Psychophysical Elements of Place and Modality Specificity in the Thalamic Somatic Sensory Nucleus (Ventral Caudal, Vc) of Awake Humans

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INTRODUCTION

Distinct thalamic anatomic structures may subserve different modalities of somatic sensation as components of segregated pathways from the periphery to the cortex (Johnson 2001; Kaas and Pons 1988). For example, anterior-posteriorly oriented rods have been described within the monkey thalamic principal sensory nucleus (ventral posterior, VP) (Jones et al. 1982; Rausell et al. 1992). These rods are anatomically defined by the terminal arbors of axons from the medial lemniscus (Hirai et al. 1988; Rausell and Jones 1991) and are physiologically defined by neuronal responses to innocuous stimulation (Jones et al. 1982; Kaas et al. 1984; Lenz et al. 1988b; Morrow and Casey 1992; Tremblay et al. 1993). Thalamo-cortical fibers parallel the rod from which they originate (Landry and Deschenes 1981) and terminate in cortical columns (Jones et al. 1982), consistent with the modality-specific organization in the primary sensory cortex (Jones et al. 1982; Kaas 1983; Rausell et al. 1992). Similarly, thalamic rods subserve different cutaneous structures (e.g., glabrous or hairy skin) consistent with the place-specific organization in the primary sensory cortex (Jones et al. 1982).

The primate spinothalamic tract (STT) may also terminate in discrete anatomic structures. Anatomic studies after cordotomy demonstrate that the STT terminates as “disseminated bursts” of axonal arbors in monkey VP and in the corresponding human nucleus (ventral caudal, Vc) (Apkarian and Shi 1994; Mehler 1962; Mehler et al. 1960; Rausell et al. 1992; Willis et al. 2001). These disseminated bursts may correspond both to the location of neurons responding to thermal or noxious stimuli and to the calbinden staining matrix that is located between rods (Apkarian and Shi 1994; Bushnell et al. 1993; Casey and Morrow 1987; Lee et al. 1999; Rausell and Jones 1991). The STT also terminates in the area below and behind Vc, where stimulation evokes thermal and pain sensations (Davis et al. 1999; Ohara and Lenz 2003). These results suggest the hypothesis that different modalities of cutaneous sensation might be relayed through psychophysically defined modality- and place-specific elements in Vc.

The existence of such elements and psychophysics of their activation has not previously been reported. We have now studied the sensations evoked by activation of these thalamic elements in humans using microstimulation in an ascending staircase protocol. Each step along the staircase is a stimulus train characterized both by the number of pulses (4, 7, 20, 50, or 100) and by the stimulus frequency (10, 20, 38, 100, or 200 Hz) (see Fig. 3). We tested a corollary of the preceding hypothesis, that the same modality of sensation will be evoked at any site by different steps along the staircase (modality consistency). Further, we tested the corollary that the evoked sensations at different steps along the staircase at a site will be located on the same part of the body (place consistency). The results provide strong psychophysical evidence for place- and modality-specific representation of somatic sensation in the thalamus of awake humans.
METHODS

These studies were carried out at the Johns Hopkins Hospital during the thalamic exploration that preceded thalamotomy or implantation of deep brain stimulating electrodes for the treatment of movement disorders (Garonzik et al. 2002). The protocol used in these studies was reviewed and approved annually by the Institutional Review Board of the Johns Hopkins University. All subjects signed an informed consent for these studies. No patient had abnormalities on standard sensory testing (Lenz et al. 1993) or preoperative MRI scans or had a diagnosis of chronic pain (Merskey 1986).

In the present study, subjects were operated on for treatment of movement disorders (men: 32, women: 18) including: 35 with essential tremor, 11 with Parkinson’s tremor, and 4 with dystonia (Watts and Koller 1998). Somatic sensations were evoked by thalamic microstimulation (110 sites) with different stimulus trains, each defined by the number and frequency of pulses as steps along an ascending staircase (see Fig. 3). The present population was a subset of the 116 patients (124 thalami) in which microstimulation at 300 Hz evoked mechanical or movement sensations (Ohara et al. 2004) and thermal or pain sensations (Ohara and Lenz 2003). We have previously described the response to stimulation along the staircase at sites where pain was evoked in both the present population and a population of patients with chronic pain (Lenz et al. 2004).

Recording protocols

Physiologic exploration of the thalamus was carried out as an image-guided stereotactic procedure under local anesthetic using the Leksell frame (Lenz et al. 1993). The stereotactic coordinates of the anterior commissure (AC) and posterior commissure (PC) were determined by computer-assisted tomography or magnetic resonance imaging and were used to estimate the location of the Vc (Hua et al. 2001). Specifically, the sagittal sections of a standard atlas (Schaltenbrand and Bailey 1959) were translated to match the subject’s ACPC line and so form a map of the subject’s thalamus. The 13.5-mm lateral section was a sagittal map of the subject’s thalamus that was used as the first estimate of nuclear location (Fig. 1A).

Physiological corroborration of anatomical loci was then performed under local anesthesia (i.e., subject fully conscious) by using single-unit recording and microstimulation (Lenz et al. 1988a,b). EMG activity was routinely monitored in four muscles on the contralateral arm to assess involuntary movements at the time of the sensory examination (Lenz et al. 1988c). The first trajectory targeted Vc because the response of neurons in this region to somatosensory stimulation was the most reliable physiologic landmark with which to guide the operation (Lenz et al. 1995b).

As illustrated in Fig. 1, sites were explored starting 1 cm above the target and were characterized by the location of the sensation evoked (projected field) by threshold microstimulation (μA current levels). Projected fields at a stimulation site were characterized by inclusion of one or more parts of the body progressing from medial (intra-oral) to lateral (toes; Table 3) (Lenz and Byl 1999). Single neurons were characterized by their spontaneous activity and by their response to innocuous or noxious mechanical and temperature stimuli (Lee et al. 1999). Neurons responding to stimulation of the skin were termed cutaneous neurons, whereas deep neurons were those that responded to stimuli applied to deep structures (joints, ligaments, etc.) but not to stimulation of skin deformed by these stimuli.

The core region of Vc was defined as region where the majority of neurons responded to innocuous cutaneous stimulation (Fig. 1) (Ohara and Lenz 2003; Ohara et al. 2004). The analysis of thalamic location was based on the borders of the core as illustrated in Fig. 1B. The ventral border of the core of Vc is indicated by the dashed line parallel to AC-PC line and is determined by the location of the most ventral neuron responding to innocuous, cutaneous stimulation (neuron 48 in Fig. 1C). The dotted and solid lines perpendicular to the AC-PC line are the anterior and posterior (Z axis) borders of Vc, respectively. These lines are determined by the location of the most anterior neuron (33) and posterior neuron (48) responding to innocuous, cutaneous stimulation.

Microstimulation protocol

Microstimulation at 300 Hz was delivered in trains of ~1 s duration by using a biphasic square-wave 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 carried out at 40 or 50 μA at sites located at regular intervals along the trajectory until a sensory response was evoked.

At each stimulation site, subjects were first asked whether they felt anything (Lenz et al. 1993, 1998). If a sensation was evoked, then a threshold was established by increasing and decreasing the stimulation current. If no sensation was evoked at 40 or 50 μA, then a no response (NR) was entered at that site. Sites were named by the first sensation described by the subject so that a site where microstimulation evoked a cool sensation was termed a cool site. The current 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 evoked again. This procedure was often repeated to verify the threshold. The sites where microstimulation evoked sensations were plotted with respect to the borders of core region of Vc in the parasagittal plane (Fig. 1).

The constant location of the electrode during the stimulation protocol was confirmed at each site. Before and after the stimulation protocol, 300-Hz stimulation was applied at the initial threshold to confirm that the projected field was unchanged. During recording, we compensated for movement of the electrode in the brain by making small electrode movements (<100 μm) to keep the size of the action potential constant. In addition, the receptive field, and the size and shape of the action potential were checked for consistency before and after microstimulation at each site. Nevertheless, we have no anatomic measure of the error in our estimate of the location of the electrode.

Psychophysical protocols

The patient was questioned to determine the location of the microstimulation-evoked sensation (projected field). The microstimulation-evoked sensation was described using the questionnaire (Fig. 2) during repeated stimulation. The patient was asked (question 1) 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.” The patient was then asked to decide if the sensation was located either on the surface of the skin or below the surface of the skin, or both (Fig. 2, question 2). Neither of these questions was a forced choice.

If the sensation was nonpainful (question 3), the patient chose a descriptor(s) from the upper list under heading 4, labeled “nonpainful.” If the sensation was painful, the patient chose a descriptor(s) from the lower list labeled “painful.” In this section, the patient was asked first to identify which of the categories of sensation applied (e.g., mechanical, movement, etc.) and then to identify descriptors within the chosen category. Patients were allowed to specify the category (e.g., tingle) and were encouraged to use their own words. After choosing a descriptor in one category, the patient was asked if the other categories might apply to a component of the sensation. The descriptors were classified as the mechanical/tingle modality if they were chosen from Fig. 2: question 4, nonpainful: mechanical, movement, and tingle categories, or as thermal/pain modality if they were chosen from either question 4, nonpainful; temperature, or question 4, painful. Nonpainful sensations were designated by NP, and painful sensations were designated P.

At sites where pain was evoked, the intensity of pain was documented using a visual analog scale (VAS) anchored by the statement
FIG. 1. Map of receptive and projected fields for trajectories in the regions of the ventral caudal nucleus (Vc) in a patient with essential tremor (180–02). A: positions of the trajectories relative to nuclear boundaries as predicted from the position of the anterior commissure-posterior commissure (AC-PC) line. The AC-PC line is the solid, approximately horizontal line in A and B. PC is indicated in A. The microelectrode trajectory is represented by the solid, oblique line. B: location of the neurons, microstimulation sites, along trajectory P1. The locations of microstimulation sites are indicated by tics to the left of the trajectory in B, while the locations of the neurons are indicated by tics to the right of the trajectory. Microstimulation sites at which a response was evoked are indicated by long tics, while those without a response are indicated by short tics. Neurons with identified activity, e.g., activity related to sensory stimulation or tremor, are indicated by long tics; those without are indicated by short tics. Sites where cool sensations were evoked are indicated by filled circles, warm by open circles. C: P1 shows the site number, projected field (PF, left of the line), and receptive field (RF) for that site (right). Each site where a neuron was recorded, or microstimulation was carried out, or both, is indicated by the same number in B and C. The threshold (in μA) is indicated below the PF diagram.
Which words describe the sensation that you feel?

1. Totally Natural/Almost Natural/Possibly Natural
   /Rather Unnatural/Totally Unnatural

2. Clearly on the skin surface/Definitely below the skin surface/Both

3. Non-painful/Painful

4. Quality of Sensation
   Non-painful (NP)
   - Mechanical
   - Touch
   - Pressure
   - Sharp
   - Movement
   - Vibration
   - Movement through the body or across the skin
   - Temperature
   - Warm
   - Cool
   - Tingle
   - Electric current
   - Tickle
   - Itch

   Painful (P)
   - Mechanical
   - Drilling
   - Stabbing
   - Squeeze
   - Tugging
   - Tearing
   - Dull
   - Splitting
   - Temperature
   - Hot
   - Burn
   - Cold

   Movement
   - Spread
   - Flash
   - Flicker
   - Throb

   Tingle
   - Itch
   - Electric

   Emotion
   - Frightful
   - Nauseating
   - Cruel
   - Suffocating
   - Fatiguing

FIG. 2. Questionnaire employed to describe the sensation evoked by threshold microstimulation as described in Microstimulation protocol.

that –10 is no sensation, 0 is the most intense sensation that is nonpainful, and 10 is the most intense pain imaginable. At sites where stimulation did not evoke pain, the following statement was used as an anchor of the scale –10 is no sensation, 0 is the most intense sensation imaginable. Microstimulation at 300 Hz was repeated to determine the projected field and to complete the questionnaire (see Microstimulation protocol).

This psychophysical protocol was followed at each stimulation site, and data were reported for all sites, including those where no sensation was evoked. To confirm that responses were reliable, the patient was asked to identify the onset and termination of the stimulus for both actual and sham trials of microstimulation, i.e., verbal cue without microstimulation. This protocol has been validated (Lenz et al. 1993) and used in multiple studies of sensations evoked by thalamic microstimulation (Lenz et al. 1995a, 1998, 2004).

The current level of 300-Hz current threshold was applied at stimulus trains arranged in a multiple ascending staircase protocol. This type of protocol is commonly used for psychophysical studies of thermal and experimental pain sensations (Gracely et al. 1988; Lenz et al. 2004; Yarnitsky and Sprecher 1994). Each stimulation train or step consisted of one of five different numbers of pulses (4, 7, 20, 50, 100—horizontal axes in Fig. 3), and one of 5 different frequencies of stimulation (10, 20, 38, 100, 200 Hz—vertical axes in Fig. 3). This staircase consisted of 24 stimulation trains because the step for 100 pulses—10Hz was excluded due to the duration of the train. The order of presentation of steps was as follows; four pulses, 10 Hz; four pulses, 20 Hz; . . . four pulses, 200 Hz; 7 pulses, 10 Hz; 7 pulses, 20 Hz, etc. This protocol resulted in a factorial delivery of all possible pairs of frequencies and numbers of pulses (Figs. 3 and 5). Stimulation of the steps on the staircase was repeated to define the projected field, questionnaire descriptors, and VAS score.

Statistical analyses

The threshold for evoking sensation was analyzed by the frequency and number of pulses at the location in the grid which was closest to the origin, i.e., the step with four pulses, 10 Hz (Fig. 3). The thresholds for number of pulses or frequency were determined as the lowest value of that variable in any row or column, respectively. The pulse × frequency (p×f) product was defined as the least value of the product of the number of pulses and frequency among all steps in the staircase where a sensation was evoked. If two sites were equidistant from the origin then the p×f product threshold was taken to be the lowest pulse number multiplied by the lowest frequency. These thresholds were compared between different evoked sensations by nonparametric tests as the distributions were not normally distributed. The Mann-Whitney U test was used for comparisons of two variables and the Kruskal-Wallis, with post hoc Dunn multiple comparison test, was used for comparisons of more than two variables.

The effect of the number of pulses and the frequency on VAS scores evoked by microstimulation in the staircase was examined with a two-way ANOVA. Post hoc testing with Tukey’s honestly significant difference test (HSD) was employed for multiple comparisons. Differences in pairs of proportions were tested statistically by a Fisher test or χ² test, as appropriate. Differences between more than two proportions were tested by a contingency analysis with post hoc using χ² or Fisher using an α which was corrected for multiple comparisons (Bonferroni). All analyses were carried out using Statistica (Statsoft, Tulsa, OK); the null hypothesis was rejected for P < 0.05.

R E S U L T S

The staircase was applied at sites (n = 110) where threshold stimulation at 300 Hz evoked somatic sensations including thermal/pain or mechanical/tingle sensations as previously described (Lenz et al. 2004; Ohara et al. 2004). Along the staircase, there were changes in the descriptors of the microstimulation-evoked sensations at 11 sites with exclusion of changes between cool and warm sensations (n = 3). A change in modality occurred along the staircase at 11 of 28 pain sites (Lenz et al. 2004). These staircases were counted with both modalities for a total of 121 staircases. The number of staircases was the denominator for analyses of modality consistency, VAS and thresholds, whereas the number of sites was the denominator for analysis of place consistency.
Modality of evoked sensations: characteristics and effect of thalamic location

The proportion of thermal/pain or mechanical/tingle sensations evoked along the staircase at a site was studied as a function of location in the core, posterior superior, or posterior inferior thalamic region (Table 1). The single site in the anterior inferior quadrant (Fig. 1) was not included in the analysis. Proportions of natural versus unnatural and surface versus deep versus both categories (Fig. 2: questions 1 and 2, Table 1) were calculated as a fraction of the total number of sites for each category because these questions were not forced choices. There were no significant differences in the location of sites where stimulation evoked the following categories: natural/unnatural, and surface versus deep versus both.

The modality of staircases was classified as follows: pain (n = 28), NPCool (27), NPWarm (11), and mechanical/tingle (n = 55). Mechanical/tingle (all NPMechanical, NPMovement, and NPTingle) tended to be evoked by microstimulation in the core more frequently than in the posterior inferior and posterior superior regions (Table 1, P = 0.08, 3 × 2 χ²). Thermal/pain sensations were more likely to be evoked by stimulation in the two posterior regions combined than in the core (Table 1, P = 0.009, χ²).

Among descriptors of microstimulation-evoked sensations significant differences (P < 0.05, 4 × 2 contingency analysis via χ² tests) were found both for the natural-unnatural category (Table 2) and for deep versus surface versus both categories (Table 2). Post hoc testing of the deep/surface category revealed that painful sensations were more likely to be described by a nonsurface descriptor than NPCool or NPWarm (P = 0.002, Fisher with Bonferroni correction, see Table 2) and mechanical/tingle sensations (P < 0.004, see Table 2). A similar analysis of the natural versus unnatural category by modality showed no significance (P = 0.3, see Table 2). Thus the location of the stimulation site and the modality of the microstimulation-evoked sensations were determinants of different characteristics of microstimulation-evoked sensations, e.g., natural/unnatural.

Reliability of evoked sensations along the staircase

We expected that at any site all steps in a staircase above the pulse–frequency threshold would evoke a response. However, at many sites (Fig. 3, A, B, and D–F), the staircase was characterized by a pattern of steps above threshold in which stimulation-evoked sensations were evoked at some (■) steps but not at other steps (□). For example, the site illustrated in Fig. 3E contained gaps (□) at three steps i.e., at 50 pulses, 20-Hz step; 50 pulses, 38-Hz step; and at 100 pulses, 20-Hz step. These were all above the pulse frequency threshold (20 pulses: 20 Hz). These gaps were defined relative to the expected right upper rectangle of the staircase, i.e., above and/or to the right of the 50-pulses, 20-Hz step in Fig. 4E. Missing steps were assumed to have properties intermediate between those of steps above and below, as usual, i.e., the assumption of linearity (Gracey et al. 1988).

The proportion of sites in or posterior to the core containing a gap was not significantly different between thermal/pain (36/66, 55%) and mechanical/tingle sensations (32/55, 58%; P = 0.67, χ² test). Neither was the proportion of sites with a gap significantly different (P = 0.2, χ²) among mechanical/tingle (32/55, 58%), NPCool (12/27, 44%), NPWarm (9/11, 82%), and pain (15/28, 54%). Therefore by this measure the reliability of detection of a sensation was not significantly different between modalities.

Modality consistency: sensations along the staircase

If the thalamic elements of modality and place representation are discrete and nonoverlapping, then the sensations should be consistent (see INTRODUCTION) across different steps along the staircase at any site. Microstimulation-evoked cool sensations (NPCool) were usually consistent (25/27 sites), although NPCool changed to NPWarm along two staircases, at 20 pulses–20 Hz and at 20 pulses–38 Hz. NPWarm sensations were consistently NPWarm except for a change to NPCool at 20 pulses—200 Hz at one site and a change to painful heat at 20 pulses–20 Hz at another site (see following text). NPCool and NPWarm sensations were considered to be of the same modality—thermal, as usual (Mountcastle 1980; Willis and Coggeshall 1991). Thus nonpainful thermal sites had the same modality along the staircase except for one change from NPWarm to painful heat.

Along staircases where microstimulation evoked NPMechanical, NPMovement, and NPTingle sensations there were five cases where these sensations [NPTingle: n = 4 sites, NPMovement: n = 1, see (Lenz et al. 2004)] changed to pain as stimulation ascended the staircase. Overall, changes in modality along the staircase were more common for pain sensations (39%, 11/28) than for nonpainful thermal (1/38, P < 0.001, Fisher), or for mechanical/tingle sensations (10%, 5/55, P < 0.002) (Lenz et al. 2004).

This high degree of modality consistency might be due to a bias for any subject to describe all stimulation-evoked sensa-

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**Table 1. Characteristics of sensations and thalamic region by results of 300Hz stimulation**

<table>
<thead>
<tr>
<th>Vc Thalamic Region</th>
<th>Core</th>
<th>Post-inferior</th>
<th>Post-superior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural</td>
<td>22</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Unnatural</td>
<td>31</td>
<td>11</td>
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<tr>
<td>Surface</td>
<td>22</td>
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<tr>
<td>Deep</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Both surface and deep</td>
<td>14</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Mechanical/tingle sensations</td>
<td>36</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Thermal/pain sensations</td>
<td>28</td>
<td>21</td>
<td>13</td>
</tr>
</tbody>
</table>

Vc, ventral caudal.

**Table 2. Characteristics of associated sensations and RF-PF matches as a function of sensory modality**

<table>
<thead>
<tr>
<th></th>
<th>Mechanical</th>
<th>Thermal</th>
<th>NPWarm</th>
<th>NPCool</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
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<td>18</td>
<td>26</td>
<td>6</td>
<td>13</td>
<td>7</td>
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<tr>
<td>Unnatural</td>
<td>31</td>
<td>30</td>
<td>8</td>
<td>8</td>
<td>14</td>
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<tr>
<td>Surface</td>
<td>21</td>
<td>25</td>
<td>9</td>
<td>14</td>
<td>2</td>
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<tr>
<td>Deep</td>
<td>8</td>
<td>12</td>
<td>3</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Both surface and deep</td>
<td>14</td>
<td>15</td>
<td>3</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

RF and PF, receptive and projected fields; NP, nonpainful.
tions using the same descriptors across sites, or at different steps along a staircase. To the contrary, different steps along a staircase evoked different descriptors at many pain sites (39%, see preceding text). In addition, stimulation at different sites in a patient often evoked different descriptors within a category. For example, natural and unnatural were chosen at different sites in 35% of subjects in whom those descriptors were chosen at two or more sites. In the same way, surface and deep were chosen in 38% of subjects, NP Warm and NPCool in 40%, NPMechanical and NPMovement in 60%, painful hot and painful cold in 17%, painful mechanical/movement for 33% of subjects. Therefore the modality consistency along most staircases is compatible with similarity in sensations evoked across steps within a staircase and not with a bias to choose the same descriptors either across steps within a staircase or across sites within a subject.

Place consistency: changes in projected fields along the staircase

As a test of place consistency, we measured the size of the projected field evoked by stimulation at different frequencies and numbers of pulses (Lenz et al. 1988b). The parts of the body which were considered to be different anatomic locations are given in Table 3. Using this classification, the projected field changed between steps along the staircase at a site for 5% (6/110) of sites. These sites were classified as mechanical/tingle (4), NP thermal (1), and pain (1) and were located in the core (3 sites), posterior superior (1), and posterior inferior (2). This suggests that, for most sites, the same set of neurons and axons were activated at all steps in the staircase above the pulse and frequency threshold.

Modality and place representations: incidence of more than one descriptor and more than one part of the body as a function of current threshold in the core of Vc

If there are subnuclear elements mediating modality and place specificity in Vc, then the numbers of both descriptors and parts of the body should increase with the current of microstimulation. If these elements are discrete, then the increase in the proportion of sites with more than one descriptor or a projected field with more than one part of the body (Table 3) should increase in a stepwise manner. Therefore we plotted the current threshold (300 Hz) against the cumulative proportion of sites in the core with more than one descriptor (Fig. 4, A and B) and with more than one part of the body (E and F).

The proportion of sites with more than one part of the body often rose from the lowest level and then stayed constant with increasing threshold current—a plateau, (defined below) e.g., 20–30 μA in Fig. 4, E and F. At the higher currents, the proportion of sites with more than one part of the body sometimes rose again (Fig. 4, E and G, 25 μA). To examine the properties of sites where only one modality (mechanical/tingle or thermal/pain) was evoked, we re-plotted the data for such sites and defined these sites as mechanical/tingle only (Fig. 4, E and G) and thermal/pain only sites (F and H).

The most striking aspect of Fig. 4 is the large number of plateaus in the plots of more than one part of the body (Fig. 4, E–H), particularly in comparison to plots of more than
one descriptor (Fig. 4, A–D). We defined the presence of a plateau by a constant proportion of sites with more than one descriptor (Fig. 4, A–D) or part of the body (E–H) across any three adjacent current levels, i.e., across a range of 10 μA. Three adjacent current levels were considered to constitute a plateau even if the proportion (y axis) was zero, e.g., cold sensations. We required the highest and lowest currents in the plateau to include at least one stimulation site as indicated by symbols with black rather than gray perimeters. The presence of a plateau was more common (P < 0.001, Fisher) for plots of proportions of more than one part of the body (10/10, Fig. 4, E–H) than for those of descriptors (1/10, A–D).

Figure 4 also demonstrates that the proportions of sites with more than one descriptor were higher, across all current thresholds, than those with more than one part of the body. Specifically, the proportion of sites with more than one descriptor at 30 μA was significantly higher for descriptors (0.59 ± 0.25 mean ± SD; Fig. 4, A and D) than for parts of the body (0.21 ± 0.15, E and H, P < 0.01, t-test). The proportions of sites with more than one descriptor at 5 μA (0.19 ± 0.18) tended to be larger than those with more than one part of the body (0.8 ± 0.8, P = 0.09, t-test). Therefore in comparison with the psychophysical elements of modality specificity, the elements of place specificity for both mechanical/tingle and thermal/pain sensations seem to be larger or more discrete. There were not

![Figure 4](https://www.jn.org)
TABLE 3. Sequence of medial-lateral somatotopy in the core of Vc

<table>
<thead>
<tr>
<th>RF/PF Categories</th>
<th>Assigned Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial Vc core</td>
<td></td>
</tr>
<tr>
<td>Intraoral</td>
<td>1</td>
</tr>
<tr>
<td>Perioral</td>
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<td>D1</td>
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<td>D4</td>
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<tr>
<td>D5</td>
<td>8</td>
</tr>
<tr>
<td>Multiple digits</td>
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</tr>
<tr>
<td>Palm/hand</td>
<td>10</td>
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<tr>
<td>Forearm</td>
<td>11</td>
</tr>
<tr>
<td>whole arm</td>
<td>12</td>
</tr>
<tr>
<td>upper arm</td>
<td>13</td>
</tr>
<tr>
<td>Waist</td>
<td>14</td>
</tr>
<tr>
<td>Trunk</td>
<td>15</td>
</tr>
<tr>
<td>Leg</td>
<td>16</td>
</tr>
<tr>
<td>Upper leg</td>
<td>17</td>
</tr>
<tr>
<td>Lower leg</td>
<td>18</td>
</tr>
<tr>
<td>Pelvis</td>
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</tr>
<tr>
<td>Ankle</td>
<td>20</td>
</tr>
<tr>
<td>Foot</td>
<td>21</td>
</tr>
<tr>
<td>Toes</td>
<td>22</td>
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<tr>
<td>Lateral Vc core</td>
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</tbody>
</table>

sufficient data to carry out a similar analysis of the posterior regions.

The number of plateaus in the proportion of sites with more than one part of the body was equally high among mechanical/tingle and thermal/pain sites (Fig. 4, E and F, 6/6) and among mechanical/tingle only or thermal/pain only (Fig. 4, A and B and E and F, 4/4). To test whether these proportions are significantly different from those expected at random, we assumed that the second and third points on any plateau had a \( P = 0.5 \) of being greater than the preceding point. This probability was chosen based on the expectation that a reliable increase in evoked sensation will result from increased stimulation of the somatic sensory system (Dostrovsky et al. 1993; Lenz et al. 2004; Ochoa and Torebjork 1983). Therefore the probability of any plateau of three points on a cumulative proportion plot for any set of stimulation sites is estimated to be \( P = 0.25 \). A ratio of 4/4 or 6/6 is unlikely to occur at random based on the preceding assumptions and the assumption of a binomial distribution (\( P < 0.05 \)). NPMechanical sensations in the core of Vc involved one part of the body (Fig. 4, F and H, plateaus of 4 and 6 points) and one descriptor (cool, B and D, plateaus of 3 points each) much more commonly than expected at chance (\( P < 0.05 \), binomial). These results and the uniformity of the plots in Fig. 4, E–H, suggest that elements of place-specificity are equally reliable for mechanical/tingle and thermal/pain modalities, particularly in the case of cold sensations.

An increase in the \( y \) value (Fig. 4, proportion of sites) from a lower to a higher level was defined as a rise if the higher level met the criteria for a plateau (see preceding text). Rises were significantly less common among plots for descriptors (Fig. 4, A–D, 0/10, \( P < 0.002 \), Fisher) than for parts of the body (7/10). In plots of proportions of parts of the body (Fig. 4, E–H), rises ended at plateaus having a current of 20 \( \mu A \) in all cases excepting one ending at 15 \( \mu A \) (nonpainful mechanical). These results suggest that the proposed elements of place specificity are of similar size for both mechanical/tingle and thermal/pain sensations.

Place representations: overlap of RFs and projected fields

The degree to which neurons are responsible for stimulus-evoked sensations may be estimated by correlating neuronal RFs with projected fields evoked by stimulation at the site closest to (\(<1 \) mm) the recording site for the neuron. An overlap of projected fields and RFs suggests that the neurons and axons in that area represent the same part of the body. Therefore as an additional aspect of the place representation we correlated neuronal RFs with microstimulation evoked projected fields. The medial-lateral location of each one of the cutaneous RF or projected field was assigned a number based on the established sequence of somatotopic representation in Vc from medial to lateral, i.e., intraoral to toes (Table 3) (Lenz and Byl 1999; Lenz et al. 1988b).

The overlap of the receptive and projected fields was assessed through linear regression of somatotopy of the RF with that of projected field at a site (Table 4). The NPMechanical, NPMovement, and NPTingle sensations within the mechanical/tingle modality all had significant RF-projected field correlation. Among thermal/pain sensations, RF-projected field correlation was significant only in the case of NPMWarm and painful tingle sensations. This suggests that microstimulation-evoked mechanical/tingle sensations are represented in discrete thalamic elements of place specificity, which are composed of neurons and axons representing the same part of the body. NPMWarm and painful tingle sites aside, such elements are less clearly defined in the case of the thermal/pain modality.

Analysis of staircase results by VAS ratings

We next examined the possibility that different patterns of stimulation evoke different intensities of sensation. The stimulation data including VAS scores for different numbers of pulses and frequencies is shown for a single site in Fig. 5 (patient 193–02, site 28). NPMechanical sensations were evoked by stimulation throughout the grid starting at 7 pulses/10 Hz and

<table>
<thead>
<tr>
<th>Thalamic Location</th>
<th>No. of Sites</th>
<th>( R^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core</td>
<td>49</td>
<td>0.14</td>
<td>0.008</td>
</tr>
<tr>
<td>Posterior Inferior</td>
<td>17</td>
<td>0.38</td>
<td>0.008</td>
</tr>
<tr>
<td>Posterior Superior</td>
<td>9</td>
<td>0.73</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Correlations that achieve statistical significance are underlined.
Sensations were matched with sensations evoked by cool stimuli evoked by a VAS as indicated (see cool, nonpainful, surface sensation in the area indicated on the upper lip with highest rating of cool was increased steadily in intensity to 100 pulses/200 Hz. The highest rating of cool was −2 (scale from −10 to 10, see Psychophysical protocols), at the 100 pulses—100- and 200-Hz steps, corresponded to a temperature of 6°C using the Peltier stimulator applied in the projected field for this site (Fig. 5A, Peltier correspondence).

Ratings of NPCool sensations across all sites demonstrated a significant dependence on the numbers of pulses (a 2-way ANOVA by frequency and numbers of pulses, \( F = 3.6, df = 4, P = 0.007 \)) but not on frequency (\( F = 0.3, df = 4, P = 0.884 \)) or interaction (\( F = 0.5, df = 14, P = 0.940 \)). Post hoc analysis showed that the sensory rating at 100 pulses (VAS = −5.9) was significantly higher than that at 7 pulses −7.3, \( P = 0.009 \) or at 20 pulses (−9, \( P = 0.023 \)). Ratings of NPWarm sensations showed no dependence on frequency (\( F = 0.8, df = 4, P = 0.515 \)), the number of pulses (\( F = 0.7, df = 4, P = 0.573 \)) or the interaction (\( F = 0.3, df = 16, P = 0.996 \); Fig. 6).

Thus among nonpainful thermal sensations only the intensity of the NPCool sensation was dependent on the number of pulses in the stimulus train to a significant degree.

Ratings of painful heat/burn sensations showed no significant dependence on frequency (\( F = 0.9, df = 4, P = 0.503 \)), the number of pulses (\( F = 0.3, df = 3, P = 0.846 \)), or the interaction (\( F = 0.3, df = 4, P = 0.884 \)). Painful mechanical/tingle sensations showed no significant dependence on the frequency (\( F = 1.3, df = 4, P = 0.286 \)), or the number of pulses (\( F = 0.5, df = 4, P = 0.760 \)), or the interaction (\( F = 0.5, df = 12, P = 0.913 \)). The results at pain sites may be the result of the large number of sites where pain intensity had an all-or-none (binary) dependence on frequency, often at low pulse thresholds (Lenz et al. 2004). For example, pain characterized by mechanical, movement, or tingle descriptors (Fig. 6E) was commonly evoked at pulse thresholds of 4, whereas nonpainful sensations characterized by the same descriptors were never evoked at 4 pulses (Fig. 6, A and B).

Ratings of mechanical/tingle sensations were variably related to stimulus parameters. Analysis of mechanical/tingle sensations showed a significant effect of number of pulses (\( F = 4.8, df = 3, P = 0.004 \)) but not frequency (\( F = 1.4, df = 4, P = 0.25 \)) or interaction (\( F = 0.4, df = 12, P = 0.976 \)). Post hoc analysis by number of pulses revealed that the sensory rating at 100 pulses was significantly higher than at 7 pulses (\( P = 0.021 \)) and 20 pulses (\( P = 0.022 \); VAS ratings: 7 pulses, −7.7; 20 pulses, −7.2; 50 pulses, −6.5; 100 pulses, −5.6). Ratings of NPTingle sensations showed a significant dependence on the number of pulses (\( F = 3.6, df = 3, P = 0.018 \)) but not frequency (\( F = 1.2, df = 4, P = 0.312 \)) or interaction (\( F = 0.2, df = 12, P = 0.996 \)). Post hoc analysis showed the VAS rating at 100 pulses (−6.1) was significantly higher than that at 7 pulses (−7.8; \( P = 0.047 \)). NPMovement showed no dependence on frequency (\( F = 0.4, df = 4, P = 0.837 \)), the number of pulses (\( F = 0.9, df = 3, P = 0.477 \)) or interaction (\( F = 0.6, df = 11, P = 0.776 \); Fig. 6). Overall, the intensity of mechanical/tingle sensations overall, and of both NPTingle and NPCool sensations was dependent on the number of pulses. The intensity did not covary with the frequency or the interaction of pulses and frequency for any type of sensation.

### Analysis of staircase thresholds by pulse, frequency, and \( p \times f \) product

Thresholds along the staircase (Table 5) demonstrated that the threshold \( p \times f \) product for mechanical/tingle sensations was significantly higher (\( P = 0.018 \), Mann-Whitney U test, see Table 5) than that for thermal/pain sensations. This suggests that thermal/pain sensations were evoked at lower numbers of pulses and frequencies on average. On subgroup analysis, mechanical/tingle sensations displayed a trend for difference in \( p \times f \) product threshold across all modalities (\( P = 0.11 \), Kruskal-Wallis, see Table 5). Mechanical/tingle sensations were evoked with the highest \( p \times f \) product, followed by pain, NPWarm, and NPCool (Table 5).

Mechanical/tingle sensations displayed higher frequency thresholds than did thermal/pain sensations (\( P = 0.01 \), Mann-Whitney U test, see Table 5). Frequency thresholds

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**FIG. 5.** Sensory ratings of thalamic and cutaneous stimuli in an individual patient. A: response to microstimulation at a site in the posterior inferior region (site 28) where microstimulation at 300 Hz and 15 μA produced a natural, cool, nonpainful, surface sensation in the area indicated on the upper lip with a VAS as indicated (see Microstimulation protocol). Microstimulation-evoked sensations were matched with sensations evoked by cool stimuli evoked by application of different stimuli with a Peltier device, as indicated under ‘Peltier Correspondence’. B: map of RF and PF for this site.
tended to be different between all modalities (\( P = 0.09 \), Kruskal-Wallis, see Table 5). Pulse threshold for mechanical/tingle sensations was significantly higher than that for thermal/pain sensations (Table 5, 2nd row, \( P < 0.04 \)). Pulse thresholds showed a tendency for a difference among mechanical/tingle sensations, NPWarm, NPCool, and painful sensations (\( P = 0.09 \), Dunn). Pulse thresholds were highest for mechanical/tingle sensations, followed by NPWarm, pain, and NPCool sensations. Thus detection a microstimulation-evoked sensation, indicated by threshold, occurred at higher numbers of pulses for mechanical/tingle than thermal/pain sensations

**DISCUSSION**

Based on consistency of descriptors along the staircase, modality-specificity is very commonly found for sites where microstimulation evokes NPCold, NPWarm, NPMechanical, NPMovement, or NPTingle sensations but not pain. Evidence of place specificity was found for all types of evoked sensations. Plateaus in the proportion of sites in the core with more than one descriptor as a function of current (Fig. 4) are less common than are plateaus in the proportion of sites with more than one part of the body. This suggests that the elements of modality specificity are smaller than and located within the

**TABLE 5. Number of pulses and frequency (staircase) thresholds for microstimulation-evoked sensations**

<table>
<thead>
<tr>
<th></th>
<th>Mechanical/Tingle</th>
<th>Thermal/Pain</th>
<th>NP Warm</th>
<th>NP Cool</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse threshold</td>
<td>41 ± 5</td>
<td>25 ± 4</td>
<td>31 ± 10</td>
<td>17 ± 3</td>
<td>30 ± 6</td>
</tr>
<tr>
<td>Frequency threshold, Hz</td>
<td>85 ± 10</td>
<td>51 ± 7</td>
<td>55 ± 17</td>
<td>45 ± 10</td>
<td>56 ± 13</td>
</tr>
<tr>
<td>Pulse-frequency product</td>
<td>5581 ± 1031</td>
<td>2840 ± 656</td>
<td>3622 ± 1751</td>
<td>1461 ± 469</td>
<td>3770 ± 1216</td>
</tr>
</tbody>
</table>

Values are means ± SE.
elements of place specificity. Both the threshold and the intensity of evoked sensations showed examples of significant correlation with the pattern of stimulation, usually with number of pulses but not frequency. Therefore present results show psychophysical evidence supporting the existence of thalamic elements of modality specificity for nonpainful sensations and of place specificity, which encode the intensity of somatic sensation.

Basis of classification of thermal/pain and mechanical/tingle sensations

It is important to consider critically the interpretation of the present results in terms of the anatomy and physiology of the primate somatic sensory pathways (Ohara and Lenz 2003). Microstimulation of mechanoreceptors can evoke sensations like those reported here for mechanical/tingle sensations (McComas et al. 1970; Ochoa and Torebjork 1983; Torebjork et al. 1984; Vallbo 1981; Vallbo et al. 1984; cf. Wall and McMahon 1985). These mechanoreceptive fibers project largely through the dorsal column (DC) and medial lemniscus to Vc, and mediate mechanical/tingle sensations as demonstrated by stimulation (Emmers and Tasker 1975; Lenz et al. 1993; North et al. 1993; Ohara et al. 2004; Tasker et al. 1982; Willis and Coggeshall 1991) and lesion studies (Nathan et al. 1986; Vierck 1998; Willis and Coggeshall 1991; cf. Wall 1970; Wall and Noordenbos 1977). These sensations may be the perceptual substrate of performance of cognitive tasks based on tactile function (Romo and Salinas 2003; Salinas et al. 2000).

Microstimulation of mechanoreceptors can evoke cool sensations (Iggo 1985). These fibers terminate on STT and spinal trigemino-thalamic neurons (Jones 1985; Willis 1985) which mediate thermal/pain sensations as demonstrated by lesion studies (Bosch 1991; Tasker 1992; Tasker et al. 1982; White and Sweet 1969) and by the stimulation of the STT in the spinal cord or midbrain or within and behind Vc (Bosch 1991; Davis et al. 1999; Lenz et al. 1993; Mayer et al. 1975; Ohara and Lenz 2003; Tasker et al. 1982; White and Sweet 1969). These results suggest that thermal/pain sensations reported in this study are the result of activation of thalamic structures receiving input from the STT.

The lateral thalamic structures receiving input from the STT may be Vc and subnuclei (Fig. 1A) or VMpo or both. The present results (Table 1 and results) suggest that microstimulation evoked thermal/pain sensations are evoked both within and behind the core (Dostrovsky et al. 1991; Lenz et al. 1993; Ohara and Lenz 2003). Therefore these results support the view that both Vc and the region below and behind it, including VMpo (Craig et al. 1994), mediate pain and thermal sensation (Graziano and Jones 2004; Ohara and Lenz 2003; Willis et al. 2001).

Several pieces of evidence demonstrate overlap of STT and DC function. Nonpainful brushing can activate STT neurons (Willis 1985; Willis et al. 1973), and cold stimuli can activate neurons in the DC pathway (Ferrington et al. 1988). Noxious visceral stimuli can activate neurons in the postsynaptic DC pathway and lesions of this pathway can relieve visceral pain (Hirshberg et al. 1996; Nauta et al. 2000; Willis et al. 1999). Therefore our model that the input of the medial lemniscus and the STT to Vc are functionally segregated must be viewed with caution.

Thalamic elements of specificity of mechanical/tingle sensations

Microstimulation evoked sensations in projected fields which were consistent across the staircase in 94% of sites overall suggesting the presence of thalamic elements mediating place specificity. The presence of these elements is also suggested by the plateaus in the proportion of sites where more than one part of the body was evoked (Fig. 4, E–H). The present psychophysical evidence of elements mediating place specificity is congruent with the anatomic and physiologic evidence that cytochrome- and parvalbumin-positive thalamic lamellae and rods are elements of place specificity for input arising from mechanoreceptors (Jones 1985; Jones et al. 1982; Lenz et al. 1988b; Mountcastle and Henneman 1952; Rausell and Jones 1991). These rods or lamellae, respectively, have a radius or mediolateral dimension of ~200–600 μm in coronal section, based on anatomic and physiologic studies (Rausell et al. 1992; Fig. 10 in Jones et al. 1982). These dimensions are congruent to those suggested by rises in the proportion of sites with more than one part of body (20 μA, Fig. 4, E and G) (Fig. 1 in Ranck 1975) and by the small proportion of sites having projected fields on more than one part of the body (Fig. 4, E–H) (Jones et al. 1982; Ranck 1975; Rausell and Jones 1991).

Similar evidence suggests that the thalamic elements of modality specificity are smaller than those for place specificity. Microstimulation-evoked mechanical/tingle sensations are always constant at 300 Hz and along the staircase, which demonstrates the existence of thalamic elements of modality specificity. However, the proportion of sites with more than one descriptor (Fig. 4, A and C) was commonly higher than that for one part of the body (Fig. 4, E and G), and plateaus in the descriptor plots (Fig. 4, A and C) were usually absent for NPMechanical or NPMovement sensations. The lack of plateaus in the plot of proportions of descriptors (Fig. 4, A and C) suggests that the anatomic element of modality specificity is smaller than that for place specificity, perhaps a small bundle of lemniscal fibers (see Figs. 18 and 19 in Jones et al. 1982). Therefore several elements of modality specificity may be located within a rod, the probable element of place specificity for mechanical/tingle sensations.

Thalamic elements of specificity of thermal/pain sensations

The preceding review suggests that the elements of place specificity of thermal/pain sensations may be STT terminations in Vc or VP that consist of “disseminated bursts” of axonal arbors (Mehler 1962) that are located in the calbindin positive “matrix” between thalamic rods (Rausell and Jones 1991). The location of these STT terminations is coincident with that of neurons responding to noxious stimuli (Apkarian and Shi 1994). The approximate diameter of these structures is <300 μM (Fig. 8 in Rausell and Jones 1991) consistent with 20-μA current of plateaus in the proportion of more than one part of the body versus threshold for thermal/pain sensations (Fig. 4, F and H) (Ranck 1975).

The cool sensations evoked by microstimulation were highly consistent across the staircase for modality and place. Plateaus
in the relationship between proportions of sites with greater than one descriptor or part of the body were very commonly found for cool sensations (Fig. 4). The magnitude of the cool sensation varied significantly with the number of pulses in the pattern of stimulation and had the lowest pulse threshold (Analysis of staircase results by VAS ratings).

These results are congruent with the stimulus-response function of neurons in Vc that respond to cold stimuli (Lenz and Dougherty 1998a) and with the short bursts occurring in the spontaneous and evoked spike trains of neurons that respond to cold stimuli (Lee et al. 2005). Therefore cool sensations are mediated through discrete elements of place and modality specificity that transmit graded responses signaling the intensity of cold stimuli. Both the presence of short bursts of action potentials and the number of pulses in the stimulation train seem to be related to the microstimulation-evoked cool sensation.

Pain was often evoked at “analog” sites at which microstimulation-evoked pain commonly had both more than one descriptor at 5 μA, changes in that descriptor, and changes in intensity from the nonpainful to the painful range along the staircase. These sensations may be mediated by wide dynamic range neurons (Lee et al. 1999; Lenz et al. 2004; Price et al. 2003; Willis 1985). Pain was also evoked at “binary” sites where the descriptors and pain ratings did not change along the staircase, perhaps mediated by nociceptive specific neurons. The large number sites with more than descriptor and the lack of plateaus suggest that the modality elements of pain are small, perhaps a few thalamic neurons located within place-specific elements—the matrix between rods.

Significance of thresholds for numbers of pulses and frequencies

The present results demonstrate that thermal/pain staircase thresholds were significantly lower than for mechanical/tingle sensations. This is consistent with the response of neurons in Vc to somatic stimuli which is includes brief bursts of action potentials (low-threshold spike-bursts) (Lee et al. 2005). The burst rate is highest among neurons responding to cold stimuli, whereas microstimulation at cold sites has the lowest pulse × frequency threshold and pulse threshold. The combination of stimulus-evoked thalamic bursting (Lee et al. 2005) and sensations evoked by short bursts of microstimulation pulses (Fig. 6 and Table 5) is strong evidence that burst firing patterns encode somatic stimuli, particularly cold stimuli (Lenz and Dougherty 1998b).

The prolonged stimulus trains at threshold in the present results are consistent with earlier reports of the duration of thalamic or cortical stimulation required to evoke paresthesias (Libet et al. 1979, 1991). In these previous reports, thresholds for detection of paresthesias were determined in subjects with thalamic or cortical electrodes in place. These subjects were able to identify correctly, in a two alternative forced choice paradigm, the occurrence of stimuli that were not perceived consciously, demonstrating that the stimuli which were subthreshold for perception could be detected subconsciously (cf. Nolan and Caramazza 1982). These reports may be consistent with the present results that relatively long trains of microstimulation in Vc are required for detection of paresthesias. The present report demonstrates that as few as four pulses are often adequate for detection of microstimulation-evoked thermal/pain sensations. Therefore subconscious detection must occur over a shorter interval in the case of thermal/pain sensations (Figs. 5 and 6 C–F), which suggests that pain reaches consciousness more reliably than mechanical/tingle sensations.

The short trains of microstimulation that reach conscious-ness at pain sites are consistent with the observations that short bursts of action potentials occur more commonly in thalamic neurons signaling pain (Lee et al. 2005) and that the response to stimulation along the staircase often evokes a constant response above threshold - an alarm (Lenz et al. 2004). An alarm is a binary, “all-or-none” response to a stimulus that is independent of the intensity of the stimulus once the threshold of the alarm is exceeded. Thalamic binary sites as an alarm, whereas analog sites serve pain transmission by encoding the quality and intensity of pain— unlike a labeled line (Craig 2003; Lenz et al. 2004; Perl 1998).

Binary processes have been reported in the cortical potentials evoked by infrequent stimuli, including infrequent painful stimuli, which produce a state of alertness and attention (Becker et al. 1993; Lenz et al. 2000; Picton and Hillyard 1988; Zasransky et al. 1995). Binary responses also characterize blood flow signals evoked by graded, experimental, cutaneous pain in some functional imaging studies (Bornhovd et al. 2002; Coghill et al. 1999).

The binary nature of thalamic processes, pain-related imaging signals and cortical potentials signaling alertness may all reflect a common mechanism. Thalamic bursts that encode experimental pain may be a mechanism by which painful stimuli sound the alarm to produce a state of alertness and attention. Similarly, the thalamic bursts that occur in patients with chronic pain (Lenz et al. 1998c; Radakrishnan et al. 1999; Weng et al. 2000) may contribute to the increased attention to painful stimuli that occurs in these patients (Asmundson et al. 1997; Roelofs et al. 2004).

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