THERMAL SENSIBILITY AND THERMORECEPTORS

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The sensing of changes in skin temperature is important (a) in contributing to the total sensory information about an object making contact with the skin, and (b) in assessing body heat loss or gain, that occurs over a large part of the body surface. These functions depend on (a) resolution of small, local, shifts in skin temperature, and (b) effective spatial summation by the central nervous system of thermal stimulus information. Aδ cold fiber populations excited uniquely by cooling the skin and unmyelinated warm fibers excited only by warming the skin constitute the "labeled lines" that signal all the immediate information available to the brain about changes in skin temperature.

We have correlated the capacity of human subjects to identify incremental differences within pairs of warming or cooling temperature pulses and the neural events evoked by similar stimuli in the cutaneous nerve fiber populations of monkeys (Macaca nemestrina). The conclusions are that human discrimination of incremental changes in skin temperature depends on (a) information coded at the single fiber level as cumulative impulse count or rate over an integration interval of about 2 sec, (b) the brain using information signaled by all the thermoreceptive fibers engaged by the stimulus, (c) the dependent variability among fibers of the responding population being slight, and (d) the brain integrating this information by some method of "weighted" averaging, which biases the process to favor these fibers that most effectively relay stimulus information.

HUMAN THERMAL SENSIBILITY: GENERAL CHARACTERISTICS

A trained observer can resolve remarkably small incremental changes in skin temperature if these changes occur rapidly. If about 1 cm² of his palm is stimulated, the observer can identify correctly the larger of two transient warming stimuli differing by about 1/20 of a degree C (Fig. 1). When the area of stimulation is increased, even if the increase is discontinuous, this resolution of intensive changes will improve further, since spatial summation is a striking feature of thermal sensibility [1]. Intensity discrimination at this level depends on the rate of change of the skin temperature, which in the above context would approximate the rate at which the skin temperature changes when one touches a warm metallic block (rise time of about 250 msec). However, if the skin temperature drifts slowly by as much as 6 to 7°C over a period of 20 to 30 min, the subject may be entirely unaware of the shift.

With rapid changes in skin temperature, the subject may additionally appreciate the time course and any fluctuations in intensity in a scale of seconds. He can also scale the apparent magnitude of the stimulus [2]. However, he has difficulty in characterizing other stimulus features, and he may confuse stimuli of differing intensities if there is a simultaneous change in other parameters. For example, two warming stimuli, in which the total heat transfer to the skin is similar but the heat flux and the area of stimulation are traded off against each other, may not be differentiated. Similarly, the observer may not be able to identify the spatial pattern of the stimulus or whether a single or two adjacent areas of skin are being stimulated. He makes considerable errors in locating a warming or cooling stimulus [3,4].

Finally, in contrast to the tactile sense, olfaction, taste, vision, and hearing, the range of dissimilar sensations evoked by the changing of skin temperature is quite limited. The subject reports warming or cooling of his skin and qualifies this in terms of its intensity and duration. He also reports a clear-cut change in the character of the sensation (to one of pain) if the skin temperature rises to about 45°C or higher, or falls below about 15 to 18°C. But he never reports other qualitatively distinct sensations evoked by thermal stimulation in any way comparable to the array of sensations elicited by touching glass, woven material, a wet spongy surface, or an oily surface.

What behavioral and physiologic adjustments do we make in response to these local or more widespread changes in skin temperature? Particularly with local changes in skin temperature resulting from contact with, for instance, a metallic object, the coincident thermal and tactile information signaled to the brain complement each other. Recognition of the stimulus site, its area, and its contours depends on excitation of the mechanore-
ceptive fibers innervating the skin. Supplementary information regarding the rate of transfer, if any, of heat to or from the skin to the object is signaled to the brain by the thermoreceptive fibers; this information contributes to the overall sensory image of the physical characteristics of the stimulus and signals whether the stimulus is likely to injure tissue because of its temperature (e.g., whether it is a metallic or wooden surface at room temperature, skin at body temperature, or a hot iron).

A changing skin temperature is also important in determining both the behavioral and more automatic physiologic adjustments for maintaining a steady body temperature. Transfer of heat energy to or from the body at a level that threatens homeostasis typically occurs by radiation. Locally the skin temperature may change only slightly, but the heat transfer also depends on which area of the skin is losing or gaining heat, and consequently both of these physiologic parameters must be continuously assessed. With mammalian thermoreceptive systems, the price paid to achieve this monitor function is the loss of spatial acuity. One bases a decision to put on a sweater after sitting in a cool room more particularly on the assessment of the overall loss of heat from one's body surface rather than by locating the part of one's body surface that is losing heat.

This brief survey of human thermal sensibility emphasizes that the resolution of intensive changes in skin temperature is functionally very important and that this resolution is achieved at the expense of the observer's capacity to identify spatial and temporal characteristics of the heat exchange occurring at his body surface.

We now wish to focus on the neural mechanisms underlying this intensity discrimination in human beings. Sensory behavior of any type and the underlying neural events are never simple, but there is a sufficient directness in the correlation between the peripheral neural processes and the behavioral discrimination of changes in skin temperature to allow a quite rigorous analysis of the coding of sensory information in the fiber populations of a cutaneous nerve. It is this particular aspect of thermal sensibility that interests the sensory physiologist.

In comparison with other modes of sensation, the events in a peripheral nerve evoked by changing skin temperature are quite simple. Sensations of touch and pressure are evoked by a variety of mechanoreceptors activating nerve fibers with different structural and functional characteristics. A single gustatory fiber in the glossopharyngeal nerve may be responsive to a number of taste-producing substances. On the other hand, in those nerves which innervate the glabrous skin of the monkey's hand, a small rise in skin temperature excites a single, functionally homogeneous population of nerve fibers; a fall in skin temperature activates a second, quite separate fiber population. Here we have unique, experimentally accessible "labeled lines" that are the sole relay from the skin to the brain of all the stimulus information on which the subject's sensory response is based.

THE RESOLUTION OF SMALL CHANGES IN HUMAN SKIN TEMPERATURE

Every day we experience two rather stereotyped patterns of thermal stimulation of the skin. When a region of one's skin is suddenly exposed to a radiant heat source, as when one steps from shade into the sun or comes close to a radiator, for the first 5 to 10 sec the steady absorption of heat energy causes an approximately linear increase in skin temperature with time; a temperature "ramp" results. The second common stimulus pattern occurs when one touches for a few seconds a cool or warm metallic object. On contact, the skin temperature shifts rapidly from its previous steady value to a new steady value approximating that of the metallic object; it then returns to its original level after contact is broken—a near-rectangular cooling or warming "pulse" is generated at the skin surface. In most earlier experimental studies a radiant heat source was used to stimulate the skin, i.e., temperature ramps were used [5-8]. More recently we have used a temperature pulse generated by a servocontrolled contact stimulator so that we can precisely set the baseline temperature, the intensity (±0.006°C), the stimulus duration, the temporal profile, and the stimulus repetition rate [9].

Once precise control of local skin temperature was achieved by using a good contact thermal stimulator, we could ask detailed questions about an observer's ability to resolve small incremental changes in temperature. Furthermore, we could parallel these behavioral experiments with similar studies of the neural events that determine the sensory behavior.

We used the difference limen, a classical psychophysical measurement, to determine the ability of human subjects to identify incremental differences in the intensities of successive temperature pulses. The difference limen in these experiments was the minimum difference in temperature (ΔT) in a pair of temperature pulses presented in sequence that could be identified by a subject with a defined probability (0.75 in our experiments). This laboratory experiment parallels the more common experience of briefly touching one, and then another, cold (or warm) metallic object and judging which of the two resulting thermal stimuli is colder (or warmer). It is important to appreciate the characteristics of the stimulus sequences used for determining the difference limen, because in our neurophysiologic studies of thermoreceptive fibers we wanted to use exactly this sequence. This stimulus sequence is illustrated in Figure 1. A temperature pulse lasting 4 sec was presented every 10 sec; successive pairs of stimuli differed in intensity by a small increment. The subject had to indicate (a) which was the more intense stimulus of each pair, and (b) the probability of correct identification.
types in the median nerves of human beings and monkeys. To maximize the flexibility of our experimental designs, we have used human subjects in our behavioral studies and monkeys in our examination of single fibers in a cutaneous nerve.

What fiber populations respond to sudden cooling or warming of the glabrous skin on a monkey’s hand? Three distinct groups have been identified:
1. “Cold” fibers, which are uniquely excited by cooling the skin, suppressed by warming the skin, and quite unresponsive to mechanical deformation of this region [17–19].
2. “Warm” fibers, which are uniquely excited by warming the skin, suppressed by cooling the skin, and unresponsive to mechanical stimulation [20–22].
3. About two-thirds of the slowly adapting Aβ mechanoreceptive fibers innervating a monkey’s hand are excited not only by deformation of the skin but also by local cooling. However, they are at least tenfold less responsive than cold fibers to a sudden cooling.

The ability of human subjects to differentiate changes in the intensity of cooling pulses is shown in Figure 2. The plotted function relates the difference limen and the mean intensity level (T-step or T) at which the discrimination was made. This relationship (the Weber function, not the Weber fraction), is linear and does not change over a wide range of baseline temperatures (29 to 39°C). Note how small the differentiated increments are (e.g., 0.043°C at an I value of 4°C).

The interrelationship between the difference limen, T-step (T), and the baseline temperature (T-base) is quite different for warming pulses (Fig. 3). At a fixed T-base, the difference limen decreases rather than increases over the I range of 0 to 6°C. When the T-base is dropped at 29°C, the subject's discriminative capacity is impaired, although the same general form of the Weber function is sustained.

This Weber function is of a most unusual form. The classical relationship observed for many discriminative tasks involving an intensive parameter (as in Fig. 1) is that, as the intensity level at which the discrimination is made increases, so does the difference limen.

THERMORECEPTIVE FIBER POPULATIONS IN PRIMATE CUTANEOUS NERVE

Ideally, correlational studies of perceptual and neural events should be done in one species. Several studies of cutaneous nerve fibers in human beings have been done [13–16]. The most important finding from our viewpoint is that there is a close functional identity of the different receptor
and detailed studies have shown that these fibers in no way contribute to success in the discriminative tasks we have examined [11].

Cold fibers that innervate a monkey's palm and fingers are common, making up about one-third of all Aδ fibers in the median nerve. They have a mean conduction velocity of about 14.5 m/sec (n = 147; SD = 4.9) and minute receptive fields with diameters of less than 1 mm [23,24]. Individual cold fibers respond to a cooling pulse with precision, as is shown in Figure 4. Each trace illustrates the train of impulses evoked by a single cooling pulse. The stimuli were graded in intensity (I); responses to the more intense stimuli are shown in the upper part of the sequence. Features of the response pattern that can be seen in Figure 4 are: (a) the onset transient, (b) the correlation of the discharge rate over any segment of the response with the stimulus intensity, and (c) the burst discharge occurring in the late part of the response that typifies nearly all cold fibers [21,25].

Warm fibers innervating a monkey's palm and fingers are probably at least as common as cold fibers. These fibers are unmyelinated, with a mean conduction velocity of about 1.25 m/sec (n = 50; SD = 0.5). Their receptive fields are similar to those of cold fibers, i.e., less than 1 mm in diameter. The warm fiber response to a warming pulse typically lacks the large onset transient that we see with most cold fibers. A typical sequence of responses is shown in Figure 5.

One important feature of both cold and warm fiber populations innervating a monkey's palmar and digital skin is functional uniformity. Each of the functional properties of the fiber populations that have been carefully examined so far varies about a single mean value; each has a unimodal distribution. This is true for receptive field size, axon diameter, response profile to a temperature pulse, the various intensity functions relating specific response parameters to I, the effect of changes in T-base on these intensity functions, the pattern of interaction that occurs when a thermoreceptive

Fig. 4. Responses of a cold fiber evoked by cooling pulses of graded intensity applied to monkey palmar skin. T-base was 34°C. The stimulus intensity is indicated on the right side of the figure. A 25-sec interval was used between stimuli to reduce suppressive interaction (From [11])

![Fig. 4. Responses of a cold fiber evoked by cooling pulses of graded intensity applied to monkey palmar skin. T-base was 34°C. The stimulus intensity is indicated on the right side of the figure. A 25-sec interval was used between stimuli to reduce suppressive interaction (From [11])](image)

Fig. 5. Responses of a single warm fiber to graded warming pulses applied to the skin. The skin was adapted at 34°C.

![Fig. 5. Responses of a single warm fiber to graded warming pulses applied to the skin. The skin was adapted at 34°C.](image)

fiber responds to a pair of recurring stimuli, and the variability of responses to defined thermal stimuli. So far our studies have not demonstrated any functional subgroups within either the cold or the warm fiber populations. This finding is important in relation to any attempt to synthesize the responses of a population of thermoreceptive fibers that is based on observations of fibers sampled from this whole population.

It should be noted that there are differences between primate thermoreceptive afferents innervating glabrous and hairy skin of the forearm. Cold fibers from the forearm skin have larger or punctate receptive fields, and although they are Aδ fibers, they have a lower conduction velocity (mean = 7.0 m/sec) than fibers innervating the palm.

PERIPHERAL NEURAL DETERMINANTS OF INTENSITY DISCRIMINATION

Now let us try to relate the peripheral neural and behavioral events in intensity discrimination. For our purpose, the sensory processes underlying a human subject's discrimination of pairs of stimuli that differ only in their intensities may be divided into a succession of events (shown diagrammatically in Fig. 6). These events are:

1. A temperature pulse of intensity I excites the thermoreceptive fiber population innervating the skin that is being stimulated. This peripheral neural response P(I) signals to the brain information not only about intensity I,
Which of the various neural and behavioral events represented in Figure 6 can be measured experimentally? We certainly have no direct measure of the final neural events on which the decision is based. However, the psychometric function, from which the difference limen is derived, relates the probability with which a human observer correctly identified $\Delta I$ in a paired comparison of two stimuli of intensities $I$ and $I + \Delta I$ to the actual value of $\Delta I$. In other words, the subject’s decision process is related to the stimulus events, but not to any of the intervening neural events. The difference limen is simply one value of this psychometric function when the probability of a correct identification of the stimulus increment $= 0.75$.

All neural events in the discriminative processing outlined in Figure 6 that are accessible to experimental measurement can be related to $I$ and $I + \Delta I$ by a function that exactly parallels the psychometric function for human sensory behavior. This enables a direct matching of the neural and behavioral events and an answer to the question: Can this neural response measure account for the discriminative behavior of human beings? If so, the next step in the analysis must focus on determining whether the brain uses this response measure in the discriminative process. Such an analysis has been described by Johnson, Darian-Smith, and LaMotte for cold fibers, and recently a more extensive analysis of the coding of incremental changes in warming pulses by warming fiber populations in primate cutaneous nerve has been completed (unpublished data). Some of these findings are now presented in summary form and are illustrated by use of our data on warm fibers and warm fiber populations.

One major advantage of examining the role of peripheral nerve fiber populations in sensory processing is that no qualification is required for the statement: all the immediate information available to the brain about each of the stimuli applied to the skin must be relayed by the fiber populations of the cutaneous nerve innervating that zone. Since we can record the activity in single fibers of all groups in the nerve, it is experimentally feasible to describe fully the peripheral neural events that code this information. A comparable description is rarely possible when examining the transmission of information within neuron groups at successive levels in the central sensory pathways: parallel processing of information in these pathways and the experimental factors that preclude unbiased sampling of the active neuron populations prevent it.

Consider first the information signaled to the brain by a single warm fiber responding to a train of identical warming pulses of intensity $I$. What is the minimum stimulus increment, $\Delta I_{0.75}$, that can be resolved with a probability of $0.75$? Figure 7 illustrates an experiment to determine the value of $\Delta I_{0.75}$ when $I = 4.00 \degree C$ and $T{\text{-base}} = 34 \degree C$. Part of a long train of stimuli with intensities alternating between $4.00 \degree C$ and $4.50 \degree C$ is shown. Several stas-
tics of the fiber's response can be estimated from this sequence: (a) the mean cumulative count over successively longer intervals of the stimulus period $R(I)$, (b) the standard deviation of this Gaussian response $\sigma_{R}$, and (c) the fiber's sensitivity to incremental changes in $I$, $dR/dI$. For any particular integration interval it can be shown that when $\Delta I$ is small, if:

$$\Delta R = \sigma_{R}$$

then

$$R(I + \Delta I) > R(I) \text{ with a probability of } 0.75$$

The stimulus increment that generates $\Delta R$ is estimated from the relationship

$$\Delta R = \frac{dR}{dI} \cdot \Delta I$$

and hence

$$\Delta I_{0.75} = \frac{\sigma_{R}}{dR/dI}$$

$\Delta I_{0.75}$ is termed the = discriminable stimulus increment (DSI).

We now have a measure of the fiber's capacity to resolve changes in the intensity of the warming pulse that can be directly compared with the discriminative capacity of human subjects (the difference limen).

Figure 8 illustrates the function relating DSI to the cumulative impulse count over successively longer intervals of the stimulus; the relationship for three separate fibers is shown. In each instance the function has a similar form: the resolution rapidly increased as the integration interval was extended to 2 sec, but beyond this period little further intensity resolution was achieved by examining more of the fiber's response. When we examined a large sample of warm fibers, we found that no single fiber signals sufficient information to the brain over the whole 4-sec period of stimulation to account for the human subject's ability to resolve incremental changes in intensity.

Inherent in this finding is the implication that some integrative process within the central nervous system combines the information signaled by individual warm fibers to provide more precise stimulus information. Perhaps the simplest explanation for this mechanism is that the brain "views" the total input from active warm fibers as a single response and in no way differentiates the input of individual fibers, but rather sums or averages the total input. The resulting input, then, is a simple, unweighted averaging of the responses of the individual fiber. If the DSI is calculated on the basis of the total activity of the responding warm fibers, the result is shown in Figure 9. The family of curves relates the DSI to the integration interval for successively larger numbers of active warm fibers. The uppermost curve is the function of the "average" single warm fiber, and the lower curves are the functions for 10, 20, 30, 50, and 100 fibers. The shaded area defines the zone bounded by a human subject's DSI (his difference limen) and the time required for this differentiation (i.e., the subject's measured decision time). Only when the curves describing fiber response overlap the shaded zone defining human behavior (i.e., in the analysis illustrated, only when 20 or more warm fibers contribute to the coding of the stimulus intensity) does the population of the warm fibers signal sufficient information to match human intensity resolution.

Any averaging process such as the one we have specified is most effective in describing the stimulus only when the responses of the fibers are entirely independent of each other. If a component of each fiber's variability is common to all fibers in

![Fig. 7. Basis for determining the discriminable stimulus increment (DSI) for a single warm fiber. Left side: The sequence of responses to warming pulses.](image)

![Fig. 8. Functions for three warm fibers that relate the discriminable stimulus increment (DSI) to the stimulus duration over which the response was measured. The response measure was the cumulative impulse count over this integration period. Stimulus parameters were: $I = 4^\circ$C; $T$-base = $34^\circ$C.](image)
certainly are demanding on the central neural processing.

What we need is a more efficient integrative process that does not simply average the input of individual fibers, but rather biases the averaging procedure in favor of those fibers that signal the most information, i.e., some form of "weighted" averaging. Weighted averaging to provide the optimal estimate of the input to a system such as the warm fiber population is a general statistical problem that has been examined carefully by Rao [27] and by Cramer [28]. Using their analyses, one may show that the optimal DSI for a population of n warm fibers, i.e., the maximal possible resolution of increments of I, is obtained with the following weighted averaging procedure:

\[
\frac{1}{(DSI_{\text{optimal}})^2} = \sum_{i=1}^{n} \frac{1}{(DSI_i)^2}
\]

Figure 10 compares the DSI for 50 independently responding warm fibers when the integrative processing is unweighted on the one hand, and optimally weighted on the other. Weighted averaging reduces the DSI to less than half the human difference limen. A further advantage, not illustrated, is that although dependent variability among warm fibers would degrade the DSI regardless of the averaging process, the optimally weighted average is significantly less sensitive to this population characteristic.

Clearly, central processing of the input of a population of warm fibers that maximizes the contribution of the most responsive fibers and downgrades the contribution of the less responsive noisy fibers would have important biologic advantages. Our experiments suggest that some such processing does occur in the central nervous system of primates. Several local neuronal circuits could ef-

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**Fig. 9.** Family of curves relating the DSI to the integration interval for successively larger numbers of active warm fibers. This sequence was constructed from data obtained from 18 warm fibers. Stimulus parameters: I = 4°C, T-base = 34°C. The hatched zone, bounded by the difference limen (=DSI) and the decision time of 2.5 sec, defines the intensity resolution achieved by a trained observer. Only when the function for a particular fiber population overlaps the hatched zone does the population signal sufficient information to the brain to account for human discriminative behavior.

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**Fig. 10.** Comparison of the DSI for 50 independently responding fibers when the integrative processing is optimal weighted averaging (see text) on the one hand, and simple unweighted averaging on the other.
fect such a bias in transmission. Suppose that second-order neurons in the thermal sensory pathways have two main inputs: (a) an excitatory input from individual thermoreceptive fibers, and (b) a sustained inhibitory input, perhaps mediated by an interneuron population in the spinal dorsal horn. If each discharging thermoreceptive afferent fiber has two actions related to the fiber's response, i.e., excitation of each relay cell with which it has direct synaptic contact and reduction of the inhibitory input to that cell, the output from the second-order relay neuron population will be a weighted average of the primary afferent input.

In summary, the more peripheral neural mechanisms of thermal sensation in primates have provided a useful model for examining the contributions of single neurons and of populations of neurons to the coding of the intensity of a stimulus. Of course, no generalizations can be made from these studies concerning frequency or rate coding, because there are many types of rate coding, as Perkel and Bullock [29] have emphasized. Nevertheless, the analysis does permit a moderately rigorous description of a specific example of rate coding. Several substantial problems concerning these peripheral mechanisms still need to be examined experimentally. A measure of the dependent variability within a discharging population of thermoreceptive fibers is necessary. A psychophysical study of the effect of changing the stimulus area, and hence the number of responding fibers, is needed to test our model; such a study is currently under way. Correlative studies of human discrimination and peripheral neural events that use stimulus patterns other than a temperature "pulse" are needed to analyze more critically the coding mechanism. Again, these studies are currently under way.

Unfortunately, at present there is a dark side to the picture of thermal sensibility. Central neural events determining these sensations are poorly understood. Older clinical and experimental lesion studies and more recent analyses of dorsal horn neurons uniquely excited by changes in skin temperature establish that the spinal anterolateral system mediates thermal sensibility. However, functional localization of sensory pathways within the forebrain, comparable to that seen for tactile sensation, has not yet been clearly demonstrated; this lack of clear-cut evidence deters study of the central neural transformation of the peripheral events we have been examining.

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