Area 3a Neuron Response to Skin Nociceptor Afferent Drive

Area 3a neurons are identified that respond weakly or not at all to skin contact with a 25–38°C probe, but vigorously to skin contact with the probe at ≥49°C. Maximal rate of spike firing associated with 1- to 7-s contact at ≥49°C occurs 1-2 s after probe removal from the skin. The activity evoked by 5-s contact with the probe at 51°C remains above-background for ~20 s after probe retraction. After 1-s contact at 55–56°C activity remains above-background for ~4 s. Magnitude of spike firing associated with 5-s contact increases linearly as probe temperature is increased from 49–51°C. Intradermal capsaicin injection elicits a larger (~2.5×) and longer-lasting (100×) increase in area 3a neurons response rate than 5-s contact at 51°C. Area 3a neurons exhibit enhanced or novel responsivity to 25–38°C contact for a prolonged time after intradermal injection of capsaicin or α, β methylene adenosine triphosphate. Their 1) delayed and persisting increase in spike firing in response to contact at ≥49°C, 2) vigorous and prolonged response to intradermal capsaicin, and 3) enhanced and frequently novel response to 25–38°C contact following intradermal algogen injection or noxious skin heating suggest that the area 3a neurons identified in this study contribute to second pain and mechanical hyperalgesia/ailodynia.

**Keywords:** hyperalgesia, neurophysiology, nociception, pain, primary somatosensory cortex

**Introduction**

Observations obtained using the method of near-infrared optical intrinsic signal (OIS) imaging prompted Tommerdahl et al. (1996) to propose that neurons in cytoarchitectonic area 3a in contralateral anterior parietal cortex are selectively responsive to noxious skin-heating stimulation. This proposal and the corollary suggestion that the spike discharge activity of area 3a neurons underlies aspects of pain perception in both human and nonhuman primates (Tommerdahl et al. 1998; Whitisel et al. 2000) are not widely accepted. Perhaps the most significant concern which confronts the proposal that area 3a neuronal activity contributes to pain perception is that, due to limitations in sensitivity and spatial resolution, results obtained using the method of OIS imaging may not accurately reflect the true cytoarchitectural locus of the neuronal spike discharge activity evoked by noxious skin stimulation (Kenshalo et al. 2000).

The goal of this study was to obtain evidence which would clarify existing uncertainty about: 1) whether, 2) to what extent, and 3) how reliably area 3a neuron spike discharge activity alters in response to stimuli that activate skin nociceptors. The initial experiments demonstrated that a subpopulation of area 3a neurons in the contralateral hemisphere responds unambiguously and reliably to transient noxious skin-heating stimulation. Subsequent experiments acquired information about 1) the effects on nocireponsive area 3a neurons spike discharge activity of conditions of thermo-mechanical skin stimulation shown by previous studies to be effective for eliciting and characterizing 2nd or “slow” pain perception in humans; 2) the spatial distribution of nocireponsive neurons within area 3a; and 3) the effects of selective activation of C-nociceptors (by capsaicin or α, β methylene adenosine triphosphate [ATP]) on the “spontaneous” and stimulus-evoked spike discharge activity of area 3a neurons.

Several of the findings have been reported in preliminary communications (Li et al. 2000, 2001, 2002, 2003; Favorov et al. 2007).

**Materials and Methods**

All methods and procedures were approved in advance by an institutional animal care and use committee (IACUC) and are in full compliance with National Institutes of Health policy on animal welfare.

**Subjects, Anesthesia, Surgical Procedures, Euthanasia**

Subjects were adult male and female squirrel monkeys (*Saimiri sciureus* and *peruviensis, n = 10*). The subject was placed in a light-tight enclosure and general anesthesia induced with a gas mix (4% halothane in a 50/50 mixture of oxygen and N₂O). Tubing connecting a veterinary anesthesia machine to an external port on the enclosure enabled delivery and effective confinement of the anesthetic gas mix to the interior of the enclosure. After induction of anesthesia the subject was removed from the enclosure and placed on a surgical table. The trachea was intubated and connected via tubing to the anesthesia machine. Methylprednisolone sodium succinate (20 mg/kg) and gentamicin sulfate (2.5 mg/kg) were injected intramuscularly to protect against cerebral edema and bacterial septicemia, respectively.

The composition of the anesthetic gas mix was adjusted (1.5–3.0% halothane in 50/50 N₂O/oxygen) to ensure maintenance of adequate and stable general anesthesia throughout performance of the following procedures. A valved polyethylene cannula filled with saline was inserted into the femoral vein of the subject’s right hindlimb to enable administration of drugs, glucose (5%), and electrolytes (0.9% saline). A 1–1.5 cm² opening was made in the skull overlying the central sulcus in the right hemisphere, and a cylindrical Lexan recording chamber placed over the opening and attached to the surrounding skull with dental acrylic. The dura was incised and removed, and the recording chamber filled with artificial cerebrospinal fluid and sealed with a glass plate to prevent cortical dehydration. Sensory input from tissues within the surgical fields on the head (in the vicinity of the recording chamber) and right hindlimb was minimized by topical application of local anesthetic in oil (Cetacaine), and skin wounds were closed with silk sutures.

After completion of the surgical procedures neuromuscular blockade was achieved by intravenous administration of Norcuron (loading dose: 0.25–0.5 mg/kg; maintenance dose: 0.025–0.05 mg/kg/h). For the remainder of the experiment a 50/50 mix of N₂O and oxygen was...
provided via a positive pressure ventilator, and the halothane concentration adjusted (typically between 0.5% and 1.0%) to maintain heart rate, arterial blood pressure (recorded noninvasively using pressure plethysmography—blood pressure monitoring system BP-3Plus, VetSpecs, Canton, GA), and electroencephalography slow-wave content at values consistent with general anesthesia. Rate and depth of ventilation were monitored and adjusted to maintain end-tidal CO₂ between 3.0% and 4.5%. Rectal temperature was maintained at 37.5 °C with a heating pad. Euthanasia was achieved by injection of pentobarbital (50 mg/kg; i.v.), followed by intracardial perfusion with 0.9% NaCl, and subsequently with fixative (10% formalin in saline).

**Neurophysiological Recording Methods**

Extracellular recordings of the spike discharge activity of area 3a neurons and small neuron groupings were obtained using glass-insulated tungsten wires (impedance 300–500 kΩ at a test frequency of 10 kHz). Micropositioners enabled placement of the tip of recording microelectrode at any site within the hydraulically sealed chamber. A microdrive was used to advance (through an "O-ring" in the glass coverplate) the microelectrode tip from a point above the cortical surface to intracortical position(s) at which neuronal spike discharge activity was detected. At the maximal depth of a penetration, and/or at a site where recordings of particular interest were obtained, an electrolytic lesion was created by passing 5–10 μA of DC current through the microelectrode. Such a lesion typically allowed post-experimental identification of the laminar location of the recording site (Fig. 1).

**Thermotactile Stimulator, Stimulation Protocols**

**Stimulator Characteristics**

The stimulator used in all experiments (CS-540, Cantek Enterprises, Canonsburg, PA) enabled simultaneous delivery of precisely controlled thermal and mechanical stimulation to a preselected skin site. The stimulator made contact with the site via a cylindrical copper probe (5 mm diameter; flattened at the tip). Probe temperature could be varied from one contact to the next, or maintained at a temperature (25–56 °C; accuracy ±0.1 °C) over a series of successive contacts. The stimulator’s control system allowed probe temperature to be modified only when the probe was not in contact with the skin. When the probe attained the desired temperature (investigator-specified via software) it was rapidly advanced (20 mm/s) from its "rest" position (~5 mm above the skin site targeted for stimulation) until the tip of the probe indented the skin by ~1 mm. The probe then remained stationary for an investigator-specified interval (1–7 s) after which the stimulator’s control system abruptly (20 mm/s) retracted the probe to the rest position. Controlling software permitted precise specification of probe temperature, duration of probe contact with the skin, number of successive contacts delivered at a given probe temperature, time interval between successively applied same-temperature contacts, and the time interval between successive contacts applied at different temperatures.

Throughout each experiment probe temperature was continuously displayed and recorded as part of the permanent experimental record. To minimize sensitization of a skin site: 1) "control" skin contact stimuli were delivered with the probe at a temperature selected from the range 25–38 °C; 2) a series of successive skin contacts was used (typically 6 when contact duration was 5–7 s; 10 contacts were used when contact duration was 1 s) to characterize the area 3a neuron response to probe temperatures ≥49 °C; 3) the probe did not contact the skin before, after, or between successive stimuli; and 4) at a probe temperature ≥49 °C a substantial no-stimulus period (never less than 30 s) separated successive contacts when contact duration was >1 s.

**Stimulation Protocols (n = 3)**

The initial experiments made extensive use of a 3-phase protocol (Protocol #1) to study the effects of 5- to 7-s heated skin contact on the spike discharge activity of area 3a neurons. First, a series of contacts was applied with the probe preheated to a temperature selected from the range 25–38 °C ("Control"). Next, a second series of contacts ("Test") was applied to the same site. The contacts in this series were identical in all respects except one to those delivered during the initial series—that is, throughout this second series the probe was maintained at a temperature selected from the range 47–51 °C. And finally, a third series of contacts ("Recovery") was reapplied to the same skin site.
once again with the probe at the temperature used in the initial series. All contacts were 5-7 s in duration. A 15-s interstimulus interval (ISI) was allowed between successive contacts in the control and recovery phases of the protocol; an ISI of 30 s separated successive contacts in each phase. A 3-min no-stimulus delay separated the control, test, and recovery phases.

A different protocol (Protocol #2) was used to assess the temperature-dependency of area 3a neurons. In this protocol the response of a neuron was recorded to 6 series of contacts delivered to the same skin site (each series consisted of 4 contacts; total contacts = 24). Each series included one contact with the probe at 38°C, 49°C, 50°C, and 51°C, respectively; order of the different-temperature contacts within a series was varied from one series to the next. A 30-s ISI separated successive contacts in the same series. A 3-min no-stimulus delay separated the last contact of one series and the first contact of the next.

The third protocol (Protocol #3; repetitive 1/3 s, 0.8- to 1.0-s contact with a 5 mm diameter skin site by a probe maintained at a temperature between 49-56°C) that was used was especially well-suited for study of the cerebral cortical mechanisms relevant to second pain. Previous studies have shown this protocol to 1) be uniquely effective for evoking second ("slow") pain in a conscious subject (Vierck et al. 1997); 2) enable clear demonstration of the slow temporal summation characteristic of second pain in humans (Vierck et al. 1997); and 3) evoke a temporal profile of spike discharge activity from lamina 1 neurons in the spinal cord dorsal horn (the initial stage of central nervous system [CNS] processing of the input from C-nociceptors) that closely resembles the temporal profile of second pain in humans (Andrew and Craig 2002). The range of probe temperatures chosen for study was based on the very different perceptual experiences that result when a site on the thenar eminence is contacted with the probe at a temperature selected from within the range 25-56°C (Vierck et al. 1997; Li et al. 2000). The investigators rated a 5-s exposure to static contact of the thenar with 25°C as "thermoneutral/nonpainful," "warm/marginally painful" at 47°C, "marginally/moderately painful" at 48°C, and as "moderately-strongly painful" at a temperature between 49.5°C and 51°C. Also relevant is the published observation (Vierck et al. 1997) that contact for 1 s by a probe maintained at 50°C evokes a delayed second ("slow") pain percept that is maximal in intensity at 1-2 s after the probe is withdrawn from the skin, and grows progressively stronger in intensity when the probe contacts the skin repetitively at a frequency > 1/3 s (exhibits prominent slow temporal summation). At no probe temperature used in the experiments described in this paper did a single or repetitive contact stimulus elicit escape when it was applied to the skin of the investigators. Nor did any of the conditions/protocols that were used result in either visually apparent skin damage or skin sensitization.

Neural Data Collection
Area 3a neuron spike discharge activity occurring before, during, and after each contact stimulus was collected, digitized (sampled at 20 kHz), and stored as an electronic file. The activity attributable to a single unit (SUR) or to small neuronal groupings composed of 2-3 neurons (MUR) was amplitude-discriminated using nonoverlapping voltage windows (2-3 units per neuronal groupings could reliably be distinguished in this way at a single recording locus). The electronic file generated for each voltage window recorded at a cortical depth registered the time of occurrence (accuracy ±100 ms) of each action potential whose peak voltage fell within that window, as well as the times of each stimulator event of interest (e.g., onset of probe contact with the skin; onset of probe withdrawal from the skin).

Use of OIS Imaging
In 7 of the 10 squirrel monkeys subjects the method of OIS imaging (Tommerdahl et al. 1996, 1998) was used initially. Images obtained with this method were used in the subsequent (neurophysiologically recording) component of the experiment to guide the placement of microelectrode penetrations. Availability of images of the cortical optical response to the same conditions of noxious skin heating used to

study the response of individual neurons ensured that extracellular recordings of neuronal spike discharge activity were obtained from the same region of anterior parietal cortex that developed a prominent (typically the maximal) OIS in response to noxious skin-heating stimulation.

The OIS imaging method was not used in the final 3 experiments because by that point it was evident that noxious heating stimulation of either the glabrous skin of the hand or foot evokes vigorous spike discharge activity from neurons within a highly consistent location in contralateral anterior parietal cortex. In each of the 7 subjects that provided OIS imaging results, the region of the primary somatosensory cortex (SI) that responded maximally to > 49°C contact with a site on the hand occupied a part of area 3a located 1-4 mm more medially than the region (in area 3b) that responded maximally to same-site 25-38°C skin contact or 25 Hz flutter; whereas the sector of area 3a that developed the maximal optical response to contact of a site on the volar foot with a probe > 49°C was located >1 mm lateral to the region (in area 3b) that responded maximally to same-site 25-38°C skin contact or 25 Hz flutter.

Area 3a Neuron Sample/Approach to Placement of Microelectrode Penetrations
Ten squirrel monkeys were studied. The spike discharge activity of 103 single neurons (SURs) or small neuronal groupings (typically 2-5; MURs) was recorded during 21 microelectrode penetrations performed in area 3a (Fig. 1A). Fourteen of the 21 penetrations traversed the area 3a region that in the same subject developed the maximal OIS in response to noxious heating of the same skin site used to evoke area 3a neuron spike discharge activity. The region of area 3a targeted by the remaining 7 penetrations was determined using a different strategy—that is, each of these penetrations was performed subsequent to determining (using extracellular recordings of neuronal spike discharge activity) the anterior parietal locus of neurons highly responsive to gentle mechanical stimulation of the volar surface of the radial hand. Once that region was identified, the position of the recording electrode was shifted anteriorly (by 1-2 mm) and medially (by 1-4 mm)—in accord with the relative locations of the distinctly different SI regions that develop a maximal OIS in response to same-site tactile versus noxious-heating stimulation (Tommerdahl et al. 1996, 1998).

Intradermal Injection of Allogen
The final 3 experiments used extracellular recording methods in combination with an approach (intradermal injection of either capsaicin or N-methyl ATP) that develops OIS imaging results, the region of the primary somatosensory cortex (SI) that responded maximally to > 49°C contact with a site on the hand occupied a part of area 3a located 1-4 mm more medially than the region (in area 3b) that responded maximally to same-site 25-38°C skin contact or 25 Hz flutter; whereas the sector of area 3a that developed the maximal optical response to contact of a site on the volar foot with a probe > 49°C was located >1 mm lateral to the region (in area 3b) that responded maximally to same-site 25-38°C skin contact or 25 Hz flutter.

The spike discharge activity of 29 area 3a neurons was recorded before, during, and for an extended period (typically >1 h) following intradermal allogen injection (capsaicin—21 neurons; N-methyl ATP—8 neurons). Recordings were obtained from each neuron in the absence of intentional skin stimulation ("spontaneous activity"), and also during and following the delivery of precisely controlled thermomechanical skin stimulation. Capsaicin or N-methyl ATP was infused in the skin 15-20 s prior to the infusion of algogen. Infusion required <5 s to complete, and at that time the needle was withdrawn.

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Histological Procedures, Identification of Cytoarchitectural Boundaries

In each subject the region of SI traversed by microelectrode penetrations was removed, fixed in 10% formalin, placed in a cryostat, and serially sectioned either in the sagittal or coronal planes. All sections were stained with cresyl fast violet and inspected microscopically to distinguish anterior parietal regions on the basis of established cytoarchitectonic criteria (Powell and Mountcastle 1959; Jones and Porter 1980; Friedman and Jones 1981; Sur et al. 1982; see Fig. 1). Boundaries between adjacent cytoarchitectonic areas were identified by scanning sections separated by no more than 300 μm. For each subject a 2-dimensional plot showing the locations of area 3a, 3b, 1, and 2 was generated using a microscope and drawing tube attachment. The sites at which recordings were made along each track were reconstructed using 1) micrometer readings of the depth at which recordings were obtained during each microelectrode penetration, and 2) depth at which a microlesion was placed in each penetration.

Results

General Attributes of Area 3a Neuron Sample

Recordings of neuronal spike discharge activity were obtained in laminae II–VI of area 3a during penetrations of cortical regions identified initially on the basis of the optical response to skin flutter stimulation, and subsequently (post mortem) on the basis of cytoarchitecture. At every area 3a recording site the initial approach to neuron classification involved assessment of the effects of hand-held “search” stimuli (i.e., skin indentation, stroking, flutter, vibration) which reliably increase the spike discharge activity of those neurons in cytoarchitectonic areas 3b and 1 (i.e., the rapidly adapting, slowly adapting, and pacinian neurons) activated at short-latency by the afferent drive that arises in cutaneous mechanoreceptors.

At most area 3a recording sites application of mechanical skin stimuli to a relatively restricted skin region (e.g., distal volar hand or foot) was accompanied by a modulation of undifferentiated population-level activity. Nevertheless, in no instance prior either to the delivery of noxious skin-heating stimulation or intradermal algogen injection did any single nocireceptive area 3a neuron or small neuron group exhibit a robust or reliable elevation of spike firing in response to a non-noxious mechanical skin stimulus. In addition, no recording of single- or multiunit area 3a neuron activity obtained in the microelectrode penetrations of this study exhibited a responsivity to any of the natural stimuli (e.g., tendon stretch, muscle palpation, joint rotation) commonly used to identify area 3a neurons that receive their main input from mechanoreceptors located in skeletal muscles, tendons or joint capsules (for review of area 3a organization/connections see Jones and Porter 1980; Huffman and Krubitzer 2001).

At every area 3a neuron recording site the thermo-mechanical stimulator was positioned so that the stimulator probe made contact with a site located centrally within the skin region from which the most vigorous population-level activity was evoked by a hand-held skin brushing or indentation stimulus. This approach is consistent with published demonstrations (Tommerdahl et al. 1996, 1998; Whitsett et al. 2000) that although the area 3a optical responses to non-noxious mechanical versus noxious skin-heating stimulation of the same skin site differ substantially in magnitude and time course, they do not differ in spatial location—the implication being that both the Aβ and nociceptor afferent drives evoked by stimulation of a skin region are projected to the same locus within area 3a (i.e., the area 3a representations of skin Aβ mechanoreceptors and nociceptors are in register).

Area 3a Neuron Stimulus Selectivity and Response Characteristics

Examples of Area 3a Neuron Response to Long-Duration (5–7 s) Skin-Heating Stimulation

The raster-type plots in the panels at the top of Figure 2 show the spike train responses of 3 representative area 3a neurons (neurons “A”, “B,” and “C”) to 5- to 7-s skin contact by the probe of the thermo-mechanical stimulator. The data summarized in the plots in Figure 2 were obtained using the first (3-phase) stimulation protocol described in Materials and Methods. In the initial phase a series of 6 skin contacts was delivered with the probe at 38°C. In the second phase the same site again was contacted 6 times in succession, but this time with the probe at 51°C. In the third phase another series of 6, 38°C skin contacts was reapplied to the same site. In all 3 phases successive contacts were separated by a 30-s no-stimulus period.

Inspection of the spike trains in Figure 2 reveals that when probe temperature was 38°C, each of these exemplary area 3a neurons failed to respond with a significant increase in spike discharge activity to 5- to 7-s contact (for each neuron in Fig. 2 compare the activity recorded in the “stimulus” vs. “post-stimulus” periods during trials 1–6). When the same skin site was contacted with the probe at 51°C (trials 7–12), however, the mean rate of spike firing that was recorded during each stimulus trial exceeded that recorded during the trials when probe temperature was 38°C.

Interestingly, not only did the mean firing rate (MFR) of each of the area 3a neurons in Figure 2 increase in response to 51°C skin contact, but on most of the 6 trials delivered at this temperature the neuron attained its maximal or near-maximal spike firing rate 1 s or more after the probe was withdrawn from the skin (solid vertical line in each panel in Fig. 2 indicates time of probe retraction). Moreover, although skin contact with the probe at 38°C initially (i.e., prior to the exposure to 51°C skin contact) was not accompanied by a significant increase of spike firing for neurons A and C, contact with the probe at 38°C after the exposure to 51°C stimulation was accompanied by a substantial elevation of spike discharge activity both during and following probe contact with the skin—see difference peri-stimulus time (PST) histograms for neurons A and C in panels at bottom of Fig. 2.

All 36 of the neurons studied using the above-described protocol exhibited an unambiguous elevation of spike discharge activity in response to 5–7 s skin contact with the probe at a temperature between 48°C and 51°C, and 24 of the 36 (67%) exhibited a novel responsivity to 38°C skin contact subsequent to the exposure to 51°C skin contact (e.g., A and C in Fig. 2). The remaining 12 neurons (33%) resembled neuron B in Figure 2 in that exposure to 6 successive contacts with the probe at 48–51°C (during trials 7–12) was not followed by a novel responsivity to contact at 38°C (in trials 13–18).

The histograms in Figure 3A summarize the data obtained from another exemplary area 3a neuron (neuron “A”) which exhibited little or no alteration of spike firing in response to 6 skin contacts at either 38°C or 49°C (2 panels at top left in Fig. 3). Unlike the approach used to study the neurons illustrated in Figure 2, probe temperature was not returned
to 38 °C after the second series of 6 contacts (phase 2) was completed. Instead, the 6 contacts delivered subsequent to phase 2 were again applied with the probe at 49 °C. Collectively therefore, this modification of Protocol #1 involved the delivery (subsequent to the initial series of 6 contacts with the probe at 38 °C) of twelve successive 5-s contacts at 49 °C. Comparison of the plots in the 4 panels of Figure 3 reveals that although this area 3a neuron's response to the initial 6 contacts at 49 °C contact was not substantially greater than its response to 38 °C contact (2 panels at top left), increasing the exposure to 49 °C stimulation (achieved by delivering an additional 6 contacts at this temperature—in trials 13–18) revealed a substantial responsivity to noxious skin heating (see superimposed PSTs and difference PST in panels at right in Fig. 3A). Figure 3B shows similar results from another area 3a neuron (recorded in a different subject) studied in the same way.

Temperature Dependency of Area 3a Neuron Response

The temperature-dependency of the response of area 3a neurons to heated skin contact was evaluated by recording the response of each member of a sample population of area 3a neurons (n = 17) to 5-s contact with the probe at a reference temperature (38 °C), and also to 5-s contact of the same skin site at each of 4 higher "test" temperatures (48 °C, 49 °C, 50 °C, or 51 °C). For more detailed description of the protocol used to study these neurons see Materials and Methods ("Protocol #2"). The 6 plots in Figure 4A show that under the above-described conditions average area 3a neuron (across-neuron; n = 17) mean rate of spike firing increases linearly and statistically significantly with increasing probe temperature during 2 temporal intervals after the onset of skin contact—that is, between 5–8 s (P = 0.0004) and 8–11 s (P = 0.0053) after stimulus onset. In addition, the plot in Figure 4B (showing how slope value of the regression varies with time after stimulus onset) demonstrates unambiguously that for this sample of 17 nocireponsive area 3a neurons the increase of spike discharge activity associated with probe temperatures between 48 °C and 51 °C developed gradually during stimulus application, peaked at 1–3 s after the probe was removed from the skin, and persisted for an additional ~10 s.

Response to Repetitive Brief Contact with a Heated Probe

Figure 5 (format same as Fig. 2) shows the spike train responses of 3 exemplary area 3a neurons to brief (0.8 s duration) repetitive skin contact stimulation (series of 10 successive contacts at a frequency of 1/3 s; "Protocol #3" in Materials and Methods). Although repetitive probe contact at 38 °C failed to significantly increase the spike discharge activity above that recorded in the absence of intentional stimulation (with the
exception of the brief OFF-response of neuron B), all 3 neurons responded with prominently increased spike discharge activity to probe contact at 55 °C. More specifically, for neurons A and B (but not neuron C) spike firing increased substantially not only during the time the 55 °C probe was in contact with the skin, but also for more than a second after the probe was retracted. For neuron C, however, mean rate of spike firing increased significantly only during the 1- to 2-s interval following probe withdrawal from the skin.

Effect of Long-Duration versus Brief Skin Contact
Each plot in Figure 6 shows the average difference (AMFR) between area 3a neuron MFRs evoked by contact of the skin with the probe at a temperature that a conscious normal human subject experiences as nonpainful (<39 °C) versus contact at a temperature (>49 °C) that normal humans reliably experience as painful. The top plot shows the data from the sample population of area 3a neurons (n = 56) studied using the repetitive skin contact protocol (i.e., 3 series of 6–10 contacts

**Figure 3.** Effects of exposure to 49 °C skin contact. (A) Superimposed PSTs (top panels) comparing MFR responses of neuron "A" to 38 °C skin contact versus 6, 49 °C contacts (top left) and versus additional 6, 49 °C contacts (top right). Difference PSTs (panels in second row from top) showing that neuron A gradually developed a substantial responsivity to 49 °C contact. (B) Observations from neuron "B" (same format/study design as in A). Arrow along ordinate indicates MFR in the absence of intentional stimulation—determined during 5- to 10-s period immediately preceding onset of stimulation protocol.
were delivered; contact duration was 0.8–1.0 s; repetition rate was 1/3 s; the lower probe temperature used to study a neuron was selected from the range 25–38 °C; the higher probe temperature was between 55–56 °C. The bottom plot shows the average (across-neuron; n = 34 neurons) difference between the area 3a neuron MFRs evoked by 5-s contact with the probe at 38 °C versus 50–52 °C (i.e., ΔMFR = MFR50-52°C – MFR38°C; the data in the bottom plot were obtained using Protocol #1).

Interestingly, the plots in Figure 6 reveal that at both durations of skin contact (1 and 5 s) the increment in the area 3a neuron MFR associated with noxious skin heating is similar (for both the 1- and 5-s stimulus conditions ΔMFR is ~8 spikes/s), and for both the 1- and 5-s contact stimuli ΔMFR was greatest during the 1- to 2-s period after the probe was withdrawn from the skin. The length of time that the area 3a neuron spike firing attributable to noxious skin heating remains elevated after probe retraction, however, is quite different for the 5- versus 1-s stimuli. Linear regression analysis of the measures of spike activity obtained following withdrawal of the stimulator probe from the skin showed that for both contact durations the increment in area 3a neuron MFR attributable to noxious skin heating (ΔMFR) decays with time (for 5-s contact: P = 0.01; for 0.8- to 1-s contact: P < 0.001), and returns to prestimulus levels at 20.2 s (5-s contact) and 3.9 s (0.8- to 1-s contact) after probe retraction.

**Figure 4.** Temperature-dependence of area 3a MFR response. (A) Solid line in each panel shows average across-neuron (n = 17) difference between the MFRs (ΔMFR) associated with the “base temperature” (38 °C) and each “test” temperature (48 °C, 49 °C, 50 °C, and 51 °C) during the indicated time interval after onset of probe contact. Dotted line in each panel shows best fitting linear regression line; β = regression slope value; P = statistical significance. (B) Regression slope value varies systematically with time after stimulus onset, and is maximal during the interval 5–8 s after stimulus onset.

**Location of Area 3a Neurons Responding to Hand versus Foot Stimulation**

Although detailed characterization of the spatial distribution of nocireponsive neurons within area 3a was not attempted, the...
experiments of this study did provide limited information relevant to this issue. For example, the 2 microelectrode penetrations illustrated in Figure 7 were performed at very different mediolateral levels of area 3a in the same subject. Each detected neurons which (like the area 3a neurons described in previous sections) responded poorly, or not at all, to skin contact at 38 °C, but elevated their rate of spike firing in response to same-site skin contact with a probe at a temperature > 49 °C (see difference PSTs in Fig. 7).

The observations illustrated in Figure 7 suggest that 1) nocireponsive neurons are widely distributed within area 3a; and 2) C-nociceptor input to area 3a is topographically organized. More specifically, the medially located penetration A encountered neurons responsive to ≥49 °C contact with sites on the volar foot, and contrariwise, the laterally located penetration B encountered neurons responsive to ≥49 °C contact with a site on the volar hand. The microelectrode penetrations illustrated in Figure 7 are representative of the penetrations performed in the other subjects of this study in that they detected nocireponsive neurons at multiple levels (i.e., in laminae III, IV, V, and VI) of the cell columns that comprise area 3a.

**Area 3a Nociresponive Neurons**

**Area 3a Neuron Response to Chemically Evoked C-Nociceptor Afferent Drive**

**Area 3a Neuron Response to Intradermal Capsaicin Injection**

The spike discharge activity of 21 area 3a neurons was recorded before, during, and for ≥1 h following intradermal injection of capsaicin. The plots in Figure 8 show, for 2 representative neurons (recorded simultaneously with the same electrode), that the area 3a neuron MFR response to capsaicin injection is prolonged and multiphasic. The data in Figure 8 show that for both of these area 3a neurons the initial phase of the response to intradermal capsaicin injection was a rapid and very large (>10× background) increase of MFR that occurred within 10–20 s of the injection. This initial phase was, in turn, followed by a return of MFR to near-background levels within 1–3 min. Furthermore, for both neurons illustrated in Figure 8 the initial phase of the capsaicin-induced MFR response was followed within the next hour by additional episodes of above-background spike firing, each lasting for ~3–5 min and separated from the next by a period of near-background activity. In addition, the spike discharge activity recorded during each episode of above-background firing was for both neurons strikingly irregular (“bursty”) in character.

The summary plot in Figure 9 shows the average (across-neuron; n = 21) time course of the initial phase of the area 3a neuron MFR response to intradermal capsaicin. Consistent with the representative observations illustrated in Figure 8, average MFR during this initial phase of the area 3a neuron response to capsaicin attained its highest value within 10–20 s of the injection, and MFR then declined irregularly over the next 60 s. Average across-neuron MFR declined to ½ the maximal value attained during the initial phase of the area 3a neuron response to capsaicin at ~51 s after the injection (downward arrow in Fig. 9).

**Effect of Capsaicin on Area 3a Neuron Stimulus Selectivity**

Twelve area 3a nocireponsive neurons were studied in a way designed to assess the impact, if any, of intradermal capsaicin
contact occurred primarily (but not exclusively) during the period after withdrawal of the stimulator probe from the skin. Comparable observations were obtained from all 12 area 3a neurons studied in the same way.

Figure 11 shows the effects of intradermal injection of another algogen (α, β methylene ATP, Hamilton et al. 1999, 2000, 2001; Tsuda et al. 2000) on the MFR of another area 3a neuron. Like the pain experience that accompanies intradermal injection of this agent in conscious humans and animals, intradermal injection of α, β methylene ATP evoked a vigorous and transient (15-20 s) increase of MFR that, in turn, was followed by a prolonged (20-50 min) period of much lower, but nevertheless above-background spike firing (top panel in Fig. 11). In addition, similar to capsaicin’s enhancement of area 3a responsiveness to skin contact at probe temperatures below 40 °C (Fig. 10), intradermal injection of α, β methylene ATP not only enhanced this area 3a neuron’s response to 38 °C skin contact (0.3 s duration), but was followed by an above-background elevation of MFR that on each stimulus trial occurred 1-1.5 s after the probe was withdrawn from the skin (for example, see PSTs and ΔPST in middle and bottom panels of Fig. 11).

Effects of Capsaicin on Area 3a Neurons are Reversed/Reduced by Local Anesthesia
Figure 12 summarizes the findings from a nociceptive area 3a neuron studied using the 3-phase, repetitive (1/3 s) brief contact (1 s) protocol (Protocol #3) described in Materials and Methods. The first and third phases of this protocol each consisted of a series of 10, 1-s contacts delivered with the stimulator probe at 25 °C (the “control” and “recovery” phases, respectively); in the second phase a series of 10, 1-s contacts was delivered to the same skin site with the probe at 56 °C (the “test” phase).

Although the spike discharge activity of the neuron in Figure 12 increased to above-background levels in association with both the onset and termination of each skin contact at 25 °C, contact of the same site at 56 °C consistently was accompanied by a more prominent and biphasic increase in MFR associated with the termination of probe contact with the skin (see PSTs and ΔPST in panels on left of Fig. 12). The plots in the center panels of Figure 12 demonstrate that intradermal capsaicin injection was followed by a substantial increase of this area 3a neuron’s initially limited responsivity to 25 °C skin contact. Notably, although the temporal profile of this neuron’s postcapsaicin response to 25 °C skin contact strongly resembles the profile of its precapsaicin response to 56 °C skin contact before capsaicin.

The plots in the panels on the right of Figure 12 were obtained 10-20 min after intradermal injection of local anesthetic (25 μL of 1% Xylocaine; the injection was placed at a location midway between the capsaicin injection site and the site contacted by the stimulator probe). Inspection of the plots (PSTs and ΔPST) on the right in Figure 12 reveals that the local anesthetic eliminated the capsaicin-induced enhancement of this area 3a neuron’s response to 25 °C contact (just as it eliminates capsaicin-induced hyperalgesia in humans—Gottrup et al. 2000). Notably absent in the response to 25 °C contact after local anesthetic injection is the substantial poststimulus elevation of MFR which was quite prominent...
prior to the injection of local anesthetic. Results consistent
with those in Figure 12 were obtained from 3 other area 3a
neurons studied in the same way.

Quantification of Stimulus Selectivity of Nociresponsive
Area 3a Neurons

Recordings of spike discharge activity were obtained from
19 area 3a neurons over a period of time (1.5--2 h) sufficient to
assess each neuron’s response to 1) repetitive contact of a skin
site (6--10 contacts at 1/3 s; each contact 1 s in duration) with
the stimulator probe at 38 °C ("Tap"); 2) repetitive contact
(same parameters as above) of the same site with the probe at
55--56 °C ("Hot-Tap"); and, finally, 3) intradermal injection of
capsaicin ("CAP") at a site located 5--10 mm adjacent to the site
contacted by the stimulator probe. For each of these 19 neurons
average MFR was computed for the period just prior to
stimulus application, and also for the period between onset of
38 °C skin contact and 2.0 s after stimulus termination. The
response to capsaicin injection was measured as the largest
MFR recorded during any 1-s period following the injection.
For purposes of statistical analysis each neuron’s spontaneous
MFR, and the MFRs associated with Hot-Tap and CAP
were normalized by its MFR response to Tap. The bar plot in
Figure 13 summarizes the findings.

Statistical analysis of the across-neuron findings in Figure 13
yielded outcomes fully consistent with the idea that area 3a
nocireceptive neurons exhibit a pronounced stimulus select-
itivity (i.e., the response to mechanical contact is poor relative
to the response to noxious skin heating) prior to an exposure
to vigorous skin C-nociceptor afferent drive (as evidenced in
Figs 2--12). In particular, the response of the sample population
of 19 area 3a neurons, summarized in Figure 13, to 55--56
°C contact was 1.55 ± larger (P < 0.01) than the response of the
same neurons to 38 °C contact. Of the 3 stimulus conditions
evaluated (Tap, Hot-Tap, CAP), the largest elevation of area 3a
neuron MFR was evoked by intradermal capsaicin (the MFR
response to CAP was 4.35 ± larger than the response to 38 °C skin
contact; P < 0.01). Interestingly, the average across-neuron
MFR response to CAP exceeded by 2.81 ± the response to Hot-
Tap, P < 0.01), an outcome that closely parallels Simone et al.’s
(1989) report that the magnitude of pain evoked by in-
tradermal capsaicin injection in humans is on average 2.6×
more intense than the pain produced by locally heating the
skin to 51 °C for 5 s. Furthermore, the average MFR response of
this sample population of area 3a neurons to 38 °C skin contact
was not statistically different than the average MFR recorded in
the absence of intentional skin stimulation ("spontaneous
activity"/SPONT).
Contending Views
There is widespread agreement that each of the widely recognized classes of mechanoreceptive neurons in areas 3b and 1 contributes importantly and differentially to tactile perception, but opinion about the contribution(s) of area 3b/1 neurons to nociception and pain remains sharply divided. The currently prevalent view is that a subpopulation of 3b/1 neurons distinct from those that process mechanoreceptive afferent drive responds to noxious skin stimulation and accounts for the sensory-discriminative aspects of pain perception. This view derives from pioneering neurophysiological recording studies (Kenshalo and Isensee 1983; Kenshalo et al. 1988, 2000; Kenshalo and Willis 1991) that identified a relatively small number of neurons confined to the middle layers of areas 3b and 1, which 1) respond to noxious thermal and mechanical skin stimuli, and 2) increase their rate of spike firing as the intensity of skin stimulation is increased.

Results obtained using the method of OIS imaging, however, led some investigators to a quite different view of how SI cortex responds to noxious skin-heating stimulation. Tommerdahl and colleagues (Tommerdahl et al. 1996, 1998; Li et al. 2001; for review see Whitsel et al. 2000) interpreted OIS imaging results obtained in their studies of anesthetized squirrel monkeys to indicate that noxious skin-heating stimulation suppresses neuronal activity in the regions of areas 3b and 1 that receive input from the stimulated skin site and, at the same time, evokes increased neuronal activity within the topographically corresponding region in area 3a. Chen et al. (2002b) subsequently reported OIS imaging observations (again from anesthetized squirrel monkeys) fully consistent with this view—their observations showed that the OIS evoked in areas 3b and 1 by innocuous mechanical stimulation of

Figure 8. Representative examples of area 3a neuron response to capsaicin. Plots showing MFR of 2 simultaneously recorded area 3a neurons before, during, and subsequent to intradermal injection of 20 μL of 1% capsaicin. Onset of injection was at time 0; injection required ~10 s to complete. The needle was withdrawn from the skin immediately after completing the injection. No mechanical or thermal stimuli were applied during the indicated time period. Note vigorous, protracted (~1 h) and multiphasic increase in MFR that followed the injection.

Figure 9. Time course of initial phase of area 3a neuron response to capsaicin. Average normalized across-neuron (n = 21) MFR response to intradermal capsaicin injection. The activity of each area 3a neuron was recorded before and for 80 s following the injection (CAP; at time “0”). Downward arrow indicates time at which the initial increase in MFR that followed capsaicin injection declined to half-maximal. Brackets indicate ±1 SEM.
a finger pad declines during simultaneous noxious mechanical stimulation of an adjacent finger pad and, at the same time, increased optical activity consistent with neuronal excitation occurs in an adjoining region of area 3a.

**Direct Comparison of Imaging Results Obtained in Human and Animal Studies**

Studies which used functional imaging methods (functional magnetic resonance imaging [fMRI], positron emission tomography [PET], single photon emission tomography [SPECT], magnetoencephalography [MEG]) in healthy human subjects have reported that a noxious skin stimulus activates SI cortex and multiple other regions in the same hemisphere (e.g., SII, anterior cingulate cortex, primary motor cortex, prefrontal cortex, insula, etc.; for review see Bushnell et al. 1999). In addition, the findings obtained in multiple human imaging studies (Pleger et al. 2000—using MEG to compare the responses evoked in SI by electrical nerve versus cutaneous laser stimulation; Ohara et al. 2004—using evoked potential recordings to compare the responses of SI to cutaneous laser versus vibrotactile stimulation; Moulton et al. 2005—using fMRI to compare the SI responses to noxious skin heating versus innocuous skin stimulation) appear fully consistent with the possibility that a noxious stimulus activates an SI region distinctly different from the region activated by touch. More specifically, both the above-described human imaging investigations and the squirrel monkey OIS imaging studies of Tommerdahl et al. (1996, 1998) report that 1) the SI region that responds to painful stimulation of the hand lies anterior and medial to the hand tactile locus; and 2) the locus of the SI
response to painful stimulation of the foot is anterior and lateral to the tactile locus.

Published human imaging observations and the OIS imaging results obtained from squirrel monkey also have revealed that whereas both the human SI fMRI activation and the squirrel monkey SI optical response to a tactile stimulus occur in relatively tight temporal synchrony with the evoking stimulus, the SI fMRI activation (human) and the SI optical response (squirrel monkey) to noxious skin heating develop more slowly. In particular, the peak fMRI activation (human) and peak optical response (squirrel monkey) of SI to noxious skin heating not only do not occur until well after the stimulus is terminated (6–8 s—human fMRI, Chen et al. 2002a; Moulton et al. 2005; 10–15 s—squirrel monkey OIS; Tommerdahl et al. 1996, 1998), but both responses persist for an additional protracted time period (for concise recent review of human SI imaging results see Treede and Lenz 2005).

Nocireponsive Area 3a Neurons

The experimental observations described in this paper demonstrate for the first time that 1) noxious skin-heating stimulation evokes spike discharge activity in a substantial population of area 3a neurons, and 2) the activity of these area 3a neurons increases linearly as the temperature of the probe that makes contact with the skin is increased over the range 49–51 °C (Fig. 4). Not only do the magnitude and time course of the area 3a neuron response to noxious skin-heating stimulation parallel the intensity and time course of the human second pain experience evoked by the same conditions of noxious skin-heating stimulation, but the area 3a neuron response to intradermal capsaicin injection strongly resembles the human pain experience elicited by capsaicin. More specifically, the human pain experience evoked by intradermal capsaicin injection is substantially more intense (2.6×; Simone et al. 1989) than the pain evoked by a 5 s 51 °C skin-heating stimulus and, correspondingly, the increase in area 3a neuron spike firing rate evoked by capsaicin is substantially greater (2.81×) than the increase evoked by 51 °C noxious skin heating. Also, following intradermal capsaicin injection a human subject experiences pain in response to tactile stimuli applied to a site in the vicinity of the injection site, and the area 3a neurons evaluated in the present study exhibited enhanced, and in some instances, novel responsivity to probe contact with the skin at a temperature between 25 °C and 38 °C. This capsaicin-induced enhancement/promotion of area 3a neuron responsivity to non-noxious mechanical skin contact raises the possibility that such an alteration of area 3a neuron responsivity/stimulus selectivity may underlie the prominent and prolonged mechanical hypersensitivity observed routinely following intradermal capsaicin injection, skin injury, or inflammation.

Although both the human pain experience and the elevation of area 3a neuron firing induced by intradermal capsaicin injection begin virtually immediately upon injection and reach a maximum within a few seconds of the onset of the injection, the increase in area 3a neuron spike firing persists for a much longer time. This discrepancy between the time course of area 3a neuron activation and the human pain experience evoked by capsaicin raises an interesting possibility—that is, because capsaicin activates both Aδ and C-nociceptors (Baumann et al. 1991; Szolcsányi et al. 1988) the transient acute pain experience triggered by capsaicin may mainly reflect the prominent and prolonged mechanical hyperalgesia observed routinely following intradermal capsaicin injection, skin injury, or inflammation.
unlike the temporally delayed, slowly temporally summating, and persisting response of the nocireponsive area 3a neurons identified in the experiments described in this paper (and also unlike the SI activations reported in published human imaging studies), the spike firing response of the majority of nocireponsive area 3b/1 neurons is relatively tightly coupled to the temporal profile of the skin-heating stimulus used to evoke the response.

**Effects of Experimental or Clinical Pain on the Human SI Response to Tactile Stimulation**

Multiple studies have used functional imaging methods to assess the impact on the responsivity of SI cortex to tactile stimulation of 1) experimentally induced pain in healthy normal human subjects (Iadarola et al. 1998—PET; Maihofner et al. 2004—fMRI); or 2) the level of ongoing pain in patients with chronic pain disorders (Baron et al. 2000—MEG; Peyron et al. 2004—fMRI; Maihofner et al. 2005—fMRI; Schweinhardt et al. 2006—fMRI; Witting et al. 2006—PET). Although several investigations have reported that tactile-evoked SI activation/responsivity is increased in the presence of pain (Baron et al. 1999; Maihofner et al. 2004—healthy normal subjects, 2005—patients with complex regional pain syndrome; Peyron et al. 2004), others have found that in the presence of pain a tactile stimulus fails to activate SI, evokes lesser SI activation than when pain is absent (Witting et al. 2006—patients with nerve injury pain), or has no significant influence on the SI response to tactile stimulation (Iadarola et al. 1998—normal subjects; Schweinhardt et al. 2006—neuropathic pain patients).

The above-described lack of consensus in the published literature that addresses the effects of pain on the human SI response to tactile stimulation may be, at least in part,
A Spinal–Cortical (Area 3a)–Spinal Circuit for Modulation of Second Pain

Central to appreciation of the results reported in this paper is the demonstration that lamina I neurons of the spinal cord dorsal horn (unlike most neurons in the other dorsal horn laminae) are dominated by input from polymodal C-nociceptors (Craig et al. 2001; Andrew and Craig 2002; Craig and Andrew 2002; Craig 2004b). Also relevant is the now appreciable evidence (Craig 2004a, 2006; Craig and Zhang 2006) that lamina I dorsal horn neurons dominated by input from polymodal C-nociceptors comprise the initial CNS level of a spinothalamic projection path that in primates: 1) subserves second pain perception (i.e., “delayed” or “burning” pain); 2) at every CNS level consists of neurons whose response to noxious afferent drive exhibits prominent slow temporal summation, and 3) involves neurons in a specific region of the contralateral dorsal thalamus (nucleus VMpo [posterior part of ventromedial nucleus of thalamus]) that give rise to axons which terminate synapticly on neurons in the middle layers of cortical area 3a (for review see Craig 2003a, 2003b).

Collective consideration of 1) the experimental findings of the present study, and 2) the afferent (Craig 2003a, 2003b) and efferent connections of area 3a neurons (Jones and Porter 1980) raises the possibility that in a conscious subject nociceptive neurons in the contralateral area 3a signal both the intensity and location of the second pain experience. As a result, the CNS circuit formed by the ascending projection from C-nociceptors → lamina I neurons → VMpo thalamus → area 3a, and the descending projection of area 3a → rostral brainstem → lamina I of the dorsal horn may function as a dynamically adaptive, homeostatic positive feedback system (shown schematically in Fig. 14). The circuitry summarized in Figure 14 not only incorporates our observation that environmental stimuli that trigger significant C-nociceptor afferent drive evoke spike discharge activity in area 3a nociceptive neurons in the contralateral hemisphere but, in turn, posits (in accord with the finding that microstimulation of area 3a, but not areas 3b/1, exerts excitatory effects on the cells of origin of the spinothalamic tract—Yezierski et al. 1983) that area 3a neuron activation triggers a descending influence (presumably transmitted via multisynaptic pathways involving nuclei in the rostral ventral medulla—Porreca 2001; Suzuki et al. 2004; Gebhardt 2004; Dickinson et al. 2005; Zambranuelo et al. 2005; Carlson et al. 2007) that enhances the responsivity of the lamina I dorsal horn neurons to subsequent input drive. It seems likely that the increase of lamina I neuron responsivity that results from this descending influence would subserve peripheral tissue homeostasis because it would lead, in turn, to 1) enhancement of the area 3a neuron response to both Aβ mechanoreceptor and C-nociceptor afferent drive arising from the same skin region where noxious stimulation evoked the C-nociceptor activity that initiated the area 3a neuron activation, and 2) augmented second pain perception and avoidance behaviors which would ensure preservation of the integrity of the skin region exposed to noxious stimulation.

The available evidence does not allow comprehensive neuromechanistic explanation of this study’s finding that area 3a neuron responsivity to non-noxious mechanical skin stimulation is increased subsequent to exposure to noxious...
skin heating or intradermal capsaicin injection. Identification of the nature of the responsible mechanisms and the location of those mechanisms on the pathway between the spinal cord dorsal horn and area 3a will require different experimental strategies/methodologies. What the findings described in this paper do make apparent, however, is that the size of the anterior parietal cortical territory activated by a tactile stimulus subsequent to exposure of the stimulated skin site to either noxious skin heating or capsaicin is substantially more extensive than the territory normally activated by that stimulus (it includes a neighboring region of area 3a as well as the regions of areas 3b and 1 that normally respond to such a stimulus). Accordingly, therefore, although the results provided by others (Recanzone et al. 1992; see also Xerri et al. 1998) have shown that prolonged exposure of the skin to behaviorally relevant non-noxious mechanical stimulation leads to an expanded representation of tactile stimuli that engage that skin region (a representation that includes the topographically appropriate sector of area 3a), the observations obtained in this study strongly suggest that a comparable expansion occurs much more rapidly (within seconds) in response to the C-nociceptor afferent drive evoked by noxious skin heating or intradermal capsaicin. An important unresolved issue (one which bears importantly on the functional meaning of this aspect of primary somatosensory cortical plasticity) is whether the very different conditioning procedures used in this versus the experiments of Recanzone et al. (Recanzone et al. 1992)—500–700 trials of mechanical stimulation per session in multiple sessions carried out over an extended time period versus transient skin contact with a probe at $^{\circ}$C—enhance the responsivity of the same or very different area 3a neuron populations.

Although in normal individuals activity of the spino-cortico-spinal circuit illustrated in Figure 14 leads to functionally adaptive changes in second pain perception and lamina I neuron responsiveness, it is equally clear that hypo- or hyperactivity of this circuit should lead to inadequate or excessive area 3a neuron activation, respectively, and accompanying abnormalities of pain perception. For example, subsequent to the impairment of gamma-aminobutyric acidergic inhibition in the superficial dorsal horn that García-Nicas et al. (2006) have shown accompanies nerve injury, a noxious skin-heating stimulus would evoke a magnitude and duration of area 3a activation and second pain far exceeding that evoked by the same stimulus in a normal subject. Moreover, it is anticipated that in this same subject the Aβ fiber activity that accompanies tactile stimulation would lead to vigorous area 3a neuron activation and the burning pain characteristic of mechanical hyperalgesia.

### Changing Views of Area 3a

Since the 1970s the consensus view (in accordance with substantial neurophysiological recording and neuroanatomical connective traces evidence) has been that area 3a, although it receives cutaneous input (for review see Moore et al. 2000), is primarily concerned with the processing and representation of information about the status of receptors in the deep tissues of the body (e.g., muscle, joints, tendons). That this view of area 3a might be incomplete, however, was initially suggested by the finding that axons of nocicceptive neurons in the superficial spinal cord dorsal horn (lamina I, in particular) terminate only sparsely in the ventral posterolateral (VPL) and ventral posteromedial (VPM) nuclei of the thalamus, but densely in a thalamic region (VMpo in monkey) whose neurons project to the middle layers of area 3a (Craig and Dostrovsky 2001; Craig and Blomqvist 2002; Craig 2004a, 2004b, 2006; Craig and Zhang 2006). In addition, the nociceptive neurons in VMpo that receive input from nocicceptive lamina I dorsal horn neurons can be antidromically activated from area 3a, and labeled by an injection of retrogradely transported tracer into area 3a (Craig et al. 2003a).

In addition to our discovery that noxious skin-heating stimulation evokes a vigorous optical response consistent with neuronal excitation in area 3a in the contralateral hemisphere (Tonmerdahl et al. 1996, 1998), other observations appear compatible with the idea that neuronal activity in some, but perhaps not all, area 3a regions contribute to pain and nociception. First, observations of patients with localized cortical damage (Kleist 1934; Russell 1945; Marshall 1951; for comprehensive review of this early literature see Perl 1984; for recent review of the effects of lesions of parietal cortex on pain see Ploner and Schnitzler 2004) suggested that although damage of a region in the depths of the posterior wall of the central sulcus—the position of area 3a in humans (Geyer et al. 2000)—is accompanied by a prominent and selective loss of cutaneous pain sensitivity on the side of the body contralateral to the lesion, hyperpathia follows large parietal cortical lesions that spare this same region.

Second, behavioral observations from monkeys with parietal cortical ablations also appear compatible with the existence of an anteriorly located SI region that contributes to pain and nociception. For example, Kenshalo et al. (1989) reported that bilateral destruction of an extensive anterior parietal cortical region that included area 3a is accompanied by degradations of both the ability to detect and discriminate noxious thermal skin stimuli. Contrarwise, Pecile (1944) reported hypersensitivity to pinprick suggestive of hyperpathia subsequent to a large lesion involving parietal areas 1, 2, 5 and 7 (a lesion which spared area 3a).

Third, in addition to finding (in macaque monkeys) that intracortical microstimulation at loci posterior to the transition between areas 3b and 3a exerts predominantly inhibitory effects on dorsal horn nociceptive spinthalamic tract neurons, Yezierski et al. (1983) reported that microstimulation at points in area 3a and in area 4 facilitates the responses of dorsal horn neurons to noxious stimulation of their peripheral receptive fields.

The above-described evidence, together with the observations obtained in the experiments reported in this paper, is consistent not only with the existence of the putative spino-cortical (area 3a)—spinal circuit schematically illustrated in Figure 14, but also with the idea that this circuit enhances the responsivity of lamina I nocicceptive dorsal horn neurons. The circuit in Figure 14 predicts that in a normal subject area 3a nociceptive neuron activation would increase the magnitude of the pain experience evoked by a noxious skin stimulus, and after an exposure to vigorous C-nociceptor afferent drive would contribute to initiation and persistence of the secondary mechanical hyperalgesia that routinely appears following such an exposure.

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