Relationships Between Skin Temperature and Temporal Summation of Heat and Cold Pain

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INTRODUCTION

Temporal summation of pain occurs reliably when pulses of heat or electrical stimulation are delivered repetitively at rates as slow as one pulse in 3 s. Enhanced discharge of nociceptive central neurons (“windup”) can be observed under these conditions (Mendell 1966; Tommerdahl et al. 1998). Temporal summation for psychophysical and neural responses to heat is dependent on activation of unmyelinated (C) nociceptors and is dependent in part on activation of central N-methyl-D-aspartate (NMDA) receptors (Dickenson 1990; Graven-Nielsen et al. 2000; Price et al. 1994). Most investigations of heat pain summation have utilized triangular ramps from a Peltier device in constant contact with the skin. This method has the advantage of returning the skin to a baseline temperature between each ramping heat stimulus. However, because of limitations on the ramp speeds of Peltier thermodes (especially during down ramps), distinct first and second pain sensations that are attributable respectively to activation of myelinated (A-delta) and C nociceptors are not produced. Possibly because of inhibitory influences on C nociceptor input from simultaneous activation of A-delta afferents (Chung et al. 1984; Mackenzie et al. 1975; Torebjork and Hallin 1973; Wahren et al. 1989), triangular ramps to tolerable nociceptive temperatures produce moderate temporal summation (Vierck et al. 1997).

An alternative method involving brief contacts with glabrous skin by a preheated thermode that is advanced repetitively from off the skin produces a distinct second pain sensation that temporally sums substantially (Staud et al. 2001; Vierck et al. 1997). Because thresholds of C nociceptors in glabrous skin are lower than thresholds for A-delta nociceptors (Treede et al. 1995), temperatures can be delivered with brief contacts that are sufficient to temporally summate second pain but do not produce first pain. Thus inhibition by A-delta nociceptors is presumed not to occur with this method. Also, tactile stimulation of A-beta afferents during skin contact is not likely to be inhibitory to second pain sensations (Melzack and Wall 1965) for the repetition rates used to demonstrate temporal summation, where sensations evoked by A-beta and C afferents are separated by more than 1 s. This separation in time between skin contact and a late sensation is highly advantageous for unambiguous rating of sensations elicited by activation of C nociceptors.

Although repetitive tapping of the skin with a preheated thermode is optimal for demonstration of temporal summation, skin temperature increases slightly during each ISI and across a series of heat taps (Vierck et al. 1997). A potential peripheral effect must be considered when interpreting the rate of increase in heat pain. The present study addresses this issue using several approaches. First, subcutaneous temperatures were monitored with sufficient temporal resolution to determine the time-course of changes in skin temperature in the interstimulus intervals (ISIs) during long series of repetitive contacts of glabrous skin with a preheated thermode. These recordings at the site of stimulation provide information on local thermoregulatory compensations for applied heat, and they reveal any...
changes (e.g., adaptation) in compensation for each stimulus as the series progresses and skin temperature gradually changes. Second, skin surface temperatures were recorded from the site of stimulation as a series of repetitive contacts progressed, so that relationships between skin temperature and the progression of psychophysical ratings within ISIs could be assessed in individual subjects. In addition, recordings of skin temperature permitted estimation of skin temperature thresholds for pain under conditions of repetitive stimulation.

The same procedures were utilized to determine whether temporal summation of cold pain occurs with repetitive stimulation, to monitor local thermoregulatory compensations for cold and to assess relationships between skin temperature and psychophysical ratings of cold pain. Focal cold stimulation activates populations of A-delta and C afferents that overlap only partially with those stimulated by heat, and it is not known whether temporal summation of pain is produced by all forms of stimulation that activate C nociceptors.

Available information on cold pain comes primarily from ramp-and-hold stimulation from a resting skin temperature to near freezing, which produces complex changes in sensory quality that include cold, prickling, aching, numb, and burning sensations, with a progressively more aversive quality as skin temperature drops (Chery-Croze and Duclaux 1980; Croze and Duclaux 1978; Davis 1998; Harrison and Davis 1999; Kunkle 1949). The variety of sensations induced by maintained cold stimulation apparently derives from effects on many categories of afferents (Simone and Kajander 1996, 1997). A-delta afferents presumed to subserve nonnociceptive cold sensations discharge within a range of 20–40°C, with peak discharge rates at 25–30°C. Input from these afferents is inhibitory to pain (Bini et al. 1984; Davis 1998; Fruhstorfer 1984; Sandkuhler et al. 1997; Yarnitsky and Ochoa 1990). Other A-delta afferents with high thresholds for cold activation (LaMotte and Thalhammer 1982) may produce a sensation of pricking cold (Davis 1998; Yarnitsky and Ochoa 1990). Maintained cold stimulation can induce a deep radiating sensation of ache (Croze and Duclaux 1978; Kunkle 1949; LaMotte and Thalhammer 1982; Yarnitsky and Ochoa 1990). This is particularly apparent for the cold pressor test involving immersion of a limb in ice water, which cools a large surface area and affects subcutaneous receptors on blood vessels (Fruhstorfer and Lindblom 1983; Klement and Arndt 1992; Wolf and Hardy 1941). At temperatures approaching freezing, cold can evoke a sensation of burning pain, presumably from activation of a subpopulation of C nociceptors that also respond to heat (Davis 1998; Fruhstorfer 1984; Kunkle 1949; Wahren et al. 1989; Yarnitsky and Ochoa 1990). Finally, with prolonged stimulation near and below freezing, most afferents are activated and then inactivated (Franz and Iggo 1968; Simone and Kajander 1996). Blocking of afferent conduction by extreme cold accounts for sensations of numbness.

In contrast to the complexity of cold sensations during ramp and hold stimulation, repetitive cold taps produced only a diffuse aching sensation in the intervals between brief stimuli. This deep aching sensation can be masked by the traditional method of ramp-and-hold stimulation, where focal sensations of cutaneous cold and cold pain predominate. The magnitude of aching cold pain was rated during series of repetitive stimuli.

METHODS

The human subjects in experiments 1 and 2, ranging in age from 18 to 63 years, gave prior assent to experimental procedures approved by the University of Florida Institutional Review Board and were informed that they could withdraw from the study at any time. The experiments conformed with the Helsinki accord on experimentation in humans subjects, and the animal and human pain studies conformed with the guidelines of the IASP.

Experiment 1

A primary purpose of experiment 1 was to obtain subcutaneous skin temperature recordings with sufficient temporal resolution to determine thermoregulatory adaptations of the skin to applied heat or cold. These recordings from anesthetized monkeys were used to describe changes in skin temperature during individual ISIs of long series of repetitive heat or cold stimulation. Also, skin temperature data obtained in this experiment were used to relate ratings of aching cold pain throughout a series to subcutaneous recordings of skin temperature. Previously, we have related human psychophysical ratings of heat pain to progressive changes in subcutaneous skin temperature during repetitive stimulation (Vierck et al. 1997).

SUBCUTANEOUS SKIN TEMPERATURE RECORDING. Subcutaneous skin temperature during pulsed stimulation was recorded from two Macaca arctoides monkeys using pulsed stimulation with a probe temperature of 50°C (700-ms duration and 3-s ISI) and from two additional monkeys with a probe temperature of 0.3°C (at the parameters used for psychophysical testing; see PSYCHOPHYSICS). All recordings were obtained after induction with ketamine (10 mg/kg) and maintenance of full surgical anesthesia with isoflurane. Heart and respiratory rates and blood pressure were monitored continuously. A Yellow Springs thermistor (model 524 in a 25-g needle) was inserted beneath the epidermis, on glabrous skin of a hand at the site of thermal stimulation. The analog record was digitized and stored for off-line analysis. At the end of these recording sessions, the animals were killed with an overdose (80 mg/kg) of sodium pentobarbital (Nembutal) for histological analysis of spinal tissue required by another experiment.

PSYCHOPHYSICS. Seven subjects (5 male and 2 female) rated the magnitude of thermal sensations produced by contact of a precooled thermode with glabrous skin of the hand. A 2.3 × 2.3-cm square Peltier thermode was mounted on the center shaft of a solenoid, which, when activated, brought the thermode into timed contact with the thenar eminence of either hand. During testing, the thenar eminence was positioned over a 3 × 3-cm square aperture in a plexxiglass surface that provided support for the hand. When the solenoid was energized, the thermode protruded slightly above the surface of the plexxiglass hand rest, insuring reliable contact with the skin. The duration of each thermode contact and the interval between the onset of sequential stimuli (ISI) were varied. A thermistor sandwiched between the Peltier element and the copper thermode surface was used to monitor and maintain stimulus temperature. For pulsed cold stimulation, the thermode was precooled to 0.3°C.

Psychophysical ratings of sensation magnitude in experiment 1 utilized a verbal rating scale ranging from 0 (no thermal sensation) to 100 (intolerable pain sensation) in increments of 5, with verbal descriptors assigned to sensation intensities. Nonpainful warmth or cold sensations were rated in intensity from 0 to 15. A rating of 20 was identified as pain threshold, and verbal descriptors at subsequent intervals of 10 were as follows: 30 = very weak pain, 40 = weak pain, 50 = moderate pain, 60 = slightly strong pain, 70 = strong pain, 80 = very strong pain, and 90 = nearly intolerable pain. This scale was utilized for several reasons: 1) for comparison with our previously published ratings of heat pain (Vierck et al. 1997) and 2) for comparison with the visual analog scale used in experiment 2, where only pain is rated. Inclusion of ratings for nonpainful sensations.
stimuli on separate days of testing was 2, 4, 6, or 8 s for heat and 4, 6, or 8 s for cold. The temperature and pain measurements were averaged for each experimental condition and subject. The skin temperatures for pulses after which no measurement was made (i.e., all but pulses 5, 10, 15, and 20) were interpolated by a third order polynomial fit. This approach was necessary because it was possible to obtain skin temperature measurements only before and after (but not during) a series. Each skin temperature measurement required removal of the subject’s hand from the testing apparatus, and it would have been difficult to precisely reposition the hand before the arrival of the next pulse.

Statistical evaluation of psychophysical ratings and of skin temperatures across series of 20 stimuli at different ISIs utilized Statistica software (Statsoft, Tulsa, OK) and repeated measures ANOVA.

**Results**

**Experiment 1**

Relationships between the magnitude of aching pain and subcutaneous skin temperature during cold stimulation can be appreciated by comparing Fig. 1, A and B, where variations in ISI are shown, and Fig. 1, C with D, where effects of contact duration are depicted. It is apparent that subcutaneous skin temperature decreases at a faster rate than ratings of aching pain increase, but there are orderly relationships between the relative rates and magnitudes of temperature decreases and pain increases in series of 50 stimuli at different ISIs or contact durations. These results of cold stimulation contrast with previous findings that temporal summation of heat pain was highly dependent on ISI, but subcutaneous skin temperature increased almost identically for ISIs of 3–7 s (Vierck et al. 1997; see Discussion).

The magnitude and time-course of subcutaneous temperature fluctuations between pulses of heat or cold stimulation are shown in Fig. 2. Subcutaneous temperature was sampled during each ISI throughout a series of 50 stimuli. In Fig. 2A, the peaks of temperature increase or decrease within ISIs of 3 s are shown. For heat, a small temperature increase was observed following each stimulus, and the magnitude of this response did not vary across the series. Throughout the series of 50°C stimuli, subcutaneous skin temperature increased by approximately 0.3°C and peaked at 1.1 s after activation of the solenoid (Fig. 2B). At the end of each 3 s ISI, skin temperature returned nearly to the value recorded just prior to the previous skin contact.

Figure 2A shows that peak temperature changes early in a series of cold stimuli were considerably greater than for heat stimulation. The responses to cold stimulation became smaller as a series of stimuli progressed. Figure 2, C and D, compares skin temperature profiles produced by the first and last of 50 contacts at 0.3°C. During 3 s ISIs (Fig. 2C) and 8 s ISIs (Fig. 2D), early responses in the series reached a peak near the end of the interval. For either ISI, skin temperature changes following cold stimuli late in a series were small and less prolonged than early responses. In contrast, peak temperature changes after heat pulses (Fig. 2B) occurred near the midpoint of ISIs and were comparable for the first and last stimulus in a series. These observations show that thermoregulatory compensation for contact with the skin of an object sufficiently cold to induce aching pain is slow in comparison to clearing of heat after contact with an object that produces temporal summation of heat pain.
Experiment 2

The relationships between heat and cold pain intensities and subcutaneous skin temperatures were corroborated by an experiment involving measurement of surface skin temperatures in human subjects. Figure 3 shows psychophysical ratings of sensation intensity and surface skin temperatures obtained from each participant during series of repetitive stimuli at different ISIs for heat and cold stimulation. Figure 3B shows that surface skin temperature increased by 7–8°C in response to heat stimulation regardless of the ISI, which ranged from 2 to 8 s. ANOVA revealed no difference in the progression of skin temperatures across ISIs, either as a main effect (F = 0.31, df = 3, P = 0.82) or as an interaction with the number of stimuli (F = 0.70, df = 38, P = 0.95). However, ratings of sensation intensity depended critically on ISI (Fig. 3A; main effect: F = 7.07, df = 3, P = 0.002; interaction: F = 8.55, df = 38, P < 0.000). A maximal rating of moderate pain was produced only by the 2-s ISI. Thus neither surface temperature (present study) nor subcutaneous temperatures (Vierck et al. 1997) determine the rate of temporal summation of sensation intensity for repetitive stimulation at different ISIs with a heated probe.

Figure 3, C and D, reveals a good correspondence between sensation intensity and surface skin temperature for cold stimulation at ISIs of 4, 6, and 8 s. The maximal ratings and temperatures were ordered appropriately with ISI, suggesting that the magnitude of aching pain is inversely proportional to skin temperatures produced by repetitive stimulation with a cold probe. Statistical evaluation showed a significant effect of ISI on psychophysical ratings (interaction: F = 1.6, df = 38, P = 0.002) and on skin temperature (interaction: F = 4.33, df = 38, P < 0.000) as the series of repetitive stimulation progressed. For cold stimulation, ratings of sensation intensity increased slowly and reached a plateau later than skin temperature readings for each ISI, in contrast to ratings of heat pain, which increased at rates either faster or slower than skin temperature, depending on the ISI.

Figure 4, A and B, shows plots of psychophysical ratings against surface skin temperature for repetitive heat stimulation of two subjects at the 2-s ISI that produced substantial temporal...
summation of pain. Ratings of heat intensity progressed only slightly and gradually for the first 6–10 stimuli, as skin temperature approached 38°C (Fig. 4B) or 40°C (Fig. 4A). This linear relationship then broke down, and ratings accelerated greatly as surface skin temperature increased little or even decreased. In contrast, ratings of sensations produced by slower repetition of heat taps (Fig. 4, C and D; ISI of 6 s) remained minimal as skin temperature increased within the range produced by the 2-s ISI, to values in excess of 40°C. These plots show that temporal summation of heat pain occurs at a minimum surface temperature of 38–40°C, but maintenance of skin temperature in this range is not a sufficient condition.

Figure 5 shows relationships between surface skin temperature and visual analog scale (VAS) ratings of aching pain sensations produced by repetitive cold stimulation. A salient difference between relationships of heat and cold pain to stimulus repetitions is that both short and long ISIs produced substantial increases of cold pain with stimulus repetition. Also, the functions relating skin temperature decreases to psychophysical ratings of aching pain were similar for long and short ISIs. Thus measurement of surface skin temperatures as subjects rated sensation intensity confirmed conclusions drawn from comparisons of psychophysical ratings with separate recordings of sub-surface skin temperatures. With stimulus repetition, aching cold pain intensity is more closely related to skin temperature than temporal summation of heat pain. In contrast to functions relating skin temperature to temporal summation of heat pain that were frequently positively accelerating late in a series, comparable ratings of cold pain were often negatively accelerating in relation to decreasing skin temperature late in a series. Adaptation of aching pain was often observed late in series of 20 stimuli.

**DISCUSSION**

A goal of this investigation was to determine similarities and differences between temporal progressions of pain sensations produced by repetitive heat and cold simulation. Glabrous skin of the hand was tapped repeatedly by a thermode preheated or precooled to temperatures that would produce moderate to strong pain during maintained contact. Each heat tap produced a tactile sensation during contact and a distinct late sensation of warmth or heat pain welled up and receded after the probe left the skin. It is the late or second sensation of heat that summates dramatically in magnitude. Temporally summed heat pain was well localized to the skin surface and site of stimulation. Repeated contact of a precooled thermode with palmar skin produced a nonnociceptive cold sensation during contact, and then a diffuse sensation of ache developed. The ache progressed gradually across a series of cold taps, was perceived as deep to the skin, radiated substantially, and was not localized.
to the site of stimulus contact. The ache sensation could radiate either proximally within the arm or distally to the fingers.

First pain can be produced during brief contact of a heated probe with hairy skin but was not reported for 700-ms stimulation at the thermode temperatures utilized. Glabrous skin lacks low threshold A-delta nociceptors (Treede et al. 1995) that would mediate first pain for these temperatures. First sensations of warmth were not produced, because warmth depends on activation of unmyelinated (C) afferents (LaMotte and Campbell 1978). Late sensations of warmth from activation of nonnociceptive C thermoreceptors could be produced early in a series, but second pain was the dominant sensation as a series of heat taps progressed. Second pain sensations from heat stimulation are attributed to activation of C nociceptors, and temporal summation of heat pain (or comparable windup of nociceptive responses of central neurons) is dependent on activation of C nociceptors (Price et al. 1977). Accordingly, the sensation that temporally summated was painful and had a burning quality characteristic of C nociceptor activation (Ochoa and Torebjörk 1983).

The thermoreceptive afferents activated during contact of the cold probe with the skin are certain to include nonnociceptive A-delta cold receptors (Rainville et al. 1999) and could include A-delta nociceptors with thresholds below 27°C (LaMotte and Thalhammer 1982). The subjects did not rate the intensity or attend to qualitative features of sensation during skin contact but described it as cold. Pricking pain, which results from stimulation of A-delta afferents (Davis 1998), was not apparent. Sensations of cold or cold pain with distinct peaks between skin contacts were not reported. Second pain sensations from cold stimulation would likely have a burning quality (Fruhstorfer 1984; Wahren et al. 1989), but it appears that skin temperature did not become low enough to activate C polymodal receptors (Burgess and Perl 1973; Simone and Kajander 1996). The ache sensation that gradually developed with repetitive stimulation is likely attributable to activation of nociceptors located subcutaneously, on or near blood vessels (Klement and Arndt 1992; Morin and Bushnell 1998). These afferents appear to be distinct from C nociceptors that are associated with burning pain.
Comparisons of surface and subcutaneous skin temperatures with psychophysical ratings addressed mechanisms of cold and heat pain. Temporal summation of heat pain is not explained by tonic changes in surface temperature (present study) or escalating subcutaneous skin temperatures (Vierck et al. 1997). The amplitude of phasic changes in skin temperature during ISIs was consistent across stimuli within a series, but late sensation magnitudes increased with stimulus repetition. Also, changing the interval between stimuli (with ISIs of 2–8 sec) dramatically influenced temporal summation of pain but did not appreciably alter the tonic progression of skin temperatures. Therefore consistent with conclusions drawn from recordings of nociceptive afferent and spinal neuronal responses (Price et al. 1977), temporal summation of heat pain depends on C nociceptor activation of central NMDA receptor systems (Price et al. 1994; Vierck et al. 1997).

In contrast to the transient increases in subcutaneous temperatures that recovered nearly to baseline within ISIs of 3 sec for heat taps, cold taps produced prolonged reductions of subcutaneous temperatures that did not recover within 8-sec ISIs. Thus local application of heat to the skin is cleared efficiently, but skin temperature does not recover quickly from cold stimulation. These differences are depicted in Fig. 6, which utilizes data from Figs. 1 and 2 (and Vierck et al., 1997), to show that subcutaneous skin temperature drops quickly and substantially during repetitive cold stimulation compared with a small and gradual increase in skin temperature that occurs across a series of heat stimuli of the same duration and ISI. A likely mechanism for heat dissipation is that contact of a heated probe with the skin produces a somatosympathetic vasoconstrictor response of cutaneous vessels (Hirata et al. 1988; Janig 1975; Nagasaka 1987), lowering skin temperature. A similar response appears to be elicited by cold stimulation (Kurosawa et al. 1985), accounting for the prolonged reduction of skin temperature between cold taps.

Both superficial and deep skin temperature changes were proportionate to increases in aching sensation magnitude with repetition of the cold stimulus. Increases in aching sensation magnitude lagged behind decreasing surface and subcutaneous skin temperatures over the range of interstimulus intervals presented. Also, cold pain persists considerably longer than heat pain after maintained stimulation, and these differences are related to rate of return of skin temperature (Morin and Bushnell 1998). The delay in progression of aching cold mag-

FIG. 4. Plots of surface skin temperature against psychophysical ratings of heat pain for 2 subjects (left and right) and ISIs of 2 sec (top) and 6 sec (bottom). Comparing the top and bottom panels, it is apparent that skin temperatures of approximately 40°C are associated with considerable temporal summation of 2nd pain for the 2-sec ISI but not for the 6-sec ISI.

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FIG. 5. Plots of surface skin temperature against psychophysical ratings of aching pain for 2 subjects (left and right) and ISIs of 4 sec (top) and 8 sec (bottom). Temporal summation of aching pain over series of 0.3°C stimulation was related to surface skin temperatures until late in the series, when adaptation of aching pain was observed for some subjects (e.g., B and D).

FIG. 6. Storage of applied heat (50°C) and cold (0.3°C) by the skin are schematically depicted, based on recordings of subcutaneous skin temperature over 10 stimuli (700-msec duration; 3-sec ISI). Timing of thermal pulses is shown below the graph. Skin temperature drops quickly over the 1st 5 cold stimuli (thin line), because there is little or no recovery in the ISIs. Thereafter, the peak decreases in skin temperature become smaller, there is some recovery within ISIs, and skin temperature drops gradually across repeated stimuli until a plateau is reached. In contrast, small peak increases in skin temperature occur consistently between heat stimuli (thick line), there is nearly total recovery within each ISI, and subcutaneous skin temperature increases gradually across the series of 10 stimuli.
nitude and its persistence likely depend on development of vascular reactions to cold and indirect mechanical excitation of receptors in the walls of vessels (Arndt and Klement 1991; Kunkle 1949; Minut-Soroktina and Glebova 1976). Thus it is unnecessary to invoke a central process of temporal integration to account for the increase in magnitude of aching pain during series of cold taps. That is, repetitive cold stimulation appears not to induce windup of central spinal neurons in a manner comparable to the effects of C nociceptor activation by heat.

Plots of psychophysical ratings against skin surface temperatures across series of 50 heat taps (Fig. 4) revealed a dependency of temporal summation on rate of stimulation rather than skin temperature. This is apparent from the disparity between maximal ratings that were >60 or less than 10 when surface skin temperatures exceeded 40°C in series with 2- or 6-s ISIs, respectively. Furthermore, for the 2-s ISI, ratings of heat pain increased dramatically when skin temperature was stable, near 40°C. These results emphasize the dependency of heat pain magnitude on mechanisms of central summation. Also, they present practical considerations for investigations of temporal summation of heat. For probe temperatures of 48–56°C and brief contacts (Vierck et al. 1997 and the present study), increases in sensation intensity for stimuli early in a series are well related to skin temperature and are much less dependent on repetition rate than for stimuli late in a series, when increases in skin temperature are small relative to increases in sensation magnitude. That is, temporal summation that is dependent on central processing might be missed or underestimated by short series of heat stimulation.

A related difficulty with short series of repetitive heat stimuli that produce modest increases in sensation magnitude is revealed by the use of several rating scales in the present study. In experiment 1, a rating scale linked to verbal descriptors defined values of 1–15 as subthreshold for pain (i.e., levels of warmth), and ratings of 20–100 were used to describe intensities ranging from pain threshold to intolerable pain. Using 50°C stimulation, the first 3–10 stimuli in a series produced late sensations that were rated below pain threshold on the verbal descriptor scale (Fig. 1). In contrast, using a VAS scale for pain intensity that did not include ratings of warmth, the sensations early in a series were reliably rated above zero (as slightly painful) for probe temperature of 50°C or less (Fig. 2). Because subjects have difficulty discriminating faint pain from warmth, there is a tendency to rate all near threshold sensations as slightly painful on a scale that does not include the category of warmth. This is of little importance when the goal is to rate clearly suprathreshold levels of heat pain. However, short series that are rated by a VAS scale and do not eventuate in ratings of moderate pain could describe temporal summation of nonnociceptive warmth.

When the skin is heated by repetitive brief contact with a thermode, thresholds for nociception are near those reported for excitation of C nociceptors by maintained cutaneous stimulation. The lowest threshold reported for activation of C nociceptors is approximately 40°C (LaMotte and Thalhammer 1982; LaMotte et al. 1983; Torebjork et al. 1983; Yarnitsky et al. 1992) and is well below thresholds as high as 53°C for activation of A-delta thermal nociceptors in glabrous skin (LaMotte and Campbell 1978; LaMotte et al. 1983; Treede et al. 1995). Psychophysical thresholds for heat pain range from 40 to 49 for stimulation at glabrous and hairy skin sites with probes of different sizes and with widely varying ramp rates and stimulus durations (Hamalainen et al. 1982; LaMotte 1984; LaMotte et al. 1983; Morin and Bushnell 1998; Pertovaara et al. 1996; Strigo et al. 2000; Wahren et al. 1989; Yarnitsky and Ochoa 1991). Most of the mean threshold values cluster between 43 and 46°C (Craig and Bushnell 1994; Dyck et al. 1993; Hardy et al. 1952; Harju 2002; Magereal and Treede 1996; Nielsen and Arendt-Nielsen 1998; Taylor et al. 1993; Tillman et al. 1995; Torebjork et al. 1984; Verdugo and Ochoa 1992). In experiment 2 of this study, eVAS ratings of 10 represent a conservative estimate of threshold pain. For probe temperatures of 49.5 or 50°C (3 subjects), eVAS ratings of 10 were obtained when surface skin temperatures reached 37.9 and 38.1°C within ISIs of 2 and 4 s. Stimulation at longer ISIs did not produce ratings as high as 10, even though skin temperatures reached 40°C. Thus temporal summation during repetitive heat stimulation lowers thresholds for pain as well as increasing suprathreshold intensities.

Thresholds for activation of presumed nociceptors by maintained cold stimuli have been estimated to be below 12°C and generally near freezing (Burgess and Perl 1973; Georgopoulos 1976; LaMotte and Thalhammer 1982; Simone and Kajander 1996). Possibly because ramp-and-hold stimulation produces a variety of cold sensations, psychophysical thresholds for cold pain have been reported to be highly variable, depending on stimulus parameters and location. When subjects are instructed to report on cold pain, irrespective of qualitative distinctions, thresholds range remarkably from 30 to 0°C (Davis 1998; Fruhstorfer 1984; Harju 2002; Harrison and Davis 1999; Klement and Arndt 1992; Morin and Bushnell 1998; Ochoa and Torebjork 1983; Strigo et al. 2000; Verdugo and Ochoa 1992; Wahren et al. 1989; Wolf and Hardy 1941; Yarnitsky and Ochoa 1990). However, thresholds for aching pain have been reported at approximately 15°C (Davis 1998) and 18°C (Hardy et al. 1952). In the present study, threshold aching cold pain (eVAS ≥ 10) during repetitive stimulation was established when surface skin temperature reached 18.9, 19.8, and 20.4°C for ISIs of 4, 6, and 8 s, respectively. Thus thresholds for aching cold pain are within the upper range of reported cold pain thresholds and appear to be increased only slightly by slow rates of repetitive stimulation.

In conclusion, repetitive stimulation of glabrous skin with heat selectively activated cutaneous C nociceptors and produced substantial temporal summation of second pain that depends on central mechanisms rather than a storage of heat by the skin. In contrast, repetitive stimulation with a cold probe progressively elicited aching cold pain by decreasing subcutaneous temperature, with relatively more warming of the skin surface between stimuli. This preferential effect on thermal receptors deep to the skin isolates one of the sensations experienced during maintained cold stimulation, which produces a thermal gradient with the lowest temperatures at the surface. Prolonged cold stimulation effectively activates a variety of cutaneous nociceptors and evokes sensations that include cold, freezing, sharp, prickle, stinging, tingling, throbbing, aching, and burning (Chery-Croze and Duclaux 1980; Croze and Duclaux 1978; Davis 1998; Fruhstorfer 1984; Harrison and Davis 1999; Kunkle 1949; Yarnitsky and Ochoa 1990). Repetitive cold stimulation appears to provide a convenient and tolerable model of visceral pain. The activated nociceptors are located on or near blood vessels, and all forms of nociceptive visceral
stimulation appear to produce a diffuse, aching pain sensation (Hardy et al. 1952).

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