Quantitative Response Characteristics of Thermoreceptive and Nociceptive Lamina I Spinothalamic Neurons in the Cat

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Received 26 December 2000; accepted in final form 20 April 2001

Craig, A. D., K. Krout, and D. Andrew. Quantitative response characteristics of thermoreceptive and nociceptive lamina I spinothalamic neurons in the cat. J Neurophysiol 86: 1459–1480, 2001. The physiological characteristics of antidromically identified lamina I spinothalamic (STT) neurons in the lumbar-sacral spinal cord were examined using quantitative thermal and mechanical stimuli in barbiturate-anesthetized cats. Cells belonging to the three main recognized classes were included based on categorization with natural cutaneous stimulation of the hindpaw: nociceptive-specific (NS), polymodal nociceptive (HPC), or thermoreceptive-specific (COOL) cells. The mean central conduction latencies of these classes differed significantly; NS = 130.8 ± 55.5 (SD) ms (n = 100), HPC = 72.1 ± 28.0 ms (n = 128), and COOL = 58.6 ± 25.3 ms (n = 136), which correspond to conduction velocities of 2.5, 4.6, and 5.6 m/s. Based on recordings made prior to any noxious stimulation, the mean spontaneous discharge rates of these classes also differed: NS = 0.5 ± 0.7 imp/s (n = 47), HPC = 0.9 ± 0.7 imp/s (n = 59), and COOL = 3.3 ± 2.6 imp/s (n = 107). Standard, quantitative, thermal stimulus sequences applied with a Peltier thermode were used to characterize the stimulus-response functions of 76 COOL cells, 47 HPC cells, and 37 NS cells. The COOL cells showed a very linear output from 34°C down to ~15°C and a maintained plateau thereafter. The HPC cells showed a fairly linear but accelerating response to cold below a median threshold of ~24°C and down to 9°C (measured at the skin-thermode interface with a thermode temperature of 2°C). The HPC cells and the NS cells both showed rapidly increasing, sigmoidal response functions to noxious heat with a fairly linear response between 45 and 53°C, but they had significantly different thresholds; half of the HPC cells showed a very linear output from 34°C down to ~15°C and a maintained plateau thereafter. The HPC cells showed a fairly linear but accelerating response to cold below a median threshold of ~24°C and down to 9°C (measured at the skin-thermode interface with a thermode temperature of 2°C). The HPC cells and the NS cells both showed rapidly increasing, sigmoidal response functions to noxious heat with a fairly linear response between 45 and 53°C, but they had significantly different thresholds; half of the HPC cells were activated at ~45.5°C and half of the NS cells at ~43°C. The 20 HPC lamina I STT cells and 10 NS cells tested with quantitative pinch stimuli showed fairly linear responses above a threshold of ~130 g/mm² for HPC cells and a threshold of ~100 g/mm² for NS cells. All of these responses produce small, consistent, and reliable responses to thermal and mechanical stimuli. Together these results suggest that these classes of lamina I STT cells provide discrete sensory channels for the sensations of temperature and pain.

INTRODUCTION

Lamina I of the spinal dorsal horn is an integral component of the central neural representation of pain and temperature sensations (see reviews by Craig 2000a; Perl 1984). Lamina I neurons receive monosynaptic, modality-selective input from Aδ and C primary afferent thermoreceptors and nociceptors. Accordingly, the original physiological description of spinal lamina I neurons by Christensen and Perl (1970) reported cells responsive selectively to noxious cutaneous stimulation (pinch and/or heat) as well as cells responsive to innocuous thermal stimulation, some of which were selectively sensitive to cooling and inhibited by warming and some of which responded both to cold and to noxious stimuli (see also Kumazawa et al. 1975; Mosso and Kruger 1973).

Lamina I is also the major source of ascending output from the superficial dorsal horn. Lamina I axons in cats and primates ascend contralaterally in the lateral spinothalamic tract (STT), which is the critical pathway for the sensations of pain, temperature, itch, and sensual touch in humans (Craig 2000b). Studies in the cat of antidromically identified lamina I trigminothalamic cells by Dostrovsky and Hellon (1978) and lamina I spinothalamic cells by Craig and Kniffki (1985) described unit responses that were consistent with the general pattern described by Christensen and Perl (1970). We now recognize three main categories of lamina I projection neurons: nociceptive-specific (NS) cells, innocuous thermoreceptive-specific (COOL or WARM) cells, and polymodal nociceptive (HPC) cells sensitive to noxious heat, pinch, and noxious cold (Craig and Bushnell 1994; Craig and Hunsley 1991; Craig and Serrano 1994). The available evidence indicates that these three groups have different response properties, different ascending conduction velocities, and different susceptibility to descending or pharmacological modulation (Craig and Serrano 1994; Dostrovsky et al. 1983). Recent findings, based on immunoreactivity and/or labeling, indicate that these three categories are also distinct morphologically and correspond to the three major anatomical types of lamina I neurons that can be distinguished in horizontal sections (Han et al. 1998). These three physiological and anatomical categories of lamina I STT cells have also been recognized in the monkey (Craig et al. 1999; Dostrovsky and Craig 1996; Kumazawa et al. 1975; Zhang and Craig 1997).

Thus these categories of lamina I STT neurons appear to be robust and biologically significant classes of neurons. Various aspects of the physiological characteristics of these neurons have been examined in prior studies (Craig and Bushnell 1994; Craig and Hunsley 1991; Craig and Kniffki 1985; Craig and Serrano 1994). The present report provides a quantitative description of the response properties of these three classes of lamina I STT cells in the cat based on a large sample of...
neurons examined in this laboratory with standardized stimuli across several series of experiments. The present data quantitatively differentiate these classes of neurons and enable a comparison of the stimulus-response properties of these lamina I STT neurons with available psychophysical results.

METHODS

General procedures

All experiments were conducted in accordance with the guiding principles for the care and use of animals of the American Physiological Society, and the protocols were approved by the local Institutional Animal Care and Use Committee. The data reported were gathered in experiments performed on a total of 162 domestic cats (2.0–6.5 kg) of either sex across several different series of experiments (e.g., Andrew and Craig, 2001; Craig and Andrew 1999; Craig and Bushnell 1994; Craig and Hunsley 1991; Craig and Serrano 1994; Dostrovsky and Craig 1993; Han and Craig 1993; M. Karpuchina and A. D. Craig, unpublished results; B. Lumb and A. D. Craig, unpublished results). The animals were anesthetized with pentobarbital sodium (40 mg/kg ip). A catheter was placed in the right cephalic vein for administration of intravenous anesthetic supplements to maintain areflexia. The head, neck, ip, and left hindlimb were shaved. Eye saline was applied, 0.5% maricaaine was injected subcutaneously at incision sites, and a local anesthetic was sprayed in the ear canals. A single intravenous injection of dexamethasone (10 mg) was administered to prevent edema. A catheter placed in the left common carotid artery enabled measurement of blood pressure with a transducer, and the trachea was cannulated. Pancuronium bromide (–0.4 mg/h) was injected to induce paralysis, and a positive pressure respirator was used. The animals were ventilated with 75% air and 25% O₂, and end-tidal CO₂ was maintained at 3.5–4.5%. Anesthetic depth (areflexia, stable blood pressure) was verified every hour before each injection of the paralytic agent. Core temperature was maintained at 37.5°C with a heating pad and (if necessary) a feedback-controlled infra-red heat lamp from a safe distance. The ambient room temperature was maintained at 23–25°C. The animal’s head was mounted in a stereotaxic frame, and a craniotomy was made to allow access to the right thalamus. A laminectomy was performed to expose the lumbosacral enlargement, and vertebral clamps were used to suspend the animal. The spinal cord was covered at all times with Tyrode’s solution and vertebral clamps were used to suspend the animal. The spinal cord was covered at all times with Tyrode’s solution and vertebral clamps were used to suspend the animal. The spinal cord was covered at all times with Tyrode’s solution and vertebral clamps were used to suspend the animal. The spinal cord was covered at all times with Tyrode’s solution and vertebral clamps were used to suspend the animal.

Lamina I unit characterization

Recordings were obtained from cells in the superficial dorsal horn at a depth of 200–600 µm near the dorsal root entry zone of the left lumbar-sacral spinal cord (L₆ – S₁ segments) with platinum-plated tungsten-in-glass microelectrodes having tip sizes of ~15 µm. In general, the electrode first encountered large-diameter muscle spindle primary afferent fibers having regular ongoing discharge. Lamina I was recognized just ventral to these fibers by the presence of units with irregular ongoing activity. Such ongoing activity could often be inhibited by radiant warmth and excited by innocuous cooling. Lamina I was also recognizable by the presence of units antidromically activated from the thalamic electrode array. Below this, we find a 200-µm zone in the outer substantia gelatinosa where our electrodes rarely pick up unitary discharges, and this is followed by field potentials and multi-unit responses to low-threshold mechanical stimulation in inner lamina II and laminae III–V.

The microelectrode was moved so that a single unit was isolated on the basis of spike amplitude, and antidromic activation from the thalamus was verified. The antidromic nature of the activation was determined on the basis of a constant latency response, a discrete all-or-none threshold to stimulation, and the ability to follow a train (at 200–333 Hz) of at least three stimuli with constant latencies. All units that fulfilled these criteria and showed collision (extinction) with ongoing or evoked orthodromic spikes also demonstrated a definitive critical collision interval (Lipski 1981; Ranck 1975) when tested.

Antidromically activated single units were tested with natural cutaneous stimulation, including limb movement, tap, innocuous and noxious mechanical (brush, cotton wisp, flat forceps), innocuous cooling (beaker filled with wet ice), innocuous warming (radiant heat lamp), noxious heat (heat lamp), and noxious cold (ice-cold beaker for 20–30 s) stimuli (Craig and Hunsley 1991; Craig and Serrano 1994). All identified cells were tested with all stimulus modalities. The cells were classified as thermoreceptive-specific cells if they were sensitive only to cooling (COOL); NS cells if they were sensitive only to heat, pinch, or both; and polymodal nociceptive (HPC) cells if they were sensitive to noxious heat, pinch, and noxious cold. Wide dynamic range cells that respond to both innocuous and noxious mechanical stimuli also occur in lamina I, but these rarely project to thalamus in the cat (Craig and Kniffki 1985; Craig and Serrano 1994; Hylden et al. 1986).

The COOL cells (formerly called COLD cells) were recognized by their irregular spontaneous activity, which could be inhibited by innocuous radiant warming of the skin, by their vigorous and imme-
discard excitation on contact or near contact with a cold object; and by their insensitivity to mechanical stimulation with a probe warmed to neutral skin temperature. Some COOL units occasionally respond with a brief phasic discharge to pinch or noxious (“paradoxical”) heat, as described before (Craig and Hunsley 1991; Dostrovsky and Craig 1996; Dostrovsky and Hellon 1978; Kumazawa et al. 1975; or for cold-specific primary afferents: Doodt and Zotterman 1952). Poly-modal nociceptive HPC lamina I STT neurons were identifiable by their lower ongoing discharge (see Andrew and Craig 2001), their insensitivity to warming, their phasic excitation by innocuous cooling, and their sustained, graded discharge to noxious cold, noxious heat, and pinch. The thresholds of HPC cells to noxious cold vary, and their responses to noxious cold stimuli are occasionally delayed by several seconds (see Craig and Kniffki 1985; Craig and Serrano 1994). They are insensitive to innocuous mechanical stimulation with thermally neutral probes. Finally, we characterized NS lamina I STT cells by their selective, graded sensitivity to pinch or noxious heat or both pinch and heat and their insensitivity to cooling and noxious cold. Nociceptive cells recorded late in a particular experiment occasionally displayed weak low-threshold mechanical sensitivity, which was ascribed to sensitization by prior noxious stimulation.

The present analysis includes only lamina I STT cells of these three main types; other, less frequent cells that respond selectively to deep, chemical, warm or slow mechanical stimuli are described separately (Andrew and Craig 2001; Craig and Kniffki 1985; Andrew and Craig, unpublished data). Spontaneous discharge was measured over a 2-min interval prior to stimulation or characterization. Receptive fields were determined by manual mapping with threshold stimuli and indicated on figures. The receptive fields of the identified units in each class were consistent with the descriptions in prior articles (e.g., Craig and Hunsley 1991; Craig and Kniffki 1985; Craig and Serrano 1994) and are not addressed in this report.

Quantitative stimulation

Quantitatively controlled thermal stimuli were applied with a custom-built thermoelectric (Peltier) stimulator (20 × 20 mm) placed over a unit’s receptive field. A thermocouple fixed to the surface of the Peltier and covered with thermally conductive epoxy (Marlow Industries, Dallas, TX) was used for feedback control of the temperature of the thermode. However, the temperature used for analysis was the mean of repeated measurements at the interface between the thermode and the skin with a separate, calibrated thermocouple (0.005-in Type T, Omega CL23A, Stamford, CT), which differed from that of the thermocouple embedded on the face of the thermode and from the temperature of the glabrous dermis; this measured temperature, which provides a reliable standard for comparisons between laboratories, varied less than ±0.4°C between sessions. The thermoelectric stimulator we used could not deliver subzero temperature commands. The stimulus sequences were designed to measure stimulus-response functions across a broad range of temperatures with minimal habituation or sensitization (Craig and Hunsley 1991; Craig and Serrano 1994).

The cooling stimulus command sequence consisted of a descending staircase series of 4°C cooling steps of 20- or 30-s duration beginning from a baseline temperature of 34°C and proceeding to a final command temperature of 6 or 2°C. The command temperatures were 34, 30, 26, 22, 18, 14, 10, and 6°C and in some cases also 2°C, which produced thermode-skin interface temperatures of 34.5, 32.1, 28.7, 25.5, 22.1, 18.7, 15.7, 12.5, and 9°C, respectively. Warming steps (10 s) were appended at the end of this sequence to command temperatures of 44, 48, and 52°C to test for heat sensitivity, although these were of little use for quantitative analysis (see RESULTS) due to the adaptation properties of COOL cells.

The heat stimulus sequence consisted of a series of 20-s heating steps (at 9 or 15°C/s) from a baseline of 34°C to command plateau temperatures ≤58 or 62°C in 4°C increments with a 1-min hold at 34°C between steps. The heat sequence thus included command steps of 42, 46, 50, 54, 58, and 62°C, which corresponded to skin-thermode interface temperatures of 38.5, 42.7, 45.5, 48.5, 53.0, and 57.7°C, respectively. These thermal stimulus sequences produce stable and reproducible stimulus-response functions (see RESULTS).

For quantitative mechanical stimulation, we used a custom-built, hand-held, force-monitored (strain gauge) pincher with a 3-mm² circular contact surface that enabled graded pressure/pinch stimuli to be applied at a variety of skin surfaces. This device was based on the design described by Burgess and Perl (1967) as stimulator 2 in their Fig. 2. We first put the pincher in contact with the skin for several seconds to accommodate the thermal sensitivity of HPC cells (see RESULTS), and then we applied an ascending staircase series of steps of increasing forces (0–1,000 g at ~100 g increments; ~5 s per step) by monitoring the applied force visually on an oscilloscope. This device produces a graded sensation of pain in humans when applied to the skin between digits beginning at a force of ~300 g.

For most units, each stimulus sequence was repeated two or more times, with a 3- to 5-min interval between trials. Unit responses to successive thermal stimulus sequences applied at or near the same stimulation site were averaged. The orthodromic and antidromic spike waveform of every unit studied was constantly monitored to ensure that recordings from the same single unit were maintained throughout the characterization. Analog microelectrode records, feedback control signals, blood pressure, and voice records were stored on tape. Voltage-discriminated unit discharges were used to generate peri-stimulus time histograms using custom programs on a UNIX computer (Masscomp 5400) or a PowerI-401 interface and the program Spike2 (Cambridge Electronic Design, Cambridge, UK) on a PC. Thresholds were taken as the first temperature or pressure at which a response clearly distinguishable from background activity was visibly apparent (i.e., where we judged an increment larger than the range of sampled ongoing activity). Responses were measured from histograms (1-s bins) as dynamic (first 5 s), static (remainder of stimulus period), and total (entire stimulus period), beginning with the onset of each stimulus step. The force applied during each manual pinch stimulus was measured in the middle of each individual step; these records were not averaged. Parametric ($\chi^2$, r-test, ANOVA, General Linear Model, k-means cluster analysis) and nonparametric statistics (Wilcoxon rank, Kruskal-Wallis, as required by normality tests) were used with post hoc verification to compare the responses of subclasses of cells, using the programs SigmaStat/SigmaPlot (SPSS, Chicago, IL) and CSS Statistica (Statsoft, Tulsa, OK). Stimulus-response curves were fitted with linear, power or four-parameter sigmoidal functions. The linear model used was $y = ax + b$, the power law model used was $y = y_0 + ax^b$, and the four-parameter sigmoidal model used was $y = y_0 + a/(1 + e^{\left[-\left(x - x_0\right)/b\right]})$.

RESULTS

General characteristics of lamina I STT neurons

Lamina I STT neurons were recorded at depths of 200–600 μm below the surface in segments L₅–S₁. The identification of antidromically activated STT projection neurons at these depths provides assurance that the units were lamina I neurons because STT neurons are only very rarely located in laminae II–III in the cat (Carstens and Trevino 1978; Zhang et al. 1996). In addition, lesions made at the sites of lamina I STT units were identified in 37 cats, and these were all located histologically in lamina I; they were concentrated in the dorsal cap at the apex of the dorsal horn, such as that shown in Fig. 1, where retrograde labeling results indicate that lamina I STT cells are concentrated, but recordings were also made more medially.

A total of 364 units were antidromically identified as lamina I STT neurons by the demonstration of a high-frequency,
constant latency train response (Fig. 2A). This was accepted as a sufficient condition if collision (extinction) of the first antidromic action potential in the train response by a closely preceding (ongoing or evoked) action potential was observed. Definitive demonstration of a critical collision interval (2 × latency + ~1 ms for refractory period) was obtained for every cell tested (n = 65) that fulfilled these criteria (Fig. 2, B and C). The mean antidromic latency of this population was 83.2 ms, the mean conduction distance was 330 mm, and thus the overall mean conduction velocity was 5.0 m/s.

Of the total sample, 136 cells were identified as COOL lamina I STT cells, 128 as HPC lamina I STT cells, and 100 as NS lamina I STT cells. (The infrequent lamina I STT cells of other types were not included in the present analysis.) The mean conduction latencies for these classes were COOL = 58.6 ± 25.3, HPC = 72.1 ± 28.0, and NS = 130.8 ± 55.5 (SD) ms, respectively, which correspond to mean conduction velocities of 5.6, 4.6, and 2.5 m/s. The box plots in Fig. 3A graphically compare the measured conduction latencies of these classes. The conduction latencies of these three classes were significantly different (ANOVA and post hoc t-tests, P < 0.001).

Spontaneous (ongoing) discharge rates were measured for 107 COOL, 59 HPC, and 47 NS lamina I STT cells (total = 213) that were isolated prior to any intentional noxious stimulation of the hindlimb. The mean ongoing rates for these three cell types were COOL, 3.3 ± 2.6; HPC, 0.9 ± 0.7; and NS, 0.5 ± 0.7 (SD) imp/s. As shown in the box plots in Fig. 3B, the median rates were lower, being 2.7, 0.9, and 0.2 imp/s, respectively. The ongoing rate of the COOL units was significantly different from that of the HPC and NS units (P < 0.001). The difference between HPC and NS cells did not achieve statistical significance, although in an independent subset of these data (n = 97) (Andrew and Craig 2001), the difference between the ongoing rates of HPC and NS cells approached significance (P < 0.08) in accordance with our general impression from these recordings.
The thalamic electrodes from which the units were antidromically activated were compared for these classes, but in contrast to a prior comparison (Craig and Kniffki 1985), no significant correlation was observed. This must have resulted from the inherently variable placement of the fixed array in different experiments, and the failure of particular electrodes in some experiments because detailed antidromic mapping of single lamina I STT units using a mobile array has shown clear distinctions between the projections of thermoreceptive-specific and nociceptive lamina I STT cells (Craig and Dostrovsky 2001; Dostrovsky and Craig 1993).

The quantitative stimulus-response characteristics of samples of 76 COOL, 47 HPC, and 37 NS lamina I STT cells are described in the following text. The receptive field of nearly all of these units included a portion of or all of the glabrous ventral hindpaw, and the quantitative thermal and mechanical stimuli were applied to this region. Many units were tested with the standard stimulus sequences more than once: for example, 66% of the COOL cells were tested two or more times and 41% were tested three or more times. The responses to repeated standard test stimuli were in general quite reproducible. For example, Fig. 4 shows two original responses of a COOL unit to a standard cooling staircase stimulus along with the response curves for all four applications of the same stimulus, which are nearly identical. The responses of HPC cells to cold, heat and pinch stimuli and of NS cells to heat and pinch stimuli were similarly reproducible.
Characteristics of COOL lamina I STT cells

The response characteristics of COOL lamina I STT units were examined with standard staircase stimuli that tested their sensitivity to successive 20- or 30-s temperature steps of ~4°C from a baseline of 34 or 38°C down to a thermode-skin interface temperature of 12.7° (n = 64; thermode command temperature of 6°C) or 9°C (n = 12; command temperature of 2°C). This sequence evoked reproducible cooling responses (Fig. 4) that provided a stimulus-response function for each unit based on the mean discharge rate over the entire response to each temperature step for all sequences applied.

Figure 5 shows the responses of eight COOL lamina I STT units to the standard test stimulus that are representative of the variety observed with respect to onset threshold, sensitivity to decreasing temperature, and overall discharge rate. These examples also show that the static responses of COOL cells showed variable adaptation during the step stimuli, and further, they document the variable presence of a dynamic response component at the onset of each temperature step. Dynamic responses in general began at warmer temperatures than static responses and quickly saturated (and/or decremented) at cooler temperature steps. However, there was otherwise no correlation between the dynamic sensitivity and the overall response patterns of these cells (cf. Hutchison et al. 1997).

The warming steps that were included in the test sequence following the cooling staircase (shown in Fig. 4) were much less effective at demonstrating the warming inhibition that is uniquely characteristic of COOL cells than radiant heat applied over a larger field. The warming steps could not be used as a quantitative measure because the response histograms to warming were also confounded by the increases in ongoing discharge produced following each warming step (Fig. 4) that reflect longer-term (minutes) adaptation processes that we did not study (cf. Darian-Smith 1994; Dostrovsky and Hellon 1978). The warming steps included noxious heat test stimuli that produced interface temperatures of 45.5 and 48.5°C, and only 17 COOL units showed weak (paradoxical) responses to these stimuli; such responses were not graded (confirmed by supplemental use of the standard noxious heat sequence in 6 of these). One exceptional cell that did show a graded heat response was nonetheless categorized as a COOL cell (rather than an HPC cell) because it was clearly inhibited by radiant warming.

The mean stimulus-response function of the entire population of 76 COOL lamina I STT cells (Fig. 6A) demonstrates the two most salient features of the COOL lamina I STT population: the close relationship of the average discharge of the COOL units with decreasing temperature and the saturation of this response at temperatures below ~15°C. The left-most data point on this graph is based on the 12 units for which a thermode-skin interface temperature of 9°C was tested, and the standard error at this point is accordingly larger. Over the range of 15–34°C, this correlation is remarkably linear (Fig. 6B); at every point, the mean and standard error of the population response are within the 95% confidence limits of the regression line. The regression line has a correlation coefficient of r = 0.59 and a slope of −0.57 Hz/°C. The 95% confidence limits of the regression span a width on the abscissa of 1.5°C, meaning that this is the temperature difference at the skin-thermode interface that can be discriminated reliably (P < 0.05) by this population of COOL lamina I STT neurons. Plotting the mean population response on a normalized scale (that is, with the maximal discharge of each cell set at 100%; not shown), reduces the effect of the differences between cells in absolute discharge rate and provides a higher correlation coefficient (r = 0.80) with a slope of −3.91%/°C and a 95% confidence limit width of 0.8°C.

The individual stimulus-response functions of these 76 COOL lamina I STT units are shown in Fig. 7, segregated according to threshold for clarity. The majority (n = 52) responded to the initial cooling step (from 34 to 32.1°C), and the mean response of this group clearly saturated at least by 15.7°C. A few neurons had identified thresholds at the subsequent cooling steps of 28.7 (n = 12) or 25.5°C (n = 10). Two units with thresholds of 18.7°C were categorized as COOL cells because they had saturating responses to deep cold, were inhibited by warming, and had no sensitivity to heat or pinch. One exceptional COOL unit with a unique, bell-shaped response curve was not included in the present analyses (shown in Fig. 1 of Craig and Hunsley 1991).

We compared the normalized response curves of the individual units (Fig. 8), and it became visibly apparent that two subpopulations could be distinguished on the basis of their output at 28.7°C being greater or less than 50%. The mean of one subpopulation showed a rapid rise in discharge with decreasing temperature and then a decelerating response function (n = 26) and the mean of the other subpopulation showed a slower onset and then a steeper (sigmoidal) response function.

FIG. 5. The histogrammed responses of 8 different COOL lamina I STT neurons, representing the variety of response patterns observed. The records at the bottom indicate the skin-thermode interface temperature.
(n = 51). The former subset achieved a mean of 68% of maximal output at 28.5°C and the latter subset 26% of maximal discharge at this temperature. These two subsets were significantly different (ANOVA, \(P < 0.0001\), with post hoc \(t\)-test verification). Independent verification of this segregation was obtained with a \(k\)-means cluster analysis of COOL cells that differentiated the same subsets on the basis of either normalized response or absolute discharge frequency (\(P < 10^{-5}\); not shown).

**Characteristics of HPC lamina I STT cells**

The responses of HPC lamina I STT units were examined to cold (\(n = 47\)), heat (\(n = 45\)), and pinch (\(n = 20\)). The responses of HPC cells were qualitatively and quantitatively distinct from those of COOL cells and NS cells. The responses of four HPC lamina I STT cells to both cold and heat stimuli are shown in Fig. 9, and these are representative of the most salient features of the responses of HPC neurons to thermal stimulation. In general, HPC lamina I STT neurons displayed graded static responses to both cold and heat. Their responses to cold continued to increase at noxious temperatures. Their responses to heat usually were greater in magnitude than their responses to cold. None of the HPC cells were inhibited by radiant warming. The responses shown in Fig. 9 are also representative of the variety of individual characteristics observed. Individual HPC units had differing thresholds to cold and heat. A few units responded with greater discharges to cold than to heat. Most showed strongly graded responses, whereas others had rather weakly graded responses, and some showed dynamic as well as static responses. As shown in Fig. 9 (bottom 2 unit records), the earliest responses of HPC cells to cooling generally consisted of a phasic discharge, whereas static responses became evident at colder temperatures (\(\leq 18.7^\circ\text{C}\)). The same staircase cooling sequences used to characterize

![FIG. 6. A: the mean stimulus-response function for 76 COOL lamina I STT cells. B: a linear regression over the rising portion of this curve, plotted against the population mean. —, standard error. \(\cdots\cdots\), 95% confidence limits.](http://jn.physiology.org/)

![FIG. 7. The individual response functions of COOL lamina I STT cells segregated according to threshold, as indicated. The bar graph shows the distribution of thresholds. The thick lines show the mean of each subset.](http://jn.physiology.org/)

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COOL cells were used to examine HPC cells. The mean stimulus-response function of the 47 HPC lamina I STT cells tested with cooling stimuli (Fig. 10A) shows moderate ongoing discharge at neutral temperatures, a mean onset threshold of ~25°C, and an accelerating response curve that continues to rise at the coldest skin-thermode interface temperatures tested. The left-most data point on this graph is based on the seven units for which a thermode-skin interface temperature of 9°C was tested. Regression analyses of the mean population response over its entire extent using various quantitative models produced correlations with similar coefficients: linear $r = 0.64$, power $r = 0.62$ (exponent of −1.4), and sigmoidal $r = 0.66$. The linear regression against discharge rate (not shown) had a slope of $-0.3 \text{ Hz/°C}$ and a 95% confidence limit width of 1.7°C. A linear regression on the normalized mean response function (maximal response set at 100%; not shown) produced a higher correlation coefficient of $r = 0.82$ with a slope of $-3.6\%/°C$ and a 95% confidence limit width of 1.1°C.

The individual stimulus-response functions to cold of all 47 HPC units are plotted together in Fig. 10B. This shows that the units had a variety of different thresholds, different rates of increase with decreasing temperature, and different absolute discharge levels. The histogram in Fig. 10C shows that the distribution of the cold thresholds of these units was unimodal but broad. Of this sample, 40% ($n = 19$) began to discharge to cooling steps of 28.7 or 25.5°C from the baseline of 34°C and 68% ($n = 32$) of the population were activated by a 22.1°C
step; thus approximately half of the HPC cells were activated at \( \sim 24^\circ C \). As can be visually appreciated from the plot in Fig. 10B, two subpopulations could be distinguished on the basis of their discharge rate at 18.7°C \( (P < 10^{-6}, t\text{-test}) \). These subpopulations had mean discharge rates of 8.1 \((n = 24)\) and 2.1 \((n = 23)\) imp/s at 18.7°C, and they essentially divided the HPC cells into high- and low-response categories having thresholds \( \geq 25.5^\circ C \) or thresholds \( < 22.1^\circ C \). The mean response functions of these two subpopulations were significantly different \( (P < 0.0001, \text{ANOVA}) \), but nonetheless both had ascending trajectories that paralleled the overall mean curve. Nearly identical subsets were differentiated independently by \( k \)-means cluster analysis of absolute discharge rate or normalized responses \( (P < 10^{-5}) \).

A standard heat stimulus sequence was used to test 45 HPC lamina I STT cells. We tested 18 cells with heat pulses ranging to 53.0°C (skin-thermode interface), and we tested 27 cells with heat pulses to 57.7°C because some units had thresholds of 53°C and because most units tested showed response increments at this temperature. The responses shown in Fig. 9 illustrate the variety observed in the patterns of HPC heat responses. All HPC cells had responses that were maintained throughout the 20-s heat stimuli, and many showed an increasing discharge during the stimuli. Some cells evinced afterdischarge subsequent to the most intense heat stimuli that lasted several minutes. If the noxious heat stimuli were repeated several times, the HPC units often became sensitized to low-threshold stimulation (see Craig and Kniffki 1985), and accordingly, the heat test sequence was generally applied sparingly. The average number of heat trials per HPC cell was 1.5; 34% of the cells were tested with the heat sequence two or three times.

The mean heat-evoked stimulus-response function of the 45 HPC lamina I STT cells (Fig. 11A) illustrates the direct relationship of average discharge rate to increasing temperature above threshold. The regression in Fig. 11B shows that the middle portion of this response curve can be modeled by a linear function \( (r = 0.64) \). The regression line against discharge rate has a slope of 1.55 Hz/°C, and the width of the 95% confidence limits at the middle of the curve \( (\sim 48^\circ C) \) is 1.3°C. Sigmoidal and power law models over this range had similar regression coefficients. The individual stimulus-response functions of all 45 cells are plotted in Fig. 11C; these curves were similar for most of the HPC cells in this sample, though thresholds varied. The unimodal distribution of thresholds is shown in Fig. 11D; 55% of the population was activated with the 45.5°C step, and 91% was activated with the 48.5°C step.

The uniformity in the rate of rise of the responses of HPC cells to heat is clearly evident in a plot (Fig. 12A) of the individual response functions on a scale normalized to the response of each unit at the highest common temperature used \( (53.0^\circ C) \). Despite the differing thresholds, nearly all HPC units showed the same proportional increase between 45 and 50°C. The continued increment at higher stimulus temperatures is also clear in the tails of these curves at the top right of the graph. Figure 12B shows the mean population response function normalized to the relative maximum of each individual unit (i.e., including maxima at 57.7°C). A linear regression over the middle of this curve (not shown) has a high correlation coefficient \( (r = 0.82) \), equivalent to the linear correlations of the normalized response function of the COOL cell population

![Figure 11](http://jn.physiology.org/lookup/doi/10.1152/jn.00627.2000)
and the normalized cold response of the HPC cells; it has a slope of 6.8%/°C and a 95% confidence limit width of 0.83°C. Including the points at the initial rise along with the middle of the curve, however, enables a power law or exponential model to yield a similarly high correlation ($r = 0.84$; power exponent = 1.5). Nevertheless, a sigmoidal function (4-parameter model, $a = 91, b = 2.1, x_0 = 49, y_0 = 5.0$) provides a superb fit ($r = 0.91$) for the entire curve, as shown in Fig. 12B.

Quantitative responses to pinch stimulation were obtained for 20 HPC lamina I STT cells. The examples shown in Fig. 13 illustrate graded responses above the indicated thresholds using the manually applied staircase sequence of increasing forces. Thresholds varied across units and generally were between 200 and 600 g (equivalent to pressures of 67–233 g/mm$^2$). Pinches that produced visible skin damage resulted in prolonged afterdischarge (Fig. 13C). The forceps were normally placed in position on the skin for 5–10 s before pressure was applied to accommodate the thermal sensitivity of the HPC cells. Included in Fig. 13D are two examples where initial responses were obtained on contact prior to pinching (right) or during the initial stages of the pinch stimulus (left) because of adequate stimulation by the cool (room temperature) forceps. Such responses were eliminated by prewarming the forceps to neutral skin temperature, in clear contrast to the graded low threshold responses that were obtained in these experiments from non-STT wide dynamic range lamina I cells (see Craig and Serrano 1994).

A plot of the individual forces applied across all tests on these 20 HPC lamina I STT cells (Fig. 14A) shows that the

![FIG. 12. A: the individual response functions to heat of 45 HPC lamina I STT cells, normalized to the response at 53.0°C for each unit. B: a sigmoid regression curve plotted against the mean of the population, normalized to the maximal response of each unit. Bars indicate standard error.](attachment:figure12.png)

![FIG. 13. The histogrammed responses of 6 different HPC lamina I STT neurons, representing the variety of response patterns observed to graded pinch. The stimulus force records are shown under each trace. ▲, the thresholds, and the forces are given in grams for each unit [except D, left, which is confounded by thermal (cold) activation]. ▲, responses ascribed to adequate stimulation by contact with the cold (room temperature) forceps, which could be eliminated by prewarming.](attachment:figure13.png)
sampling of force was nearly continuous although the regularity of the applied force steps is clearly visible. The plot of the individual stimulus-response functions of all 20 cells (Fig. 14B) illustrates the variety of ongoing rates, thresholds, and discharge ranges and reveals that the measured response curves of some units were not smooth. The mean frequency response of this sample of HPC units, plotted with bidirectional error bars to indicate the range of measured forces at each point (Fig. 14C), shows clearly that the average threshold was almost 400 g and that the population response increased monotonically above threshold. The regression line on absolute discharge rates above threshold (not shown) has a correlation coefficient of $r = 0.54$, a slope of $1.7$ Hz/100 g, and a 95% confidence limit width at the midpoint of 150 g. The linear regression of the normalized data above threshold (Fig. 14D), which accommodates the wide range of discharge rates in this limited sample, has a higher correlation coefficient ($r = 0.79$), equivalent to the correlations for the normalized responses of HPC cells to their other two stimulus modalities, cold and heat, and to that of COOL cells. The width of the 95% confidence limits at the center of the normalized regression is 58 g.

**Characteristics of NS lamina I STT cells**

Of the total of 100 NS cells recorded, 61 were sensitive to both heat and pinch, 19 only to heat, and 17 only to pinch (and also included 3 sensitive only to deep noxious mechanical stimulation). None of the NS cells showed any sensitivity to cooling or to noxious cold. The standard heat stimulus sequence was used to characterize 37 NS lamina I STT cells. Of these, 25 were sensitive to both noxious heat and pinch, and 12 were sensitive only to noxious heat. We tested all 37 cells with heat pulses ≤48.5°C (skin-thermode interface), 35 cells with heat pulses ≤53.0°C, and 24 cells with heat pulses ≤57.7°C. The individual responses shown in Fig. 15 are representative of the variety observed among NS cells with respect to ongoing discharge, threshold, evoked discharge rate, and the rate of response increment to graded heat. All NS cells had responses that were maintained throughout the 20-s heat stimuli, and many showed an increasing discharge during the stimuli. Some cells evinced afterdischarge lasting several minutes. Repetition of the noxious heat stimuli could sensitize NS units to low-threshold stimulation (see Craig and Kniffki 1985), and accordingly, the heat sequence was applied sparingly. The average number of heat trials per NS cell was 1.8; 44% were tested two or three times.

The mean heat stimulus-response function of these 37 NS lamina I STT cells (Fig. 16A) summarizes the direct relationship of average discharge rate to increasing temperature. The plot of the individual stimulus-response functions of all 37 cells (Fig. 16B) shows that these curves were similar across NS cells although their thresholds varied. Figure 16C shows that the middle portion of this response curve is linear ($r = 0.60$); the regression line has a slope of 1.0 Hz/°C, and the width of the 95% confidence limits at the center of the curve (∼48°C) is 1.7°C. Sigmoidal and power law models had similar regression coefficients.

**FIG. 14.** A: the forces applied during all staircase pinch stimuli across 20 HPC lamina I STT cells tested, sorted and plotted in ascending order. B: the individual response functions to mechanical pinch stimulation of 20 HPC lamina I STT cells; the responses of 2 cells are truncated vertically by the limit in ordinal scale to show the range of these units’ responses. C: the mean stimulus-response function to pinch, plotted with bidirectional standard error bars to accommodate the binning of applied force at 100 g. D: a linear regression over the rising portion of this curve normalized to the maximal response of each unit. Bars indicate standard error; dotted lines indicate 95% confidence limits.
The distribution of heat thresholds for NS cells (Fig. 17) is lower and broader than that of HPC cells, and this difference is significant ($P < 0.002$, General Linear Model). For NS cells, 38% of the population was activated with at least the 42.7°C step, and 76% was activated with the 45.5°C step. The mean response functions of each separate threshold group nonetheless have a trajectory similar to the overall mean function, as shown in Fig. 17. The thresholds of NS cells sensitive to both pinch and heat did not differ from those sensitive only to heat.

The plot of the individual NS heat-response functions normalized to the response of each unit at 53.0°C is shown in Fig. 18A. Nearly all NS units showed a similar proportional increase between 45 and 50°C and continued to increase at higher stimulus temperatures. Figure 18B shows the mean population response function normalized to the relative maximum of each individual unit (i.e., including maxima at 57.7°C). This strongly resembles the corresponding curve for HPC cells (cf. Fig. 12B). The heat-evoked stimulus-response functions for NS and HPC neurons were not significantly different if compared across all temperatures or only above threshold ($P > 0.7$, 2-factor repeated-measures ANOVA), but it shows a threshold of ~300 g (i.e., ~100 g/mm²), which is noticeably lower than that of HPC cells. The regression line of the mean frequency response of these units over the entire range of forces (not shown) has a correlation coefficient of 0.75, equivalent to that of the normalized heat-response function of HPC cells, and it has a similar slope of 6.8%/°C; however, the width of the 95% confidence limit (1.9°C) is double that of the HPC normalized regression. A sigmoidal function ($a = 93$, $b = 2.7$, $x_0 = 48$, $y_0 = 4.2$) again provides a superb fit ($r = 0.88$) for the entire curve, as shown in Fig. 18B. Nonetheless comparison of this graph with the corresponding graph for HPC cells (Fig. 12B) clearly reveals the significantly lower threshold of the mean NS heat-response function.

Quantitative responses to pinch stimuli were obtained for 10 NS lamina I STT cells. All of these were responsive to both pinch and heat; quantitative results were not obtained for any cells responsive only to pinch in the present sample (see Craig and Kniffki 1985). The forces applied in studying these cells matched those applied to HPC cells (cf. Fig. 14A). The plot of the individual stimulus-response functions of all 10 NS cells (Fig. 19A) illustrates the variety of discharge rates and thresholds observed (ranging from 200 to 600 g). Nearly all cells showed a direct, monotonic relationship to force above threshold. The mean frequency response function, plotted with bidirectional error bars to indicate the range of forces at each point (Fig. 19B), reflects the large variability in absolute discharge rates in this relatively limited sample. This mean curve is not distinct from that of the HPC cells (cf. Fig. 14C; $P > 0.7$, ANOVA), but it shows a threshold of ~300 g (i.e., ~100 g/mm²), which is noticeably lower than that of HPC cells. The regression line of the mean frequency response of these units over the entire range of forces (not shown) has a correlation coefficient of 0.75, equivalent to that of the normalized heat-response function of HPC cells, and it has a similar slope of 6.8%/°C; however, the width of the 95% confidence limit (1.9°C) is double that of the HPC normalized regression. A sigmoidal function ($a = 93$, $b = 2.7$, $x_0 = 48$, $y_0 = 4.2$) again provides a superb fit ($r = 0.88$) for the entire curve, as shown in Fig. 18B. Nonetheless comparison of this graph with the corresponding graph for HPC cells (Fig. 12B) clearly reveals the significantly lower threshold of the mean NS heat-response function.
DISCUSSION

Technical considerations

The present data were necessarily obtained in anesthetized cats. The anesthetic used, intravenous pentobarbital sodium, interacts with GABA receptors and naturally causes some depression of responsiveness (Belelli et al. 1999). However, like other observers (e.g., Hori et al. 1984), we find that second-order spinal neurons are nonetheless quite responsive. When stable vital signs were uniformly maintained, the lamina I STT neurons we recorded showed similar responsiveness across different experiments, and the responses of individual cells were reproducible, in some cases over observation periods of up to several hours. We have obtained similar recordings using several different anesthetic regimens in this laboratory (e.g., chloralose, alphaxalone/alphadalone, or 1.2% halothane), and similar responses were also reported by Christensen and Perl (1970) and Kumazawa et al. (1975) in decerebrate cats without anesthesia. Higher response frequencies were reported in lamina I spino-parabrachial neurons recently by Bester et al. (2000) in the rat (under 0.5% halothane and 67% nitrous oxide) and lamina I trigeminothalamic neurons may be even more sensitive in the awake, behaving monkey (cf. Maixner et al. 1989). Nonetheless, quantitative characterization of a sample of antidromically activated lamina I STT cells of this size could practicably be obtained only in this preparation in the cat.

coefficients of $r = 0.59$, a slope of 1.4 Hz/100 g and a 95% confidence limit width at the midpoint of 174 g. Linear regression of the normalized data above threshold (Fig. 19C), which accommodates the variability in discharge rates in this limited sample, has a high correlation coefficient ($r = 0.74$), equivalent to the other normalized response functions described above, with a slope of 10.6%/100 g, and with a 95% confidence limit width of 74 g.

FIG. 17. The individual response functions of NS lamina I STT cells segregated according to threshold, as indicated. The bar graph at the top shows the distribution of thresholds. The thick lines show the mean of each subset.

FIG. 18. A: the individual response functions to heat of 37 NS lamina I STT cells, normalized to the response at 53.0°C for each unit. B: a sigmoid regression curve plotted against the mean of the population, normalized to the maximal response of each unit. Bars indicate standard error.
Relatively few standard stimuli were used for characterization. The graded, quantitative stimulus sequences we used adequately covered the response ranges of the units to the modalities tested with a discrete number of test intervals, and they were designed to minimize the possibilities of fatigue, habituation, or sensitization of responses. Lamina I nociceptive neurons are readily sensitized by repeated noxious stimuli (Christensen and Perl 1970; Craig and Kniffki 1985; Hylden et al. 1989; Woolf et al. 1994), and nociceptive activity is reduced if short interstimulus intervals are used (Christensen and Perl 1970; LaMotte and Campbell 1978). However, the stimuli used certainly did not characterize all aspects of the responses of these neurons. For example, our paradigm avoided the long-term adaptation and contrast effects in COOL lamina I cells associated with maintained temperatures, which produce significant hysteresis when descending/ascending sequences are used (e.g., Dostrovsky and Hellon 1978), although this prevented analysis of warm responses in COOL cells. Also we did not use brief thermal stimulus pulses, which have enabled demonstrations that dynamic cooling or heating responses provide behaviorally significant information (Bushnell et al. 1983; Darian-Smith 1984; Robinson et al. 1983), and we did not use subzero, freezing temperatures (cf. Beise et al. 1998; Simone and Kajander 1996). As noted further in the following text, the use of a broad range of differently sized probes and a force-controlled stimulator will enable a more thorough characterization of noxious mechanical sensitivity (e.g., Andrew and Craig 1999; Garell et al. 1996). Nonetheless the present data provide quantitative descriptions that differentiate these three categories of lamina I STT neurons and provide the basis for a comparison of their functional properties with psychophysical findings.

Last, these data should represent a relatively unbiased sample of the three main types of lamina I STT neurons. We recorded most units in the dorsal cap at the apex of the dorsal horn (or more medially), where lamina I STT neurons of all three morphological types are concentrated (Zhang et al. 1996). The thalamic antidromic electrode array was intended to activate terminal axons at most of the anatomically recognized lamina I STT projection sites in the thalamus (Craig 1987), and in many experiments, all of the electrodes at these sites were effective in activating lamina I neurons antidromically. However, the relative proportions of COOL, HPC, and NS cells sampled are not representative (cf. Zhang et al. 1994) because we sought particular types of cells in particular experiments. In addition, it is much more difficult to maintain the stable, long-term recordings necessary for quantitative characterization from NS cells, especially those with very long conduction latencies, than from COOL and HPC cells. Although quantitative characterizations of NS cells selective for pinch are not included in this sample, we have observed graded mechanical responses both informally and systematically (Andrew and Craig 1999) in such cells that were similar to those reported in the present study.

**Comparison of the distinct classes of lamina I STT cells**

The three categories of cells we have characterized constitute the vast majority of lumbosacral lamina I STT cells in the cat. These cell classes are distinguished by a variety of characteristics. The available evidence indicates that they differ physiologically in their response characteristics, their afferent fiber inputs, and their susceptibility to descending and pharmacological modulation (for references, see Craig 2000a; Han et al. 1998). Evidence has also been reported indicating that they differ anatomically in the distribution of their terminations in the thalamus, in their somato-dendritic morphology, and in their labeling for the NK-1 receptor (Dostrovsky and Craig 1993; Han et al. 1998; Yu et al. 1999).

The COOL, HPC, and NS lamina I STT cells have distinctly different responses to natural cutaneous stimuli in both cats and monkeys (Craig and Serrano 1994; Dostrovsky and Craig 1996). Thermoreceptive-specific (COOL and more rarely WARM) cells respond in a graded manner only to innocuous thermal stimuli, and nociceptive NS and HPC cells respond selectively to noxious thermal and mechanical stimuli. The HPC cells differ from the NS cells in that they respond also to
noxious cold, and they differ from COOL cells in that they have lower (colder) thresholds, are not inhibited by warming, and respond in a graded manner to noxious heat and pinch. The present data quantify these different response characteristics and clearly distinguish the cold sensitivity of HPC lamina I STT cells from that of COOL cells by demonstrating their significantly lower (colder) thresholds and their accelerating activity to noxious cold, which contrasts with the saturation of COOL cell activity below ~15°C (Fig. 20). The present data also quantitatively distinguish HPC cells from NS cells because the population of HPC cells has significantly higher heat thresholds and a steeper mean response function. Similarly, the mean response of HPC cells to pinch seems to have a higher threshold than that of NS cells.

These selective response properties probably reflect afferent input from selective categories of primary afferent fibers as discussed in detail in the following text. As shown previously using electrical stimulation of the skin and hindlimb peripheral nerves in the cat (Craig and Kniffki 1985; and confirmed during the course of the present experiments), NS cells receive predominantly Aδ-fiber input, while HPC cells are dominated by monosynaptic C-fiber input, and COOL cells respond to both Aδ- and C-fibers. [Cervero et al. (1979) similarly divided lamina I nociceptive cells into class 3a (with Aδ input) and class 3b (with Aδ and C input), but they could not distinguish HPC cells because they did not utilize cold stimuli.] Selective primary afferent convergence onto lamina I STT cells is convincingly highlighted by our recent demonstration of histamine-selective cells, which seem to receive monosynaptic input exclusively from a distinct subset of C-fibers (Andrew and Craig 2001). Such neurons are also distinguished by their unique central conduction velocities, and as confirmed in the present experiments, the central conduction velocities of COOL, HPC, and NS cells are also significantly different (see Craig and Kniffki 1985; Craig and Serrano 1994; Dostrovsky and Craig 1996): the NS cells conduct very slowly, many in the range of unmyelinated axons, whereas the HPC and COOL cells conduct progressively faster, consistent with small myelinated fibers. The statistical significance of the pairwise differences in conduction latencies among COOL, HPC, and NS lumbosacral lamina I TSTT cells, even within small subsets of these data (e.g., Andrew and Craig 2001; Craig and Dostrovsky 2001; Craig and Serrano 1994), indicates anatomical differences between these cell classes.

Anatomical differences are directly revealed by the demonstration that COOL cells have significantly different thalamic projections from nociceptive (HPC and NS) cells in the cat (Craig and Dostrovsky 2001; Dostrovsky and Craig 1993) and by recent observations, based on intracellular labeling in the cat, indicating that the somata of these physiological classes of lamina I cells are morphologically distinct: NS lamina I cells are fusiform neurons, COOL cells are pyramidal neurons, and HPC cells are multipolar neurons, as viewed in horizontal sections (Han et al. 1998; see also Light and Willcockson 1999). This anatomical and physiological correspondence is supported as well by evidence in the primate (Craig et al. 1999; Yu et al. 1999). The present physiological observations on the central conduction velocities of these cell classes directly support these anatomical correspondences because Golgi studies reported that fusiform lamina I cells have unmyelinated axons, whereas pyramidal and multipolar cells have myelinated axons (Gobel 1978; Lima and Coimbra 1986).

Furthermore the present data confirm earlier reports that these cell classes have different spontaneous discharge rates (see Andrew and Craig 2001; Craig and Kniffki 1985), which probably also reflects their different afferent inputs. In addition, these cell classes respond differently to descending and pharmacological modulation: COOL cells are not inhibited by brain stem stimulation, whereas NS cells are (Dawson et al. 1981; Dostrovsky et al. 1983); COOL lamina I STT cells are not inhibited by morphine, whereas both NS and HPC cells are (Craig and Hunsley 1991; Craig and Serrano 1994); and, most fusiform and multipolar lamina I STT cells bear NK-1 receptors, whereas few pyramidal cells do (Yu et al. 1999).

These three classes do not include all lamina I TSTT cells. The lamina I STT projection seems to constitute an interoceptive (or homeostatic) afferent pathway comprising several distinct modality-selective sensory channels that carry activity representing different aspects of the physiological condition of all tissues of the body (Craig 1996; Craig and Dostrovsky 1999; Craig et al. 2000). Additional classes of lamina I STT cells that are selectively chemo-sensitive (Andrew and Craig 2001) or responsive to warmth (Craig and Dostrovsky 2001; Dostrovsky and Hellon 1978) or to deep (muscle, joint) input (Craig and Kniffki 1985) have been documented, whereas others may be visceroreceptive, metaboreceptive or responsive to C-fiber mechanoreceptors, although these have yet to be studied in sufficient detail (Cervero and Tattersall 1987; Light and Wilcockson 1999; Rosas-Arellano et al. 1999; Urban and Gebhart 1999; Vallbo et al. 1999; Wilson and Hand 1997).

Together all of these differences substantiate the conclusion that the three categories of COOL, HPC, and NS lamina I STT cells form robust and biologically distinct classes of ascending sensory neurons that receive input from specific classes of modality-selective afferent fibers. This conclusion is consistent with the concept that these classes constitute “labeled lines” whose activity may correspond directly to psychophysically distinct sensations. As discussed in the following text, the COOL cells are clearly a unique component of the STT that provide a substrate for discriminative thermal sensibility (Craig et al. 2000); the HPC cells provide a reasonable and quantitative explanation for the thermal grill illusion of pain, which

![FIG. 20. Composite of the mean population response curves of all 3 main classes of lamina I STT cells.](http://jn.physiology.org/)

\[\text{J Neurophysiol • VOL 86 • SEPTEMBER 2001 • www.jn.org}\]
produces a sensation that mimics the burning sensation of noxious cold (Craig and Bushnell 1994; Craig et al. 1996); and the NS cells are uniquely selective for noxious mechanical stimuli and/or cutaneous heat. The specificity inherent in the lamina I STT projection is underscored by the histamine-selective lamina I STT cells we have recently documented, which clearly have the distinguishing characteristics of a labeled line for itch (Andrew and Craig 2001). Furthermore preliminary evidence with novel, sophisticated paradigms suggests that NS cells can be associated with the psychophysically distinguishable sensation of “first” (sharp) pain and HPC cells with “second” (burning) pain (see following text) (Andrew and Craig 1999; Craig and Andrew 1999).

However, the association of these cell classes with distinct sensations cannot be made without first comparing the quantitative response characteristics of these cells with the psychophysical characteristics of primary afferents and with the psychophysical characteristics of pain and temperature sensations. Furthermore these putative associations are necessarily qualified by the recognition that the activity of these cells must be integrated in the forebrain with the concomitant activity of other types of cells that project rostrally in the STT and in other pathways (Craig and Dostrovsky 1999; Price 1988; Willis 1985).

**Comparison with prior lamina I cell and primary afferent recordings**

**COOL cells.** Quantitative data on trigeminal thermoreceptive-specific COOL lamina I neurons were obtained in several prior studies (Davies et al. 1985; Dickenson et al. 1979; Hutchison et al. 1997; Poulos 1981), including lamina I trigemino-thalamic cells (Dostrovsky and Hellon 1978). Although many authors have taught that peripheral cold-specific afferent fibers have bell-shaped response functions with reduced activity at low temperatures (e.g., Darian-Smith 1984; Iggo 1969), work in the laboratories of both Hellon and Poulos first revealed that many trigeminal lamina I COOL cells have maintained responses at cold temperatures. As these investigators suggested, this probably reflects convergent input from cold-specific primary afferent fibers having a continuous range of thresholds and response maxima, that is, ranging from the most sensitive fibers that have high response maxima and reduced responses at lower temperatures (Iggo 1969) to the least sensitive fibers that only respond at low (cold) temperatures (Duclaux et al. 1980; LaMotte and Thalhammer 1982). The convergent input to COOL cells also produces receptive fields that are considerably larger than those of cold-specific primary afferent fibers, and it obscures the pronounced bursting activity often described in cold-specific afferents. On the other hand, lamina I COOL cells (with unidentified projections) having bell-shaped response curves have been repeatedly observed in the trigeminal nucleus caudalis (e.g., Davies et al. 1985; Hutchison et al. 1997; Poulos 1981); although our paradigm did not incorporate the long adaptation times (>3 min) used in many prior studies, we encountered only one such lamina I STT cell in the cat’s lumbosacral cord. Hutchison et al. (1997) separated trigeminal COOL cells in the rat into three types, distinguishing those with bell-shaped response curves from others having weaker or stronger dynamic responses; however, neither of these characteristics distinguished subsets of COOL lamina I STT cells in the present study. An unexpected statistical distinction was found between cells that were sensitive to the first cooling step but had a decelerating response curve and cells that had colder thresholds and a steeper response function; these differences could be explained by the selective convergence of cold-specific afferents that innervate the epidermis or the dermis, respectively (Ivanov et al. 1982; see also Hensel 1981), but the biological significance of this distinction depends on its thalamo-cortical processing. Nonetheless the present data demonstrate clearly for the first time that the mean population stimulus-response function of COOL lamina I STT cells shows a very linear output over the entire range of cooling sensation and that the output is maintained at a near constant level below this range. These characteristics strongly parallel the available psychophysical evidence, as described in the following text.

**HPC cells.** Although the original reports of lamina I units described cells responsive both to cooling and to noxious stimuli, most intervening studies did not utilize cold stimuli. As a result, polymodal nociceptive lamina I STT HPC cells were not distinguished in nearly all prior studies, and there is almost no prior quantitative data (Craig and Bushnell 1994; Craig and Serrano 1994). We have identified HPC lamina I STT units also in the monkey (Dostrovsky and Craig 1996), whereas cells having similar polymodal sensitivity were classified in prior studies as “high-threshold” (Willis et al. 1974; however, see Discussion in Kumazawa et al. 1975) or as “wide dynamic range” (Ferrington et al. 1987; Price et al. 1976). Lamina I spinoparabrachial neurons with similar polymodal responses were also described in the rat by Bester et al. (2000), though they were classified as nociceptive-specific cells.

The HPC cells generally receive monosynaptic input from Aδ and C fibers (Craig and Kniffki 1985), and their qualitative response pattern seems to be dominated by input from polymodal C nociceptors that are similarly responsive to noxious heat, noxious pinch, and noxious cold (Campbell and Meyer 1996; Frohstorfer and Lindblom 1983; Georgopoulos et al. 1976; LaMotte and Campbell 1978; LaMotte and Thalhammer 1982; cf. Kumazawa and Perl 1978). Two subpopulations of HPC cells with different thresholds to cold stimulation were statistically distinguishable; similar to COOL cells, this could indicate selective convergence of polymodal C-fiber afferents according to the tissue depth of their receptor terminals (see Klement and Arndt 1991), though there is no apparent functional correlate for this distinction at present. The range of cold thresholds of HPC cells can explain the graded increase in the number of c-fos-labeled lamina I neurons observed with noxious cold (Doyle and Hunt 1999; Strassman et al. 1993). The increasing response curve of HPC cells at the coldest temperatures we tested clearly suggests that greater responses would be observed at even colder temperatures, although at temperatures below ~4°C, the abrupt activation of Aδ nociceptors (due to tissue freezing) predicts the likely recruitment of NS neurons (Beise et al. 1998; Simone and Kajander 1997).

The present description of the responses of HPC lamina I STT cells to noxious heat shows that they have a median threshold of ~45.5°C and a steeply graded response function, consistent with activation by heat-sensitive C-fiber nociceptors (see Campbell and Meyer 1996). Two classes of heat-respon-
vise nociceptors with C-fibers have been identified, heat-spe-
cific (Baumann et al. 1991; Beck et al. 1974; Lynn et al. 1995) and
mechano-heat or polymodal (Beck et al. 1974; Bessou and
that innervate the glabrous skin of the cat’s hindpaw with
radiant heat, found that most fibers had thresholds in the range
40–45°C and encoded temperatures between 45 and 60°C
fairly linearly (slope \(\sim 0.3 \text{ Hz°C}^{-1}\)). They reported that about
half of the C-fiber nociceptors were also responsive to noxious
mechanical stimuli (pinching or pricking) and thus were likely
polymodal nociceptors, whereas the other half were heat-spe-
cific, a proportion that is high in comparison to later studies
(Baumann et al. 1991; Lynn et al. 1995; Schmelz et al. 2000).
Although the HPC neurons respond to heat, pinch and cold,
similar to polymodal C nociceptors, it seems likely that they
receive convergent input from heat-specific C nociceptors,
because their heat-evoked responses were usually greater
than those produced by cold or pinch. In addition, they might
receive input from insensitive C-fibers, which can respond to
heat after repeated stimuli (Campbell and Meyer 1996;
Schmelz et al. 2000). Clearly, there is spatial summation and
amplification due to considerable convergence of C-fiber
nociceptors onto HPC lamina I STT neurons because the sensi-
tivity (slope) of the heat-evoked stimulus-response function of
HPC neurons is greater than the reported characteristics of
these types of primary afferent nociceptors and because their
receptive fields are larger.

The present data also show that HPC lamina I STT cells
respond to quantitative pinch stimuli with thresholds and lin-
early graded responses that are consistent with selective acti-
bation by nociceptors. These responses are compared with
prior lamina I and primary afferent recordings together with
those of NS cells in the following text.

**NS Cells.** Graded responses to noxious heat have been de-
scribed for NS lamina I projection cells in several prior studies
in the monkey. Price et al. (1976) described NS lamina I
trigeminothalamic cells that encoded graded noxious heat, al-
beit less well than wide dynamic range cells in the deep dorsal
horn. Bushnell et al. (1984), Ferrington et al. (1987), and
Maixner et al. (1989) reported similar findings for samples
based primarily on trigeminothalamic or STT neurons in lam-
ina I, and they also concluded that NS cells encode noxious
heat intensity, albeit less well than wide dynamic range cells.
On the other hand, Price et al. (1978) and Kenshalo et al.
(1979) found similar responses to heat across categories and
across laminae (see also McHaffie et al. 1994). In contrast,
Coghill et al. (1993) concluded that unidentified NS superficial
dorsal horn cells in the rat do not encode long-term, repeated
heat stimulation. Nevertheless, all of these studies reported NS
thresholds of \(\sim 43–47°C\) and stimulus-response curves for
identified NS lamina I projection neurons using brief stimuli
(5–30 s) that were positively accelerating near threshold and
more or less linear thereafter. However, cold stimuli were not
used to categorize lamina I cells in these prior studies, so NS,
HPC, and wide dynamic range cells may have been intermixed
(see Han et al. 1998). The present data show clearly that NS
lamina I STT cells in the cat have a sigmoid response function
to noxious heat, with a range of thresholds significantly lower
than those of HPC cells, a median threshold of \(\sim 43°C\), and a
fairly linear output between 43 and 53°C. The recent quanti-
tative data of Bester et al. (2000) on NS lamina I spino-
parabrachial neurons in the rat are nearly identical (reported
mean threshold, 43.6°C).

The data available do not resolve the afferent source of NS
heat responses. NS lamina I STT cells receive predominantly
\(\alpha\) primary afferent inputs (Craig and Kniffki 1985), however, the
\(\alpha\) mechano-heat-sensitive afferents that have been iden-
tified in the hairy skin of the monkey (Campbell and Meyer
1996) have not yet been identified in the cat (Beck et al. 1974;
Fitzgerald and Lynn 1977). One type of \(\alpha\) mechano-heat
afferent in the monkey (Type II) that exhibits short-latency
responses at thresholds \(\sim 46°C\) has been associated with “first
pain,” and such fibers could explain the heat responses of NS
cells; the difference in threshold may be due primarily to
technical measurement differences. However, NS lamina I STT
cells selectively responsive to heat have been observed re-
peatedly, whereas such responses have only been observed in
recordings from C fibers in the cat (Beck et al. 1974), in
contrast to the monkey, where heat-selective nociceptors have
been observed in A-fiber recordings (Campbell and Meyer
1996). To resolve this issue, we suggest the use of slow and
fast heat ramps to differentiate \(\alpha\) and C-fiber heat-sensitive
afferent inputs to lamina I nociceptive cells (Tillman et al.

The responses of unidentified lamina I cells and identified
lamina I STT cells to mechanical stimuli were tested in prior
studies with brushes, von Frey hairs, vibrators, clips, and
handheld or force-monitored forceps (e.g., Christensen and
Perl 1970; Craig and Kniffki 1985; Price et al. 1978; Willis
et al. 1974; Woolf and Fitzgerald 1983), and thresholds were
described variously as noxious or innocuous. However, prior
to the recent study of lamina I spino-parabrachial cells in rat
by Bester et al. (2000) and the work in this laboratory (Craig and
Serrano 1994; present study), the mechanical stimulus-re-
ponse function of only one lamina I nociceptive cell had been
reported (Fig. 8 in Price et al. 1976). In addition, Cervero et al.
(1988) applied three levels of intense pressure stimulation to
the rat’s tail and reported that NS lamina I neurons (with
unidentified projections) encode mechanical stimulus intensity
better than “class 2” (wide dynamic range) lamina V cells.

The present data show that identified NS and HPC lamina I
STT cells respond to force-monitored, quantitative pinch stim-
uli with thresholds and linearly graded responses consistent
with selective activation by nociceptors. The recent data of
Bester et al. (2000) on rat NS lamina I spino-parabrachial cells
seem very comparable; despite technical differences, they also
found mechanical thresholds at about human pain threshold
and a fairly linear response function (on a semi-logarithmic
plot, approximating a sigmoid curve).

However, the data available are insufficient to determine
whether the mechanical responses of NS or HPC cells reflect
A- or C-fiber activation. Until quite recently, very little data
were available on the quantitative graded mechanical charac-
teristics of cutaneous nociceptors. Garell et al. (1996), who
studied nociceptors in cat hairy skin, and Andrew and Green-
span (1999), who studied nociceptors in rat glabrous hindpaw,
used force-controlled stimuli with probes of different tip sizes
to obtain families of stimulus-response curves that differenti-
ated the mechanical response properties of A- and C-fiber
nociceptors. These and other studies (Cooper et al. 1991; Slugg et al. 2000) indicate that A-fiber nociceptors encode the spatial and intensive aspects of noxious mechanical stimuli better than C-fiber nociceptors because the A-fiber nociceptors have steeper response functions that differentiate probes of different surface area and because C-fiber nociceptors tend to have responses that plateau at higher stimulus intensities. The present limited samples of HPC and NS lamina I STT cells have stimulus-response functions to pinch that are similar and show only a slight threshold difference. To resolve this issue, we suggest that refined stimuli like those of Greenspan and colleagues should be used to study these neurons. Indeed, preliminary evidence obtained with a simplified version of their protocol suggests that the mechanoreceptive characteristics of NS and HPC lamina I STT neurons are distinguishable and can be directly related to A- and C-fiber activation, respectively (Andrew and Craig 1999) (see following text).

Comparison with human psychophysical characteristics

The stimulus-response functions of each of these classes of lamina I STT cells for each modality showed a remarkably linear response region. All of the linear regressions had a correlation coefficient near $r \approx 0.6$ based on absolute discharge frequency, which improved to $r \approx 0.8$ if based on a normalized response function. Although we prefer the absolute rate measure a priori, a choice between these two response functions can only be based on the properties of the thalamic and cortical cells that are activated by these STT cells, along with appropriate behavioral comparisons. We briefly compare these data with human psychophysical results in the absence of comparable physiological data on lamina I STT cells in the primate.

COOL CELLS AND THE SENSE OF TEMPERATURE. The COOL cell response function was linear between 34 and 15°C and nearly flat below that. This is directly comparable to the linear magnitude estimation function of humans over this range (see Fig. 5 in Darian-Smith 1984) and also to the relatively flat, maintained sensation of cold in the noxious cold range below $\sim 15°C$ (Chen et al. 1996; Chery-Croze 1983). Similarly, a linear increase in regional cerebral blood flow between 34 and 20°C has been measured with positron emission tomography only in the cortical terminus of the lamina I STT pathway in humans (Craig et al. 2000). Although different cooling thresholds are obtained using different methods (e.g., Yarnitsky and Sprecher 1994), psychophysical data obtained with stimulus parameters similar to those we used indicate coolness thresholds of $\sim 1.2$–$2.0°C$ on the human hand (Greenspan et al. 1993; Hilz et al. 1995), which is equivalent to the $\sim 1.5°C$ temperature difference that could be differentiated reliably by the mean response function of COOL cells ($\sim 0.8°C$ for the normalized mean). Paired, forced-choice tests with brief stimulus pulses produce detection thresholds $\sim 0.1°C$ (Chen et al. 1996; Darian-Smith 1984), and comparable sensitivity has been noted for trigeminal COOL cells (Craig et al. 1999; Dostrovsky and Hellon 1978), although a direct quantitative comparison would require equivalent tests on COOL lamina I STT cells. The sensitivity to the rate of cooling changes in lamina I COOL cells was also found to parallel human psychophysical reports (Davies et al. 1983). Thus the response characteristics of COOL lamina I STT cells support the conclusion that they constitute a discrete sensory channel for innocuous thermal (cooling) sensation. There seem to be no other ascending neurons that show comparable sensitivity to innocuous temperatures, with the exception of WARM lamina I STT cells, characterization of which is needed yet to complement this analysis (Andrew and Craig, unpublished results).

HPC CELLS AND THE SENSATION OF COLD PAIN. The stimulus-response function of HPC cells to cold had a median threshold of $\sim 24°C$ and showed a fairly linear increase at colder temperatures. Prior analyses using the thermal grill illusion of pain provided evidence indicating that the burning sensation of noxious cold results from HPC lamina I STT activity that is normally inhibited in the forebrain by COOL lamina I STT activity (Craig and Bushnell 1994; Craig et al. 1996). Human psychophysical studies (Chen et al. 1996; Chery-Croze 1983; Wolf and Hardy 1941) clearly document that the perceptual attributes of cold pain are distinct from those of innocuous cooling and heat pain, and that, while thresholds for cold pain vary over a wide range, the median threshold appears to be $\sim 15°C$, at which temperature HPC cell activity is accelerating and COOL cell activity becomes saturated. At temperatures below (colder than) the threshold for cold pain, human perception of cold shows little change, but the sensation of pain increases linearly. In addition, studies in humans and monkeys have recently shown that the slope of the psychophysical response function for cold pain is significantly lower (i.e., has a larger detection limen) than that of the sensations of innocuous cooling or heat pain, and also that the pain intensity or unpleasantness of a noxious cold stimulus of $\sim 10°C$ is similar to that of a noxious heat stimulus of $\sim 47°C$ (Morin and Bushnell 1998; Rainville et al. 1999). The present quantitative data on the thresholds, slopes, and intensities of the responses of HPC cells parallel these findings in all respects. Thus our findings support the concept that the burning sensation of cold pain is engendered by HPC lamina I STT activity, integrated at thalamo-cortical levels with COOL lamina I STT activity. This is also consistent with the parallel inhibition of cold pain and of HPC lamina I STT cells by systemic and topical morphine (Craig and Serrano 1994; Han and Craig 1993). Note that this concept can also explain why ambient temperatures below $\sim 24°C$ generate an increasing sense of thermal (or homeostatic) discomfort (see Craig 1996). Nevertheless, the unexplored forebrain integration of HPC activity with the activity of lamina V STT cells that can also respond to noxious cold (below $\sim 15°C$), noxious heat and pinch in the monkey (Kenshalo et al. 1982) at present qualifies this conclusion.

HPC AND NS CELLS AND THE SENSATION OF HEAT PAIN. The stimulus-response functions to heat of both HPC and NS lamina I STT cells were sigmoidal curves with steep, linear increases between 45 and 53°C. Based on the measured 95% confidence limits of the linear regressions over the working range of these stimulus-response functions, the HPC population could reliably ($P < 0.05$) distinguish steps of $\sim 1.3°C$ ($\sim 0.8°C$ for the normalized mean), whereas the confidence limits for the NS population were larger at $\sim 1.7°C$ and $\sim 1.9°C$ for the normalized mean. The human pain report is described as linear above threshold by many investigators (Handwerker and Kobil 1993; Hardy et al. 1952; LaMotte and Campbell 1978; Robinson et al. 1983), although others who include the threshold region describe heat pain...
sensation as an accelerating power function (see Price 1988). With regard to heat pain discrimination, Hardy et al. (1952) described a "doll" scale for measuring heat pain with steps of −0.8°C, and Taylor et al. (1993) found that the difference between "slight pain" and "moderate pain" was reproducibly reported at steps of ∼1.1°C. [In addition, paired forced-choice tests in humans and monkeys indicate detection thresholds for heat pain of ∼0.1–0.4°C (Bushnell et al. 1983; Robinson et al. 1983), but further experiments are needed to compare the activity of HPC and NS cells with such results.] Although the NS and HPC heat-response curves could not be statistically distinguished, the median threshold of HPC cells was ∼45.5°C, whereas that of NS cells was significantly lower at ∼43°C, and the inflection points in the respective sigmoidal models (Figs. 12 and 18) are also offset. Similarly, humans describe heat at temperatures slightly below pain threshold as "pricking," as "heat" or as "prepain" but describe temperatures above a threshold of ∼45.5°C as "burning" pain (Boring 1942; Handwerker and Kobal 1993; Hardy et al. 1952; LaMotte and Campbell 1978). These parallel characteristics suggest that the C-fiber-dominated HPC lamina I STT cells may be associated with "second" pain, that is, the burning sensation above heat pain threshold, and that the Aδ-dominated NS lamina I STT cells may be associated with "first" pain, that is, the pricking heat sensation at temperatures below and near pain threshold. To address this question, we suggest that these associations be tested with the repeated brief contact heat paradigm recently refined by Vierck et al. (1997), who showed that, at sufficiently short interstimulus intervals and sufficiently high temperatures, repeated heat stimuli cause a selective increase in second pain reports accompanied by a reduction in first pain sensation (see also Price et al. 1978), and that this summation can be "re-set" at short intertrial intervals. Indeed, preliminary evidence using this paradigm suggests that HPC, but not NS, lamina I STT cells show responses that parallel this phenomenon (Craig and Andrew 1999).

HPC AND NS CELLS AND THE SENSATION OF MECHANICAL PAIN. The sensation of mechanical pain (pinch) is certainly distinguishable from thermal pain. However, as noted in the preceding text, there is little evidence available on the stimulus-response functions of primary nociceptors, central neurons or human perception to graded mechanical stimulation, and the present limited data set is insufficient to distinguish the role of NS neurons from that of HPC neurons in mechanical pain sensation. Recently, Greenspan and colleagues initiated use of a refined set of stimuli (Andrew and Greenspan 1999; Garett et al. 1996; Greenspan and McGillis 1991, 1994) and reported that mean pain threshold in humans is ∼100 g/mm² with probes tips having area on the order of 1 mm² and that pain sensation increases fairly linearly with increasing stimulus intensity. Notably, a differentiable sensation of "sharpness" was reported with thin probes below pain threshold. With the 3 mm² pincher used in the present study on glabrous skin, the stimulus-response functions for mechanical stimulation of NS and HPC units increased linearly above thresholds of ∼300 g (NS) or ∼400 g (HPC) or ∼100–125 g/mm². Thus the present data are consistent with the view that the response properties of NS and HPC lamina I STT cells parallel human mechanical pain perception. This comparison again recommends use of the more refined stimulus protocol of Greenspan and colleagues to extend the present characterization of lamina I STT neurons, which should enable differentiation of the functional roles of different classes of nociceptive spinal neurons in mechanical nociception. Preliminary evidence using their protocols suggests that NS, but not HPC, lamina I STT cells show responses that parallel Aδ nociceptor activity and the sensation of first pain (Andrew and Craig 1999). In addition, such experiments could elucidate prior evidence (Cervero et al. 1988) that implicated NS lamina I cells in the temporal augmentation of maintained noxious mechanical stimuli, an as yet unexplained characteristic of human pain sensation (Adriaensen et al. 1984; Andrew and Greenspan 1999; see also Schmidt et al. 2000).

Conclusions

The present results quantitatively differentiate the characteristics of the three main classes of lamina I STT cells in the cat (COOL, HPC, and NS), thereby validating the qualitative distinctions in their modality selectivity and corroborating the many other features that distinguish these cell classes. The response characteristics of these neurons parallel available psychophysical data on temperature and pain sensations, and thus our findings provide strong evidence consistent with the conclusion that these neurons constitute biologically distinct classes that receive input specifically from subsets of modality-selective afferent fibers and whose activity corresponds directly with psychophysically distinct sensations. These results support the view that lamina I STT neurons provide discrete ascending sensory channels, or "labeled lines," for pain, temperature and itch sensations. Additional experiments are in progress, using more refined stimulus paradigms, that can significantly extend these results, further differentiate these neurons from other types of ascending cells, and directly test this hypothesis in cats and monkeys.

We thank colleagues who participated in these experiments over the past several years: M. C. Bushnell, J. O. Dostrovsky, Z.-S. Han, S. Hunsley, M. Karpuchina, B. Lumb, and L. Serrano.

Support for this laboratory was provided by National Institutes of Health Grants NS-25616 and DA-07402 and by the Atkinson Pain Research Fund administered by the Barrow Neurological Foundation.

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