain and temperature in the thalamus and/or its projection site.

An alternative interpretation of the results could also be entertained. If it was possible to systematically explore the location of the PFs of stimulation-evoked pain, warm, and cold sensations, it might be expected that the proportional representation of the various body regions would be similar to the tactile system. Thus we would expect to find that the regions of the face and hand would be over-represented, whereas the trunk and the lower extremities would be under-represented. In general, the data of the present study seem to support such a proportional somatotopic representation of pain and temperature for the movement disorder patients, but not for the chronic pain patients. It seems that in the chronic pain patients, the pain/temperature representation of the trunk and leg regions of the body – where their chronic pain is usually experienced – may increase in size. Thus the proportional somatotopic representation of pain and temperature in the thalamus (or cortex) of chronic pain patients might differ from that of the movement disorder patients and from the somatotopic representation of the tactile system. However, due to the non-systematic nature of data sampling in the present study it is not possible to provide adequate evidence for or against this notion.
The present study also found a difference in the sizes of PFs at sites where either warm or pain sensations were evoked by stimulation. It was noted that the ratio of small to large PF was significantly larger for pain than for warm sensations evoked in movement disorder patients. Although no physiologic studies to date have provided relevant data with which to compare these findings, these results are in agreement with some previous psychophysical work. Nathan and Rice (1966) investigated the localization of warm radiant stimuli in human subjects. They found that the warm stimulus was localized less accurately than the tactile stimulus, but it was localized far better than could have occurred by chance. They also found that when the intensity of the radiant stimulation was increased so that the pure warm sensations perceived by the subjects changed to a sensation of pricking, stinging, or hot, the accuracy of localization improved. This effect was subsequently studied by Simmel and Shapiro (1969) who examined the ability of subjects to localize radiant heat stimuli of varying intensities applied on the volar surface of their forearm. They found that the mean error of localization decreased systematically as the intensity of stimulation was increased so as to produce sensations of warm, very warm, hot, burning, and sting. These results suggest that the accuracy of localization of noxious heat stimuli is superior to innocuous warm stimuli. Since smaller neuronal RFs are conceptually more useful in accurately localizing cutaneous stimuli than larger RFs, these findings are consistent with the results of the present study, which show a greater proportion of small pain PFs than warm PFs. An opposite relationship was found in the PSP patients where it was found that the ratio of large to small PF was significantly greater for pain than for warm sensations. These results suggest that there may be an alteration in the physiology of the pain and thermal thalamic elements of the PSP patients.
that may be involved in the mediation of chronic pain. This shift in the ratio of small to large PF for pain and warm sensations is consistent with Lenz's et al. (1998a) hypothesis that the elements that signal warm stimuli may switch to signal pain in patients suffering from chronic pain.
Section 7. Future Directions

There are two major directions for future studies. First, it is necessary to more directly address the issue of stimulation of fibers of passage within the posterior-inferior region to determine if they or the cells within that region give rise to sensations of pain or temperature. It might be possible to resolve this issue by injecting muscimol at sites within the posterior-inferior region where stimulation evoked sensations of pain or temperature. Muscimol, which is a GABA agonist, would presumably activate GABA receptors on the nociceptive and/or thermoreceptive cells to hyperpolarize them. Subsequent stimulation of these cells should fail to evoke a sensation of pain or temperature. If however, stimulation following the injection of muscimol did result in the perception of pain or temperature, it would likely be due to activation of fibers of passage and not cells. Secondly, to further reinforce the involvement of Vc and the posterior-inferior region in pain perception, it would be helpful to identify sites where cells responded to the application of noxious stimuli and microstimulation at the same site produced a sensation of pain.
Section 8. Summary and Conclusions

This thesis has reported findings that suggest the involvement of Vc and the posterior-inferior region in mediation of pain/temperature signals and chronic pain. Electrical stimulation delivered within Vc and the ventroposterior region was found to evoke pain and/or thermal sensations supporting the role of these areas in the pain and temperature CNS pathway. Stimulation of PSP patients in Vc and posterior-inferior region was found to produce pain sensations more commonly than in non-PSP patients. Furthermore, this increase in stimulation-evoked pain in the posterior-inferior region (but not Vc) of PSP patients was accompanied by a reciprocal decrease in the incidence of thermal sensations. An increased proportion of mismatches between tactile RFs and pain/temperature PFs at sites where stimulation evoked painful and/or thermal sensations was observed in PSP patients. A greater proportion of 'large' warm PFs than 'large' pain PFs was observed in movement disorder patients. An opposite trend was noted in PSP patients. Together these findings indicate that the physiologic representation of pain in Vc and posterior-inferior region (and temperature in posterior-inferior region) may be altered in PSP patients thereby contributing to the development and/or maintenance of their chronic pain.


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## Appendix: Patient Number Codes

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