Microstimulation in the Region of the Human Thalamic Principal Somatic Sensory Nucleus Evokes Sensations Like Those of Mechanical Stimulation and Movement

Shinji Ohara, Nirit Weiss, and Fred A. Lenz
Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, Maryland 21278-7713

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INTRODUCTION

Cutaneous mechanical stimulation is transduced by multiple peripheral cutaneous elements, such as the Merkel, Ruffini, Meissner, and Pacinian corpuscles (Johnson et al. 2000; Mountcastle 1984). These corpuscles give rise to afferent fibers that transmit peripheral mechanoreceptive input to the CNS via the trigeminal or dorsal column-medial lemniscal pathway. The sensations evoked by intraneural microstimulation (μA currents) of afferent fibers arising from these mechanoreceptive corpuscles have often been reported (Ochoa and Torebjork 1983; Torebjork et al. 1984; Vallbo 1981; Vallbo et al. 1984). The underlying assumption of these reports is that sensations evoked by cutaneous mechanical stimulation reflect the sensations evoked by microstimulation. However, it is not clear to what extent subcortical and cortical structures transmit or process this afferent input.

The medial lemniscal pathways arising from contralateral trigeminal principal sensory and dorsal column nuclei terminate in the neurons in the thalamic principal sensory nucleus ventral posterior (VP) (Hirai and Jones 1989; Jones 1985). Numerous cells responding to nonpainful cutaneous stimuli are found in the core of VP. The area located anterior and dorsal to the core (antero-dorsal shell) receives the inputs from deep receptors including Group I afferents of muscle spindle through the medial lemniscal pathway (Friedman and Jones 1981; Jones and Friedman 1982; Jones et al. 1982; Lenz et al. 1988; Poggio and Mountcastle 1963).

We now examine the responses to threshold microstimulation, stimulation at microampere levels (TMIS), in and around the human thalamic principal somatic sensory nucleus (ventral caudal, Vc) for evidence that TMIS-evoke sensations are like those of mechanical and movement stimuli. We also test the idea that there is segregation of thalamic elements subserving different mechanoreceptive sensations.

METHODS

These studies were carried out at the Johns Hopkins Hospital during the physiologic exploration of the thalamus that preceded thalamotomy or implantation of deep brain stimulating electrodes for treatment of movement disorders. The protocol was reviewed and approved annually by the Institutional Review Board of the Johns Hopkins University. All patients signed an informed consent. We analyzed 116 consecutive patients (28 females) of whom 43 had Parkinson’s disease and 73 had essential tremor; all had thalamic explorations during stereotactic surgery for the treatment of tremor (1990–2001). Patients with intention tremor were excluded. A total of 124 thalami were studied because eight patients had bilateral surgery.

Intraoperative procedures

Physiologic exploration of the thalamus was carried out under local anesthetic as described previously (Lenz et al. 1993). 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 by stimulating through the 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 is the most reliable physiologic landmark with which to guide the operation (Lenz et al. 1995; Mandir et al. 1997). Additional trajectories were often required to map out the anterior and inferior boundaries of Vc that were used to predict the boundaries of the ventral intermediate and oral posterior (Vim and Vop), the nuclei where the electrodes were implanted or lesions were made. Mean number of trajectories made during the surgery was 3.4 per thalamic exploration.

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 TMIS. Sites where single neurons could be recorded were characterized by spontaneous activity (Lenz et al. 1988, 1989, 1994b; Zirh et al. 1998) 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 cutaneous stimuli such as light touch, tapping or pressure to skin, and deep stimuli such as 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 application of a stimulus in one part of the body was required to identify a neuronal receptive field (RF). During surgery, a tape recording of a foot pedal indicating events during the examination, of the microelectrode signal, and of audio signal including instructions to the patient and additional comments was made. We carried out microstimulation at designated sites along each trajectory after cells recorded at that site had been studied (see following text).

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 by 0.1 ms by a cathodal pulse of the same duration and magnitude. Stimulation of somatosensory thalamus and cortex at threshold has been reported to be subthreshold for conscious sensation (Libet et al. 1967, 1991). Stimulation of somatosensory thalamus and cortex at 500–1,000 ms (Libet et al. 1967, 1991), consistent with our own observations (Lenz et al. 2000). To avoid complicating the results with this effect, we stimulated for 1 s at least, often longer. 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 every 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 was indicated at that site. The threshold was established by lowering the current for successive stimuli until a sensation was no longer evoked. The current was then increased until a sensation was again evoked. This procedure was often repeated to verify the threshold.

Psychophysical protocols

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 Table 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” (question 1). Also the patient was asked to decide if the sensation was located on the surface of the skin or below the surface of the skin or both (question 2). Neither question 1 nor 2 was a forced choice.

If the sensation was nonpainful, the patient chose from the list under question 4. Under question 4, the patient was asked to identify the four classes of sensation that were applied (mechanical, movement, temperature, and tingle) and then to identify a descriptor or descriptors within the chosen class. Patients were allowed to specify the class (e.g., tingle) as a descriptor if the descriptors within that class were not applicable. After choosing a descriptor in one class, the patient was asked if the other three 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. Sites where thermal or painful sensations were evoked have previously been reported (Lenz et al. 1993). Vibration was classified as movement as in all our previous protocols (Lenz et al. 1993) and by analogy to microstimulation protocols for peripheral receptors (Johnson et al. 2000).

Statistical analysis (Snedecor and Cochran 1967) of parametric variables was accomplished using an ANOVA or, if not normally distributed, by a Kruskal Wallis. Post hoc testing was carried out by pairwise analysis with Bonferroni correction for multiple comparisons or Dunn correction, if the variable was not normally distributed. Tests of proportion were carried out by Fisher’s exact test or χ², as appropriate. Results were identified as statistically significant for P < 0.05. Sites where more than one sensation was evoked are indicated by overlapping of the two symbols, as in Fig. 4. Each of the sites with two descriptors was counted within the two appropriate categories for analyses of the numbers of sites where individual sensations were evoked.

RESULTS

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, 1993, 1994a). Lines perpendicular to the AC-PC line and passing through the most anterior and posterior site where cells had a cutaneous RF were assumed to indicate the anterior and posterior borders of the core of Vc (Fig. 1, A and B). A line on the anterior border of the core region (nearly vertical dashed lines in Fig. 1B) is defined as the z axis. Similarly, a line parallel to the AC-PC line passing through the most inferior site with cutaneous RF was the inferior border of core of Vc. This is defined as the y axis (nearly horizontal dashed line in Fig. 1B). Our analysis focused on Vc core, inferior, posterior, and posterior inferior regions which included 897, 282, 90, and 585 sites, respectively, where sensations were evoked. The origin (0) of y and z coordinates is at the point of intersection of the y and z axes with coordinates increasing anteriorly for the y axis and dor-sally for the z axis. Regions inferior, posterior inferior, and posterior to the core region are defined by reference to these axes as illustrated in Fig. 1. The posterior inferior region was explored to study the properties of Hassler’s ventral caudal parvocellular nucleus (Vpc) and inferior ventral caudal portae
of the ventral caudal (Vc) in a single patient (85.095 microamperes) in indicated below the PF diagram. NR, no response.

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described in METHODS. Scale is as indicated. B: location of cellular recordings (ticks to the right of trajectory) and stimulation sites (ticks to the left of the trajectory) and a trajectory (P2) relative to the AC-PC line (approximately horizontal solid line) and the ventral border of the core of Vc (approximately horizontal dashed line, y axis). The approximately vertical solid and dashed lines indicate the posterior and anterior (z axis) borders of the core of Vc, respectively. Cells with receptive fields (RFs) are indicated by long ticks; those without are indicated by short ticks. The pressure sensation evoked by a filled circle at the end of the tick to the left of the trajectory. Scale is as indicated. C: each site where a cell was recorded or stimulation was carried out or both are indicated by the same number in B and C. C shows the site number, projected field (PF), and RF for that site. The threshold (in microamperes) in indicated below the PF diagram. NR, no response.

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nucleus (Vcpor), probably corresponding to monkey ventral posterior inferior (VPI) and anterior pulvinar (Pla) (Hirai and Jones 1989), respectively. Recordings in these nuclei in humans can be difficult because neurons in these nuclei tend to be smaller and sparser than in Vc. Therefore it is difficult to determine the boundaries of these human nuclei physiologically, and the posterior inferior region often includes results from fiber pathways under the thalamus.

Figure 1 shows the map of the exploration in a patient with essential tremor. TMIS at 3 μA in the core region at site 31, activated neural elements in a volume defined by a radius <70 μm (Ranck 1975) in the core region, evoked a pressure sensation. The evoked sensation was also described as unnatural and deep. PF was located at the jaw, and the cell recorded at the stimulation site had RF on the tip of tongue.

In 124 thalami we studied, 3,157 sites were stimulated and sensations were evoked in 1,854 sites. Of 1,854 sites, descriptors in mechanical and movement classes were chosen in 122 sites in 42 thalami; touch at 33 sites, pressure at 17 sites, sharp at 5 sites, vibration in 40 sites, and movement through the body or across the skin (movement) in 27 sites. Thresholds at which those sensations were evoked across all regions were not significantly different among them (P = 0.46, ANOVA). Painful and/or thermal sensations were evoked in 96 sites, and nonpainful sensations described with descriptors in tingle class were evoked in 1,636 sites. Sites where TMIS evoked sharp sensation were excluded from statistical tests of proportion because of the small number of such sites.

**Location of sites where TMIS evoked mechanical and movement sensations**

Of 122 sites, 72 sites were found in the core region, 33 sites in the posterior inferior, 4 sites in the inferior, and 13 sites in the posterior regions. The threshold was not significantly different among descriptors in the core (P = 0.93, ANOVA), the posterior regions (P = 0.69, ANOVA), and posterior inferior (P = 0.30, Kruskal-Wallis). The inferior region was not analyzed because of small sample size.

Although the distribution of sites where TMIS evoked each sensation overlapped (Fig. 2), the proportion in which those sites were located in the core region was different among four descriptors (excluding sharp; P < 0.05, χ² test; Fig. 3). Sites where TMIS evoked touch were significantly less frequent in the core region than those where movement was evoked (P < 0.05, χ² test) and tended to be less common in the core than those with pressure (P = 0.07, Fisher’s exact test). No significant difference in proportions among different descriptors was found in posterior, inferior, and posterior inferior regions (P > 0.05, χ² test; Table 2). Locations of those sites were also compared using y and z coordinates across all regions. Neither y nor z values showed significant difference among five descriptors (P = 0.17 and 0.17, ANOVA).

We also analyzed the relationship between a sensation evoked by TMIS and its PF or a cutaneous RF of a unit recorded at or adjacent to the stimulation site. Human RFs and PFs are known to be located in a medial-lateral sequence from tongue to face, hand and leg laterally (Lenz et al. 1988). Thus RFs or PFs were classified by mediolateral location of each stimulated site. Of 122 sites where mechanical and movement sensations were evoked, 27 sites were found with intraoral RF, 65 with the face, and 30 with the upper extremity RFs. No sites were found with the lower extremity RFs. Twenty-one sites had the intraoral PFs, 58 face PFs, 37 upper extremity PFs, and 6 lower extremity PFs.

The y and z coordinates of the sensations were compared for each mediolateral PF/RF (intraoral, face, upper extremity, and lower extremity; Fig. 4). For RFs, only the z coordinates found with upper extremity RFs tended to be different among descriptors (P = 0.09, ANOVA). Post hoc analysis revealed that the sites with the descriptor vibration (1.5 ± 1.9, Fig. 5B, right, ■) were located inferior (smaller z values) to those sites with descriptors (excluding sharp; P < 0.05, χ² test; Fig. 3). Sites where TMIS evoked touch were significantly less frequent in the core region than those where movement was evoked (P < 0.05, χ² test) and tended to be less common in the core than those with pressure (P = 0.07, Fisher’s exact test). No significant difference in proportions among different descriptors was found in posterior, inferior, and posterior inferior regions (P > 0.05, χ² test; Table 2). Locations of those sites were also compared using y and z coordinates across all regions. Neither y nor z values showed significant difference among five descriptors (P = 0.17 and 0.17, ANOVA).

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vibration (Fig. 4A, middle, −, mean \( z = 1.5 \pm 2.7 \)) were located inferior (smaller \( z \) values) to those with movement (Fig. 4A, middle, □, mean \( z = 4.7 \pm 3.1 \)) among sites with face PFs (\( P < 0.05 \), Bonferroni). In this analysis, sites where TMIS evoked sharp and/or pressure sensations and those found with the lower extremity PFs or RFs were not included because of small number of sites. Examination of Fig. 4 suggests that the movement sites are located anterior, dorsal, and posterior to the core (Fig. 4, A and B, middle and right), although this distribution was not testable.

To investigate modality-specific organization in a rod-like configuration (Jones et al. 1982; Lenz et al. 1988), we analyzed parasagittal planes where TMIS evoked a given sensation at two or more sites. If the same sensation was evoked at two or more consecutive sites, then those sites were considered to be in a cluster. If sites were located on the different trajectories in the same plane, only the sites which were closest to each other were considered to be in a cluster. Of 122 sites in this study, 72 sites were found to have the same sensation as that evoked at another site or sites in the same plane. Of these 72 sites, 58 (81%) were included in a cluster.

Figure 5 shows an example of clustering in a patient with essential tremor. In this patient, pressure was evoked at five sites, vibration at three, and touch at three sites where more than one descriptor was chosen. Five sites with pressure and then three sites with vibration, and two with touch were found at consecutive stimulation sites. This demonstrates modality-specific segregation in the region of Vc. The proportion of those sites which were in a cluster was not different significantly among descriptors (\( P = 0.82, \chi^2 \) test).

Characteristics of mechanical and movement sensations evoked by TMIS

Figure 6 shows the locations of RFs found at or adjacent to sites where each different descriptor was evoked. No sites were found with lower extremity RFs. Stimulation at or adjacent to cells with facial and intraoral RFs were different among four descriptors, excluding sharp because numbers were too small (\( P < 0.05, \chi^2 \) test). Touch and vibration were more commonly (\( P < 0.05 \)) found with facial RFs than was pressure. Pressure was more commonly (\( P < 0.05 \)) found with intraoral RFs than was vibration. No descriptors were significantly related to any particular PF (\( P > 0.05 \)).

The correlation of the size and location of PFs and RFs was analyzed for each descriptor. The size of PFs and RFs was approximated based on the intraoperative description of their distributions. In identifying parts (location) of the body, we

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<td>Movement</td>
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TMIS, threshold microstimulation; Vc, ventral caudalnucleus.

FIG. 3. Number of sites where TMIS evoked mechanical (touch, pressure, and sharp) and movement [movement through the body (movement) and vibration] sensations in the core and the posterior inferior regions. Note that the proportion in which those sites were located in the core region was different among four descriptors. Sharp was not analyzed because of the small number of sites. Those with movement through the body (\( P < 0.05 \)) and pressure (\( P = 0.07 \)).

FIG. 5. An example of clustering in a patient with essential tremor. In this patient, pressure was evoked at five sites, vibration at three, and touch at three sites where more than one descriptor was chosen. Five sites with pressure and then three sites with vibration, and two with touch were found at consecutive stimulation sites. This demonstrates modality-specific segregation in the region of Vc. The proportion of those sites which were in a cluster was not different significantly among descriptors (\( P = 0.82, \chi^2 \) test).

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The correlation of the size and location of PFs and RFs was analyzed for each descriptor. The size of PFs and RFs was approximated based on the intraoperative description of their distributions. In identifying parts (location) of the body, we
followed the conventions used in previous studies (Byl et al. 1996; Lenz et al. 1988; Lenz and Byl 1999). Specifically, separate parts of the body included intraoral, perioral, facial, D1 (1st digit), D2, D3, D4, D5, multiple digits, palm/hand, forearm, whole arm, upper arm, wrist, trunk, leg, upper leg, lower leg, pelvis, ankle, foot and toes (No. 1–22 in Fig. 7, right). Those parts are arranged by their representations in Vc from medial to lateral (Lenz et al. 1988). When the RF and PF were limited to the same part of the body or included both the same part of the body they were said to form a match (Lenz and Byl 1999).

Figure 7 shows the correlation between RFs and PFs in their size and the location for all sites where mechanical and movement sensations were evoked (122 sites). As for the locations of the RF and PF, we plotted the part of the body to which the RF of the recorded cell was closest against the part of the body involved in the PF. Therefore points on the 45° angle line indicate thalamic sites where the RF and PF matched. Of 122 sites where mechanical and movement sensations were evoked, the RF and PF matched at 66 sites. The proportion of match (54%) was similar to that in our previous study (58%) where only patients with essential tremor were analyzed (Lenz and Byl 1999). The proportion of match was not different between different mechanical and movement descriptors (P = 0.46, χ² test).

In general, the size of PFs was much larger than that of RFs. PFs were distributed on body parts that are represented in the more lateral part of Vc than RFs. This may be because fibers from the medial lemniscus representing parts of the body located lateral in Vc core enter the Vc postero-medially and progress lateral before terminating (Jones 1985). Thus TMIS in the part of Vc where RFs are on the face may activate medial lemniscal fibers representing arm or leg and produce sensations in those parts of the body. The PFs are larger because stimulation excites cells at the stimulation sites and medial lemniscal fibers terminating laterally. Therefore cells with RFs including one part of the body are smaller than PFs that excite cells representing that area plus fibers representing parts of the body located lateral.

Qualities of sensations were compared between sites where the RF and PF matched and those where they did not match. In all sites where mechanical and movement sensations were evoked, those sensation were more frequently described as natural when the PF and RF match (52%) than when they did not match (31%; P < 0.001, χ² test). This strongly suggests that natural sensations are evoked when the sensation results from stimulation of the neuronal soma than the axon or afferent axon.

Patients picked more than one mechanical or movement descriptor to describe sensations at 56 of 122 sites (Table 3). Touch and vibration were chosen together on 14 occasions. Other mechanical and movement descriptors did not seem to have been chosen together. Mechanical and movement descriptors were often chosen with tingle or electric. The proportion in which each descriptor in mechanical and movement classes was picked together with tingle was significantly different among four excluding sharp because of small numbers descriptors (P < 0.001, χ² test). Pressure was not picked together with descriptors in tingle class as often as touch, vibration, and movement (P < 0.001, χ² test).

In the questionnaire, patients were presented with descriptors such as natural/unnatural and surface/deep/both as well as quality of sensation descriptors such as mechanical, movement, and tingle. The proportion in which a given descriptor was chosen together with natural or unnatural were different among four mechanical and movement descriptors (P = 0.05, χ² test; Fig. 8A). Movement was more frequently described as unnatural than touch and vibration (P < 0.001, χ² test). Sites associated with natural (y = −2.6 ± 2.3, z = 1.5 ± 3.1) were located significantly posterior (smaller y values; P < 0.05,
t-test) and tended to be found inferior (smaller z values) to those with unnatural ($y = -1.7 \pm 1.8, z = 2.4 \pm 3.0; P = 0.09$).

The categories surface or deep were not associated with particular mechanical and movement descriptors ($P > 0.05, \chi^2$ test; Fig. 8B). Sites where deep was chosen were located at the antero-dorsal aspect of the region of Vc, whereas those with surface showed diffuse distribution (Fig. 9). Stimulation sites described where stimulation evoked deep sensation ($z = 3.3 \pm 2.3$) were located significantly superior (i.e., larger z values) to those where surface was evoked ($z = 1.2 \pm 3.0; P < 0.01, t$-test). No difference was found in y values between sites with deep and surface ($P = 0.87; $ Fig. 9).

**DISCUSSION**

We explored sensations like those of movement and mechanical stimuli evoked by stimulation in the region of thalamic principal sensory nucleus in the human (Vc). Sensations were described as mechanical (touch, pressure, and sharp) and movement (movement through the body or across the skin and vibration). Sites where TMIS evoked vibration were located inferior to those with movement among sites with upper extremity RFs or with face PFs like the descriptor deep, which was found superior and anterior to those described by the descriptor surface. The location of sites with deep and movement descriptors is consistent with the location of cells responding to stimulation of subcutaneous structures (Jones 1985; Lenz et al. 1988). Touch and vibration were more commonly found with facial RFs than pressure. Pressure was more commonly found in planes where cells had intraoral RFs than was vibration, consistent with the relative density of rapidly adapting (RA) fibers in face and mouth. If the same sensation was evoked at two or more sites in any plane, then 81% of those sites were adjacent and were termed a cluster. These results demonstrate that the characteristics of TMIS-evoked sensations mirror those evoked by stimulation of peripheral mechanoreceptors and that sites where these sensations are evoked may be clustered within the thalamus by descriptor.

**Methodological considerations**

There are several points to be considered in the interpretation of the results. First, it must be noted that neuronal somata and axons are both stimulated by TMIS and that there is no way to differentiate whether responses are evoked by activa-
tion of one or the other or both (Ranck 1975). Therefore these results are less precise than those of anatomic and physiologic studies where nuclear boundaries and recording sites can be determined histologically.

Because cellular location cannot be determined precisely in human studies, we estimated nuclear location from both radio-
logical and physiological data. In the present study, the anterior border of the region where cells had cutaneous RFs was assumed to be the anterior border of Vc, as a first approximation of nuclear location (Lenz et al. 1988). This excludes from Vc core the anterior dorsal shell region, which is distinct from the cutaneous core histologically (Hirai and Jones 1989) and physiologically, by the presence of cells responding to deep stimuli (muscle, tendon, etc.) (Jones et al. 1982; Lenz et al. 1988). This is unavoidable because cells responding to deep stimuli are found anterior to Vc, in Vim (Lenz et al. 1990; Ohye et al. 1989), so the anterior border of the anterodorsal shell of Vc is difficult to determine (Lenz et al. 1988). In any event, we have studied the mechanical descriptors in the region anterior to Vc and found deep and movement descriptors in this area (Fig. 4

\[ \text{FIG. 7. Correlation of the size and locations between PFs and RFs for each of mechanical and movement descriptors} \]

The size (A) and the location (B) of PFs and RFs for all sites where mechanical and movement sensations were evoked were plotted against each other. - - - - - - - linear regression lines, with equations and the correlation coefficients shown on the top of each figure. Correlation coefficients were calculated with Spearman’s rank test. Note that the size of PFs was larger than that of RFs. Locations of PFs tended to be found on the body parts, which are represented in more lateral part of the Vc (intraoral, face, upper extremity, and lower extremity from medial to lateral) than those of RFs.

\[ \text{TABLE 3. Associated sensations chosen with each descriptor in mechanical and movement classes} \]

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NA, no associated sensations.

\[ \text{FIG. 8. Number of sites where TMIS evoked mechanical and movement sensations with natural/unnatural (A) and surface/deep/both (B). No significant relationship was found between descriptors and surface/deep/both. Note that the descriptor movement through the body was significantly more commonly described as unnatural than touch and vibration.} \]
and 9). This technique allows us to align individual maps to a reliable physiologic landmark but does not allow us to measure individual differences in anatomic structure. Last, because our protocol used here was a part of clinical investigation during surgery, we could not test the effect of different stimulation frequencies or intensities on the sensations evoked.

The nonmechanical nonmovement sensations of warm, burning, pain, or cool evoked by microstimulation in the thalamus have been extensively studied. Anatomical distributions of sites where these sensations are evoked by TMIS include the core and the area below and behind the core (Davis et al. 1996, 1999; Dostrovsky et al. 1991; Lenz et al. 1993, 1998; Ohara and Lenz 2003). In this series, painful sensations were characterized by pressure, shock, and sharp. Paresthesias evoked by microstimulation in the thalamus have often been described, usually characterized by tingling, numbness, vibration, or electric (Davis et al. 1996, 1999; Dostrovsky et al. 1991; Gillingham 1966; Somjen 1972; Tasker and Organ 1972; Tasker et al. 1976). In the great majority of these studies, tingle descriptors were found uniformly throughout the region of the thalamus contrary to the present results.

Similar results have been reported with bipolar surface stimulation of the somatosensory cortex using milliampere current level at the time of epilepsy surgery. The evoked sensations were usually numbness, tingling, or feeling of electricity (Penfield and Jasper 1954; Woolsey et al. 1979), although other sensations such as movement were sometimes evoked (Penfield and Jasper 1954). A validated questionnaire was used to describe the sensations in a subset of these papers (Lenz et al. 1993, 1998; Ohara and Lenz 2003). A technique for identifying sensations evoked by microstimulation of single afferent fibers (Ochoa and Torebjork 1983; Torebjork et al. 1984; Vallbo 1981; Vallbo et al. 1984), although more than one fiber may be excited by this technique (Waller and McMahon 1985). Those studies reported that stimulation of SA-I fibers evoked pressure sensation (Ochoa and Torebjork 1983; Vallbo 1981; Vallbo et al. 1984), RA fiber stimulation evoked touch, tapping, vibration (Ochoa and Torebjork 1983; Vallbo 1981), flutter (Vallbo et al. 1984), and tickle (Vallbo 1981). Pacinian fiber stimulation evoked a sensation of vibration (Ochoa and Torebjork 1983; Torebjork et al. 1984; Vallbo 1981; Vallbo et al. 1984). No consistent sensation was evoked by stimulation of C fiber. Therefore it may be that sensations evoked by human thalamic microstimulation are related to the mechanoreceptor afferents.

The sensations evoked by microstimulation in the somatosensory cortex have been the subject of elegant studies in monkeys (Romero et al. 1998, 2000). In Brodmann’s area 3b (Brodmann 1907), clusters of cells with a rapidly adapting response characteristics were microstimulated at frequencies of ±30 Hz (Romero et al. 1998, 2000). These cortical microstimulation studies and peripheral nerve microstimulation studies (Ochoa and Torebjork 1983; Torebjork et al. 1984; Vallbo 1981; Vallbo et al. 1984) suggest that TMIS-evoked touch might be specifically related to dorsal column neurons receiving input from RA fibers, pressure from SA-I fibers, vibration from RA and Pacinian fibers. The sensation of movement might be related to the afferent input from the muscle spindle not from either of preceding pathways (McCloskey et al. 1983). It is also possible that movement sensations are evoked by the engagement of multiple afferents associated with adjacent or nearly adjacent RFs, although we cannot assess this possibility here. In the present data, at 74% (90/122) of sites where mechanical and movement sensations were evoked, the subjects chose the same descriptors as those used in the intraneural microstimulation studies in the preceding text (pressure, vibration, and touch) (Ochoa and Torebjork 1983; Torebjork et al. 1984; Vallbo 1981; Vallbo et al. 1984). Therefore thalamic TMIS-evoked responses might reflect activity in pathways from the different classes of peripheral mecanoreceptors.

Significance of TMIS-evoked sensations in relation to mechanoreceptive pathways

Previous studies show that SAI and SAI peripheral mechanoreceptors respond with a sustained discharge to step indentation of the skin (Johnson et al. 2000). RA and Pacinian afferents respond only during the dynamic phase of tissue deformation (Johnson et al. 2000). Although both RA and Pacinian mechanoreceptors respond to skin deformation transiently, RA has smaller RF than Pacinian and responds to lower-frequency (20–60 Hz) vibration. Pacinian corpuscles are sensitive to ≥120–300 Hz vibration.

Intraneural microstimulation has been reported as a technique for identifying sensations evoked by stimulation of single afferent fibers (Ochoa and Torebjork 1983; Torebjork et al. 1984; Vallbo 1981; Vallbo et al. 1984), although more than one fiber may be excited by this technique (Waller and McMahon 1985). Those studies reported that stimulation of SA-I fibers evoked pressure sensation (Ochoa and Torebjork 1983; Vallbo 1981; Vallbo et al. 1984), RA fiber stimulation evoked touch, tapping, vibration (Ochoa and Torebjork 1983; Vallbo 1981), flutter (Vallbo et al. 1984), and tickle (Vallbo 1981). Pacinian fiber stimulation evoked a sensation of vibration (Ochoa and Torebjork 1983; Torebjork et al. 1984; Vallbo 1981; Vallbo et al. 1984). No consistent sensation was evoked by stimulation of C fiber. Therefore it may be that sensations evoked by human thalamic microstimulation are related to the mechanoreceptor afferents.

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primary sensory cortex (Sur et al. 1981). Differential projection into different rods from receptors in hairy or glabrous skin (Jones and Friedman 1982; Jones et al. 1982) has been also reported. The results from these monkey studies suggest that inputs from different mechanoreceptive afferent pathways may form different subregions within each rod representing a separate body part. Similar segregation may occur in human Vc (Lenz et al. 1988, 1989, 1994b; Zirh et al. 1998). Several studies did not report proposed segregation of VP by mechanoreceptive pathway (among rapidly adapting, slowly adapting, and/or Pacinian) (Warren et al. 1986; Zhang et al. 2001). In these studies, the density of cellular recordings (1 neuron/5 mm of trajectory) (Warren et al. 1986; Zhang et al. 2001) was not sufficient to comment on the existence of rods in VP having a length of 0.4—0.8 mm (Jones 1985l Jones et al. 1982). Therefore the evidence of the literature is mixed, whereas the present results demonstrate evidence of sensation-specific organization in Vc by clustering along individual trajectories (Fig. 5). We also found evidence of organization in the distribution of stimulation sites within parasagittal planes representing intraoral, face, and upper extremity (Fig. 4).

In the monkey VP, neurons with consistent receptive-field and possibly modality characteristics were found over distances of 500—800 μm along anterior-posterior electrode penetrations, much less for other trajectory orientations (Jones and Friedman 1982; Jones et al. 1982; Kaas et al. 1984). Our penetrations were approximately in a parasagittal plane but ran from anterior superior to posterior inferior—unlike the monkey studies. Therefore consistent RFs were encountered over shorter distances. Furthermore the maps from individual patients included an average of 3.4 trajectories as compared with dozens of trajectories in monkey studies. Because trajectories were separated by ±2 mm, we were never able to get detailed somatotopic maps in individual patients, again unlike monkey studies. Therefore our maps are pooled with necessarily imperfect anatomic alignment between patients. For all these reasons, the overlap in distributions of different modalities of TMIS-evoked sensations demonstrate a significant degree of overlap, unlike monkey studies reporting results in multiple animals, each mapped individually.

Do responses to TMIS in and near Vc reflect the activity of pathways related to specific mechanoreceptors?

Our results demonstrate that vibration was more commonly evoked by TMIS at sites adjacent to a cell with a facial RF, whereas pressure was more commonly found with intraoral RF. This finding suggests that innervation of facial skin may be dominated by RA or Pacinian receptors (Ochoa and Torebjork 1983; Torebjork et al. 1984), whereas intraoral mucosa is mainly innervated by SAI fibers. Indeed, RA afferents are common in the perioral area with absent in the intraoral mucosa (Johansson et al. 1988). Most of the mechanoreceptive afferent units recorded in the peri- and intraoral area are slowly adapting (Johansson et al. 1988; Nordin and Hagbarth 1989). In those studies, units with Pacinian type response are rarely recorded in the perioral and intraoral area.

Our observation that sites associated with the descriptor deep were found superior and anterior to those with surface is consistent with the idea of antero-dorsal deep shell (Friedman and Jones 1981; Jones and Friedman 1982; Lenz et al. 1988, 1994c; Poggio and Mountcastle 1963). Additionally we found that the sites where movement was chosen were located superior and/or anterior to those where vibration was chosen (Fig. 4). Neurons in the anterior dorsal shell receive inputs specifically from Group I afferents of muscle spindle (Jones et al. 1982) and therefore respond to joint movements or muscle and tendon manipulation.

We showed that descriptors touch and vibration were often picked together (14/33). This might suggest a common pathway for those two sensations or anatomical proximity of pathways for them. In fact, this is consistent with results by intraneural microstimulation where stimulation of RA evokes vibration or touch (Vallbo 1981). Pressure is another descriptor that may be evoked by activation of a single mechanoreceptor—the SAI. Of 17 sites with pressure sensation, touch was chosen, in addition to pressure, on three occasions and others descriptors (sharp, vibration, and movement) on one occasion each. Therefore pressure was usually chosen alone. Therefore it may be that TMIS activates pathways related to specific peripheral mechanoreceptors based on submodality segregation within the primate somatosensory nucleus.

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