Medial Lateral Extent of Thermal and Pain Sensations Evoked By Microstimulation in Somatic Sensory Nuclei of Human Thalamus

Shinji Ohara and Fred A. Lenz
Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, Maryland 21287-7713

Submitted 9 May 2003; accepted in final form 27 June 2003

Ohara, Shinji and Fred A. Lenz. Medial lateral extent of thermal and pain sensations evoked by microstimulation in somatic sensory nuclei of human thalamus. J Neurophysiol 90: 2367–2377, 2003. First published July 2, 2003; 10.1152/jn.00450.2003. We explored the region of human thalamic somatic sensory nucleus (ventral caudal, Vc) with threshold microstimulation during stereotactic procedures for the treatment of tremor (124 thalami, 116 patients). Warm sensations were evoked more frequently in the posterior region than in the core. Proportion of sites where microstimulation evoked cool and pain sensations was not different between the core and the posterior region. In the core, sites where both thermal and pain sensations were evoked were distributed similarly in the medial two planes and the lateral plane. In the posterior region, however, warm sensations were evoked more frequently in the lateral plane (10.8%) than in the medial planes (3.9%). No mediolateral difference was found for sites where pain and cool sensations were evoked. The presence of sites where stimulation evoked taste or where receptive and projected fields were located on the pharynx were used as landmarks of a plane located as medial as the posterior part of the ventral medial nucleus (VMpo). Microstimulation in this plane evoked cool, warm, and pain sensations. The results suggest that thermal and pain sensations are processed in the region of Vc as far medial as VMpo. Thermal and pain sensations seem to be mediated by neural elements in a region likely including the core of Vc, VMpo, and other nuclei posterior and inferior to Vc.

INTRODUCTION

Previous studies employing anatomical and physiological methods demonstrate that the principal sensory nucleus (monkey ventral posterior, VP) and adjacent nuclei inferior and posterior to the principal sensory nucleus in the thalamus are involved in the nociceptive and thermal processing in monkeys (Apkarian and Hodge 1989b; Apkarian and Shi 1994; Berkley 1980; Boivie 1979; Burton and Craig 1983; Bushnell and Duncan 1987; Bushnell et al. 1993; Casey 1966; Casey and Morrow 1983; Chung et al. 1986; Craig et al. 1994; Gautron and Guilbaud 1982; Jones 1985; Kenshalo et al. 1980; Mantyh 1983; Mehler et al. 1960; Ralston and Ralston 1992; Willis 1985) and humans (Bowsher 1957; Lenz and Dougherty 1998; Lenz et al. 1993a, 1994b; Mehler 1962, 1966a,b, 1969; Mehler et al. 1960; Walker 1943). Microstimulation studies in humans also implicate this area in thermal and pain processing (Davis et al. 1996, 1999; Dostrovsky et al. 1991; Halliday and Logue 1972; Hassler 1970; Hassler and Reichert 1959; Lenz et al. 1993a, 1998b) and thermal sensations (Davis et al. 1999; Hassler 1970; Lenz et al. 1993a, 1998b) in patients operated on for treatment of either chronic pain or movement disorders.

The posterior part of the ventral medial nucleus (VMpo), a terminus of lamina I of the spinal and medullary dorsal horns, may mediate pain and thermal sensations in monkeys (Craig et al. 1994; Dostrovsky and Craig 1996) and in humans (Blomqvist et al. 2000; Davis et al. 1999). However, a recent study in monkey shows that lamina I spinotectal tract (STT) neurons also project to ventral posterior lateral and medial nuclei (VPL/VPM) (Willis et al. 2001). Furthermore, the idea of dense calbindin immunoreactive fiber plexus in VMpo (Blomqvist et al. 2000; Craig et al. 1994) has been called into question by the observation that it is dependent on the epitope of calbindin to which the antibody for histology was raised (Jones et al. 2001; Rausell et al. 1992). Therefore the degree to which VMpo is specific for thermal and pain processing is unknown (Willis et al. 2002). Indeed, a recent microstimulation study of thalamus demonstrated that many of the stimulation sites where thermal and pain sensations evoked were clearly lateral to the location of VMpo (Dostrovsky et al. 2000), perhaps due to stimulation of fibers at passage.

We have previously evoked pain and temperature sensations by stimulation behind the face and upper extremity representation in Vc in patients with movement disorders and chronic pain (n = 11 thalami) (Lenz et al. 1993a). Therefore that report described sensations evoked by stimulation in a relatively lateral compartment of the region of Vc. In the present study, we analyzed a much larger experience (n = 124 thalami), including our previous results (Lenz et al. 1993a), and focused on the medial-lateral distribution of these sites, particularly on medial sites. These data demonstrate the extent of the medial representation of pain and temperature. They suggest that VMpo, Vc, and other nuclei posterior and inferior to Vc are an important part of the human pathway signaling pain and temperature sensations.

METHODS

These studies were carried out at the Johns Hopkins Hospital during the physiologic exploration of the thalamus that preceded thalamot...
omy or implantation of deep brain stimulating electrodes for the treatment of tremor. The protocol used in these studies conformed to the principles stated in the Declaration of Helsinki regarding the use of human subjects and was reviewed and approved annually by the Joint Committee on Clinical Investigation of the Johns Hopkins University. Patients signed an informed consent prior to involvement in these studies.

We reviewed results in 116 consecutive patients (28 females and 88 males; 43 Parkinson’s disease, 73 essential tremor), who underwent thalamic explorations during stereotactic surgery for the treatment of tremor (1990–2001). Patients with multiple sclerosis, with poststroke tremor or with posttraumatic intention tremor, were not included in this study. Because eight patients underwent bilateral surgery, a total of 124 thalami were studied. In 49 thalami of 46 patients (14 females and 32 males: 14 Parkinson’s disease, 32 essential tremor), microstimulation evoked either thermal sensations (cold or warm) or pain or both.

Intraoperative procedures

Physiologic exploration of the thalamus was carried out under local anesthetic as described previously (Lenz et al. 1993a). Briefly, the stereotactic coordinates of the anterior commissure (AC) and posterior commissure (PC) were determined by computer-assisted tomography or magnetic resonance imaging. These coordinates were used to generate maps of the human thalamus in sagittal section.

The stereotactic target was confirmed physiologically by recording the activity of single neurons and stimulating with a microelectrode. Trajectories were directed toward Vc through a coronal burr hole 2 cm lateral to the midline and therefore passed through Vc from anterior dorsal to posterior ventral. The first trajectory targeted Vc because the response of cells in this area to somatosensory stimulation was the most reliable physiologic landmark with which to guide the operation (Lenz et al. 1995).

The exact position of electrode in the brain may shift after a cell is first isolated for two reasons. In the first place, the hydraulic microdrive advances a small amount over a few seconds after the last change in position. Second, the electrode tends to drag tissue along with it as it advances. After the last adjustment, the electrode-tissue system seems to relax so that the tip is located deeper in the brain a few seconds after the last adjustment than at the time of the adjustment. We always compensate for these effects by maintaining the size of the action potential constant throughout the recording by small adjustments. The size of the action potential is always studied before stimulation. These small adjustments are unlikely to cause similar problems because of their size (<100 microns). The recording period can last for 1–10 min and the size of the action potential is stable by 10–20 s after the last electrode movement. We have no way to estimate the error in our estimate of the absolute anatomic location of the electrode.

Sites were explored starting 1 cm above the target and were characterized by the location of the sensation evoked (projected field, PF) by threshold stimulation of thalamus at microampere current levels (TMIS). Sites where isolated single neurons could be recorded were characterized by spontaneous activity (Lenz et al. 1988, 1989, 1994c; Zirn et al. 1997) and by the neuronal response to innocuous somatosensory stimuli (Lenz et al. 1988). The activity of isolated single neurons was studied in response to stimuli including light touch, tapping or pressure to skin, deep pressure to muscles or ligaments, and passive joint movement. Cells responding to stimulation of the skin were termed cutaneous cells. Cells responding to stimulation of deep structures (joints, ligaments, etc.) but not to stimulation of skin deformed by these stimuli were termed deep cells. A reproducible response to repeated application of a stimulus in one part of the body was required to identify a neuronal receptive field (RF). During surgery, a tape recording was made of the microelectrode signal and of audio signal including instructions to the patient and additional comments.

Microstimulation was delivered in trains of ~1-s duration at 300 Hz by using a biphasic pulse consisting of a 0.2-ms anodal pulse followed in 0.1 ms by a cathodal pulse of the same duration and magnitude. Stimulation was initially carried out at 40 or 50 μA at sites located 2 mm apart along the trajectory. When a sensory response was evoked, stimulation was subsequently carried out once along every 1 mm on the trajectory. At each stimulation site, patients were first asked whether they felt anything. If a sensation was evoked, then a threshold was established; if no sensation was evoked at 40 or 50 μA, then a no response (NR) was indicated at that site. A site where a sensation was evoked was sometimes named by that sensation (e.g., cool site, pain site, etc.). The threshold was established by lowering the current for successive stimuli until a sensation was no longer evoked (TMIS). The current was then increased until a sensation was again evoked. This procedure was often repeated to verify the threshold.

Once a threshold had been established, the patient was questioned to determine the location of the sensation evoked by stimulation (PF). Thereafter, the patient described the TMIS evoked sensation by using the questionnaire shown in Fig. 1. The patient was asked to decide if the sensation was natural by identifying the stimulus and judging if the stimulus was “something that you might encounter in everyday life.” Neither question 1 nor question 2 was a forced choice. If the sensation was nonpainful then the patient chose a descriptor(s) from the upper list under heading 4, labeled nonpainful. If the sensation was painful, then the patient chose a descriptor(s) from the lower list labeled “painful” list under heading 4. In this section, the patient was asked to identify which of the classes of sensation were applied (e.g., mechanical, movement, etc.) then to identify a descriptor or descriptors within the chosen class. If the descriptors within that class were not applicable, patients were allowed to specify the class (e.g., tingle). After choosing a descriptor in one class, the patient was asked if the other classes might apply to a component of the sensation. Patients were encouraged to specify descriptors not included in the questionnaire. Microstimulation was repeated several times to determine the location of the PF and to complete the questionnaire. This protocol was followed at each stimulation site so that data are reported in terms of results at individual stimulation sites, including sites where no sensation was evoked.

Data analysis

The core region of Vc was defined as the cellular region where the majority of cells responded to innocuous somatosensory stimulation (Lenz et al. 1988, 1993a, 1994a). The sites where TMIS evoked paresthesia, cool, warm, or pain sensations were plotted with respect to the borders of core region of Vc in the parasagittal plane. A line perpendicular to AC-PC line and passing through the most posterior neuron with a cutaneous RF is assumed to define the posterior border of the core of Vc, while the most anterior neuron with such activity defines the anterior border (see legend to Fig. 2). Similarly, a line parallel to AC-PC line (Fig. 2B, - - -) and passing through the most ventral site with cutaneous RF is the inferior border of core of Vc. In each parasagittal plane, the cellular area posterior to the posterior border of the core of Vc (2 quadrants, see legend Fig. 2) was defined as the posterior region of Vc. The area inferior to the core of Vc (1 quadrant) was defined as the inferior region of Vc. Along each trajectory, results were analyzed over the length of the trajectory after the first cutaneous cell. All sites stimulated in this area were plotted according to the coordinate system described in the preceding text.

Cells with cutaneous RFs are arranged in parasagittal sheets of cells representing from medial to lateral: intraoral, facial, digits thumb through fifth, and lower extremity (Jones et al. 1982; Kaas et al. 1984; Lenz et al. 1988). Therefore a trajectory in the parasagittal plane will usually encounter cellular RFs located on one or perhaps two different parts of body (Lenz et al. 1988). Cutaneous RFs were used to identify the body part represented in the plane where a stimulation sites was
Which words describe the sensation that you feel?
1. Totally Natural/Almost Natural/Possibly Natural
   /Rather Unnatural/Totaly Unnatural
2. Clearly on the skin surface/Definitely below the skin surface/Both
3. Non-painful/Painful
4. Quality of Sensation
   Non-painful
   - Mechanical
     - Touch
     - Pressure
     - Sharp
   - Movement
     - Vibration
     - Movement through the body or across the skin
   - Temperature
     - Warm
     - Cool
   - Tingling
     - Electric current
     - Tickle
   - Itch
   Painful
   - Mechanical
     - Drilling
     - Stabbing
     - Squeezing
     - Tugging
   - Tearing
   - Dull
   - Splintering
   - Temperature
     - Hot
     - Burn
     - Cold
   - Movement
     - Spread
     - Flash
   - Flicker
   - Throb
   - Tingling
     - Itch
   - Electric
   - Frightful
   - Nauseating
   - Crul
   - Suffocating
   - Fatiguing

FIG. 1. Questionnaire used for sensory testing. This questionnaire was used to describe the sensation evoked by threshold microstimulation in a patient with essential tremor. The site where TMIS evoked both cool and warm sensations (see Table 1) simultaneously was also excluded from further analysis. In at least 32 cases, cool, warm, and painful sensations were also endorsed as descriptors at sites where mechanical, movement, and tingle classes were chosen. Among 23 cases where cool sensation was evoked, mechanical sensation was evoked in 2 sites, movement at 2 sites, and tingle at 5 sites. For 32 sites where warm sensation was evoked, mechanical, movement, and tingle sensations were evoked in 1, 3, and 17 sites, respectively. For painful sensation, mechanical, movement, and tingle sensations were evoked in 15, 5, and 13 sites, respectively, among 30 sites. Each of the sites described in the preceding text were categorized under the cool, warm, or painful categories (Table 1).

RESULTS

In 124 thalami of 116 patients studied, 959 sites were stimulated in the cellular region in and behind/below the core of Vc. Sensations were evoked in 838 sites (Table 1) with all different descriptors represented in the total (Fig. 1). There were 121 sites where NR was evoked by stimulation. Thermal and painful sensations were evoked at 86 sites (Table 1), 47 sites in the core, and 38 in the posterior region of Vc. The inferior region of Vc was excluded from further analysis because thermal or painful sensation was evoked only at one site (cool sensation) in that region. The site where TMIS evoked both cool and warm sensations (see Table 1) simultaneously were also excluded from further analysis. At some sites cool, warm, and painful sensations were also endorsed as descriptors at sites where mechanical, movement, and tingle classes were chosen. Among 23 cases where cool sensation was evoked, mechanical sensation was evoked in 1 site, movement at 2 sites, and tingle at 5 sites. For 32 cases where warm sensation was evoked, mechanical, movement, and tingle sensations were evoked in 1, 3, and 17 sites, respectively. For painful sensation, mechanical, movement, and tingle sensations were evoked in 15, 5, and 13 sites, respectively, among 30 sites. Each of the sites described in the preceding text were categorized under the cool, warm, or painful categories (Table 1).

Results in a patient with essential tremor are shown in Fig. 2. Paresthesia sensations were the commonest sensations evoked. Thermal (cool) sensations were evoked by stimulation in the area around the inferior and posterior borders of the core (sites 25–27, 55, 56, and 59). Painful sensation was not evoked by stimulation in this patient. The cool sites were located within a few mm from the posterior inferior corner of the core of Vc. Figure 3 plots the sites where NR, paresthesia, thermal, and painful sensations were evoked. Warm sensations were evoked more frequently by stimulation at sites in the posterior region (18/316) than by stimulation at sites in the core region (14/600; $\chi^2$ test, $P = 0.01$; Table 1; Fig. 3B). No difference in the proportion was found between the posterior and the core regions for pain sites (13/316 and 17/600, $P = 0.33$) or for warm sites (7/316 and 15/600, $P = 0.82$).

Threshold was examined using two-factor factorial ANOVA by “region” (core or posterior) and “quality of sensation” (paresthesia, cool, warm, or painful) and by “plane” (intraoral, face, or upper extremity) and “quality of sensation” (Table 1). In the former analysis only quality of sensation tended to be related to the threshold ($P = 0.07$). In the latter, plane was related to threshold, but neither quality of sensation nor the interaction was related to the threshold ($P = 0.05$). Post hoc analysis revealed that upper extremity plane had a significantly lower threshold than either intraoral or face (Bonferroni, $P < 0.0001$). Paresthesia sensation had a significantly higher threshold than cool sensation (Bonferroni, $P = 0.02$).

Location of sites where stimulation evoked thermal and painful sensations

Figure 4 illustrates sites where stimulation evoked cool, warm, or painful sensations in each mediolateral plane. The proportion of cool, warm, and pain sites was compared between upper extremity plane and medial two (intraoral + face) planes in the core and posterior regions of Vc. In the core, none of warm, cool, or pain sites showed a difference in the proportions between the medial two planes and upper extremity plane (Fisher’s exact probability test, $P > 0.05$). In the posterior region, warm sites were more frequently found in upper...
The proportion of thermal and pain sites was compared between the core and the posterior regions for each of three mediolateral planes. In the upper extremity plane, warm sites were found more frequently in the posterior region (9/83) than in the core (1/101; Fisher’s exact probability test, P = 0.006). The difference between core and posterior was not found for cool (3/83 and 1/101) or painful (5/83 and 4/101) sensations (Fisher’s exact probability test, P > 0.05). The face plane showed a significantly higher incidence of pain sites in the posterior region than in the core (7/186 and 3/340, Fisher test, P = 0.04), consistent with the location of VMpo (Blomqvist et al. 2000). No such difference was found for cool (4/186 and 12/340) and warm (7/186 and 11/340) sites (P > 0.05). The intraoral plane did not show any difference between the posterior and the core regions for sites where any of three sensations were evoked (Fisher tests, P > 0.05).

We also analyzed the coordinate of each site according to our coordinate system. In this system, the y axis indicates the anterior-posterior direction where a larger y value corresponds to a more anterior location. The z axis indicates the superior-inferior direction where a larger z value corresponds to a more superior location. The coordinates were compared among three planes for each quality of sensations. For warm sensation, sites in the three planes tended to have different y values (1-factor ANOVA, P = 0.07). Warm sites in the intraoral plane tended to be located anterior [i.e., larger y values; 1.2 ± (SD) 2.1] than those in the upper extremity (−0.6 ± 0.6) and in the face plane (0.6 ± 1.7). No significant difference in z values among three planes was found for warm sites.

Cool sites in the three planes had different z values (1-factor ANOVA, P = 0.04). Post hoc analysis revealed that cool sites in the face plane were located significantly superior (i.e., larger z values; 1.3 ± 0.9) than those in the upper extremity (−0.3 ± 1.3) plane (Bonferroni, P < 0.05). The location of cool sites in the face plane was not different from those in the intraoral plane. No significant difference in y coordinates among three planes was found for cool sensations.

As for pain sites, y values tended to be different among planes (1-factor ANOVA, P = 0.06) and sites in the intraoral plane were located significantly anterior (i.e., larger y values; 1.8 ± 1.6) than those in face (0.0 ± 2.0) and upper extremity (0.0 ± 1.2) planes (Bonferroni, P = 0.04 and 0.04). No difference among planes was found in z values (P = 0.34).

The coordinates were also compared between qualities of sensations in each plane. In any of three planes, neither y nor z values showed significant difference among the sensations of pain, cool, and warm.

Associated descriptors chosen to describe cool, warm, and pain sensations

The proportion in which “natural” was chosen together with cool, warm, and painful sensations was significantly different.
Cool was described as natural (82%) more frequently than warm (12%, $P = 0.001$). Cool was described as surface (80%) more frequently than warm (17%, $P = 0.0018$). Painful sensations (60%) were more frequently associated with descriptors under mechanical class than cool (10%; Fisher test, $P = 0.01$) and warm (5%; Fisher test, $P = 0.0001$) sensations. Pain sites were characterized by the descriptors “sharp” (8 sites), “hot” or “burn” (9), and “electric” (12; Fig. 5) but no significant difference was found in $y$ and $z$ coordinates of those sites (1-factor ANOVA, $P > 0.05$). The proportion of the sites where pain sensation was described as sharp, hot or burn, and electric was not different among the mediolateral planes (intraoral, face, and upper extremity; $\chi^2$ test, $P > 0.05$).

**Presence of thermal and pain sites in planes with activity related to taste and pharyngeal somatic sensation**

The presence of sites where stimulation evoked a taste and sites where RFs or PFs were on the pharynx were the reliable landmarks to indicate a plane located as medial as VMpo (Blomqvist et al. 2000; Jones et al. 1986) (taste/pharynx plane).
We found two sites where TMIS evoked taste feeling and burning hot sensations in mouth and nose. We also found 10 cells with pharyngeal RFs and 12 sites where TMIS evoked sensations in the pharynx. Figure 6 shows the results of a patient with essential tremor. Two sites with PF/RF in the area of pharynx were found within a few millimeters from the borders of the core of Vc. One of these sites (26) was located in a dense field of cells with RFs on the tongue. RF could be determined although the pharyngeal examination was possible but limited by the gag reflex. The cell was activated during swallowing but not by intraoral stimulation or limited anterior pharyngeal stimulation, strongly suggesting an RF in the pharynx or throat.

Figure 7A plotted the distribution of sites where taste or sensation in the pharynx was evoked or where RF in the pharynx was found. Two patients included in this figure were operated for conditions other than tremor (1 with dystonia and 1 with pain), and so were not included in the preceding analysis. Stimulation at three sites in these patients evoked a taste sensation (patients SB and RK in Lenz et al. 1997). The results in the remaining patients, operated on for tremor, were included in earlier summary figures (Figs. 3–5). These sites were distributed in and around the core region; some were located >5 mm anteriorly or superiorly to the core.

Figure 7B shows three cool, three warm, and seven pain sites on this taste/pharynx plane. The PFs of those thermal and pain sensations were on the lower extremity (1 site), the upper extremity (2 sites), the face (2 sites), and the intraoral space (8 sites) including the pharynx (5 sites). As for the coordinates, neither y nor z values were significantly different among cool, warm, and pain sensations (1-factor ANOVA, P > 0.05). The incidence of warm, cool, or pain sites in the taste/pharynx plane is not different from that in the other planes (P > 0.05, Fisher’s exact test). The association with other descriptors such as “natural/unnatural” and “deep/surface” was not different between sites found on taste/pharynx plane and those on the other planes (P > 0.05, Fisher test).

Discussion

This report describes the distribution of sites where microstimulation evoked thermal and pain sensations in the human thalamus. We particularly focused on the medial lateral distribution and defined three medial lateral planes on the basis of cutaneous RFs in the core (intraoral, face, and the upper extremity). Both thermal and pain sensations were evoked in the core and posterior regions of Vc in all of three planes. Warm sensations were evoked more frequently by stimulation in the posterior region than in the core. In the core, no medial lateral difference was found for thermal and pain sensations. In the posterior region, warm sites were found more frequently in the lateral plane. Thermal and pain sites were also found in a plane medial to the intraoral plane as indicated by TMIS-evoked taste sensations or pharyngeal somatic sensations, consistent with the location of medial VMpo. Equally dense thermal and pain sites are found in the region behind Vc across the medial lateral extent of this nucleus.

Methodological considerations

The definition of the region of Vc in the present study (Hirai and Jones 1989) is arbitrary but is consistent with anatomy, connectivity, and physiology of these regions. In monkeys, neurons responding to nociceptive stimulation are found in VPL (Apkarian and Shi 1994; Bushnell and Duncan 1987; Bushnell et al. 1990, 1993; Casey 1966; Casey and Morrow 1983; Chung et al. 1986; Kensahto et al. 1980), and spinothalamic tract terminals are clustered in VPL (Apkarian and Hodge 1989b; Berkley 1980; Boivie 1979; Jones 1985; Mantyh 1983; Mehler et al. 1960; Willis 1985). Similar neurons have also been found in monkey ventral posterior inferior nucleus (VPI) corresponding to human Vc parvocellularis, an inferior subnucleus of Vc (Vpcp) (Hirai and Jones 1989), in monkey pulvinar orals corresponding to human Vc portae (Vpor) (Hirai and Jones 1989), and in monkey posterior (Po), limitans, and suprageniculate nuclei corresponding to parts of human limitans nucleus (Apkarian and Shi 1994; Casey 1966; Perl and Whitlock 1961).

Recently, it is shown that the posterior portion of the ventral medial nucleus (VMpo) receives spinal input from nociceptive- and thermoreceptive-specific neurons in lamina I of the spinal dorsal horn in monkey (Craig et al. 1994). A cytoarchitectonic and immunohistochemical study suggests the presence of a corresponding nucleus in the area postero medial to Vc in humans (Blomqvist et al. 2000). In our anatomical coordinate system, these nuclei are assumed to be located in the posterior region (2 quadrants) of Vc.

In the present study, we employed microstimulation to investigate sensory function of the region of Vc. This provides a unique opportunity to compare psychophysical results with studies based on anatomy or on the neuronal response to peripheral stimulation. However, it must be noted that neuronal somata and axons are both stimulated by TMIS and that there is no way to differentiate responses due to one from the other (Ranck 1975). Therefore the relationship between the present study and previous anatomic or electrophysiologic studies must be interpreted with care.

Difference among qualities of sensations

In our previous study, pain and cool sites were found anterior to the area where warm sensations were evoked (Lenz et al. 1993a). It has been reported that cool sites were almost exclusively located posterior to the Vc in contrast to pain and warm sites (Dostrovsky et al. 2000). These authors also found that warm and cool sites were located in the medial-inferior quadrant, whereas pain sites were found within the Vc near the face/hand border (Dostrovsky et al. 2000). The present results demonstrate no difference in coordinates of the three qualities of sensations in any of three planes. However, we showed that the lateral part of the posterior region of Vc contained more sites where warm sensation was evoked by stimulation than the medial planes. Taken together the differences between the results of these studies do not support the view that cool, warm, and pain sensations were mediated through different pathways.

We showed that the descriptors associated with thermal and pain sensations were different. Cool sensations were described as natural more frequently than warm and pain sensations. Cool sensations were associated with surface more frequently than warm. Pain was associated with mechanical sensations more frequently than were cool and warm sensations. These differences in the descriptors associated with cool and pain sensations are evoked by the same parameters of TMIS and
therefore suggest that there are unique characteristics in the spike train or pathways mediating these sensations (Lenz et al. 2000).

Distribution of thermal and pain sites

We previously reported that thermal and pain sensations were evoked more frequently at sites in the posterior inferior region than at sites in the core region (Lenz et al. 1993a). Recently, it was reported that most sites where stimulation evoked thermal and pain sensations, in 49 movement disorder patients, were concentrated in the region 1–3 mm inferior and posterior to the inferior and posterior border of the Vc (Dostrovsky et al. 2000). The present results are in accord with these previous studies. However, we found more sites in the core region where stimulation evoked thermal and pain sensations than previous reports (cf. Fig. 3 in Lenz et al. 1993a and Fig. 2 in Dostrovsky et al. 2000).

The differences in definition of regions in and around Vc seems the most likely reason for the difference. For example, we restricted the present analysis to stimulation sites located in areas where neurons could be recorded; this provides a more accurate estimate of thalamic areas mediating different sensations. In our previous analysis (Lenz et al. 1993a), all stimulation sites in the posterior inferior area were included without regard for the presence or absence of neurons. This earlier approach led to a larger number of pain and thermal sites being classified in the posterior region, that certainly included fiber tracts.

At the level of spinal and medullary dorsal horn, respectively, the STT and the trigeminothalamic tract arise from cells both in the superficial layer (lamina I) and in the deeper layer (lamina V-VII) (Apkarian and Hodge 1989a; Willis 1987). In monkeys and humans, VMpo is reported to be the primary termination of lamina I of the spinal and medullary dorsal horns and to mediate pain and thermal sensations specifically (Blomqvist et al. 2000; Craig et al. 1994; Davis et al. 1999; Dostrovsky and Craig 1996). However, it has recently been shown that many retrogradely labeled neurons following tracer injection to VPL/VPM in the primate thalamus were found in lamina I as well as lamina V (Willis et al. 2001). This finding indicates that neurons in both laminae I and V contribute to the STT projections to VPL/VPM.

Dense calbindin immunoreactivity has been a useful marker for lamina I fibers and thus has been used to locate VMpo in monkeys and man by using an antibody that is no longer available (Blomqvist et al. 2000; Craig et al. 1994). However, a detailed immunohistochemical study using antibody recognizing a different epitope of calbindin has reported concentrated calbindin immunoreactivity within VPM and in a broad zone posterior to both medial and lateral VP (Jones et al. 2001). Studies of patients at autopsy following lesions of the STT show the most dense STT termination in Vc (Bowsher 1957; Mehl er 1962, 1966b; Walker 1943). Terminations are also observed posterior to Vc in the magnocellular medial geniculate (Mehler 1962, 1969), limi tants, and Vc portae nuclei (Mehler 1966b) and inferior to Vc in Vpc (Mehler 1966b).

In monkeys, cells in VP (Apkarian and Hodge 1989b; Ap karian and Shi 1994; Berkley 1980; Boivie 1979; Burton and Craig 1983; Bushnell and Duncan 1987; Bushnell et al. 1993; Casey 1966; Casey and Morrow 1983; Chung et al. 1986; Craig et al. 1994; Gautron and Guilbaud 1982; Jones 1985; Kenshalo et al. 1980; Mantyh 1983; Mehler et al. 1960; Ralston and Ralston 1992; Willis 1985) and VMpo (Casey 1966; Craig et al. 1994) respond to noxious and thermal stimuli. Recent studies in human demonstrate that Vc contains cells responding to noxious and thermal stimuli (Lee et al. 1999; Lenz and Dougherty 1998; Lenz et al. 1993b, 1994b). Neurons recorded in putative human VMpo are reported to respond to cool and painful stimuli (Davis et al. 1999) although the earlier study found such cells in more lateral planes as well (Lenz et al. 1993b).

The present and previous studies demonstrate that micro-stimulation in Vc (Dostrovsky et al. 2000; Lenz et al. 1993a) and in an area likely corresponding to VMpo produce both thermal and pain sensations (Davis et al. 1999; Dostrovsky et al. 2000; Lenz et al. 1993a). Disabling the function of neurons in monkey VMp by local anesthetic injection impairs behaviors requiring the discrimination of temperature in both the innocuous and the noxious range. Therefore it is likely that both VMpo and VPL/VPM are involved in thermal and pain processing.

In the present study, thermal and pain sites are distributed...
diffusely around Vc in planes representing intraoral, face, and upper extremity cutaneous structures. We also found such sites in medial planes as indicated by TMIS-evoked taste and RF/PPS related to pharyngeal somatic sensations. Nuclei mediating taste and pharyngeal somatic sensation are located in the proximities of VMpo (Blomqvist et al. 2000). The taste relay in the thalamus is located in monkey ventral posterior medial parvocellular nucleus (VPMpc) (Olszewski 1952; Pritchard et al. 1989) corresponding to human ventral-caudal parvocellular cellular nucleus (VPMpc) (Olszewski 1952; Pritchard et al. 1989) corresponding to human ventral-caudal parvocellular nucleus (VPMpc) (Olszewski 1952; Pritchard et al. 1989). Ventral posterior thalamic neurons differentially responsive to noxious stimulation of the awake monkey. I. Multimodal and discriminative properties of thermo-sensitive neurons. J Neurophysiol 69: 739–752, 1993.


**Lenz FA and Dougherty PM.** Cells in the human principal thalamic sensory nucleus (ventralis caudalis - Vc) respond to innocuous mechanical and cool stimuli. *J Neurophysiol* 79: 2227–2230, 1998.


**Lenz FA, Kwan HC, Dostrovsky JO, and Tasker RR.** Characteristics of the bursting pattern of action potentials that occur in the thalamus of patients with central pain. *Brain Res* 496: 357–360, 1989.


**Mehler WR.** Some observations on secondary ascending afferent systems in the CNS. In: *Pain*, edited by Knighton RS and Dumke PR. Boston, MA: Brown and Little, 1966a, p. 11–32.


