An Inquiry into the Neurophysiological Basis for Pain*

DONALD P. BECKER, M.D.,† HENRY GLUCK, PH.D., FRANK E. NULSEN, M.D., AND
JOHN A. JANE, M.D.
Division of Neurosurgery, Department of Surgery, and Department of Psychiatry, Case Western Reserve
University School of Medicine, and University Hospitals of Cleveland, Cleveland, Ohio

"Tremendous as the part is which pleasure and pain play in our psychic life, we must confess that absolutely nothing is known of their cerebral conditions. It is hard to imagine them as having special centres; it is harder still to invent peculiar forms of process in each and every centre to which these feelings may be due. And let one try as one will to represent the cerebral activity in exclusively mechanical terms, I, for one, find it quite impossible to enumerate what seems to be the facts and yet to make no mention of the psychic side which they possess."

With these words, written in 1890, William James summarized three of the major questions regarding the physiology of pain. First, does pain involve special centers or pathways; second, does a special code or pattern of neuronal activity occur; and third, what is the influence of psychic factors on the perception of pain? This study is devoted to the first two questions, with special emphasis upon the ways in which painful stimuli might be recognized by the organism.

We chose the medial mesencephalon as the locus of recording for the following reasons. First, the anterolateral quadrant of the spinal cord projects to this area and has been recognized as important in the transmission of painful stimuli since the time of Gowers (1878), a fact frequently confirmed when anterolateral cordotomy is performed to relieve pain. Second, stimulation of the smaller fibers in the peripheral nerve results in activity in this region, and the smaller fibers are of critical importance in the perception of pain. Finally, the larger fibers of the dorsal column have been found to terminate lateral to this region, and interaction between these two systems may be important in those central events following peripheral stimuli that lead to pain perception.

In our study we have been concerned not only with the presence or absence of a response in a given unit, but in its response pattern, which may correlate with information about intensity, as increasing peripheral electrical or physiological stimuli are applied through gradations considered non-noxious to reach noxious levels.

Methods

Experimental Preparation. Adult cats, anesthetized with halothane and nitrous oxide, were paralyzed with gallamine triethiodide and artificially ventilated. Each animal was placed in a Pfeiffer stereotaxic instrument and both superficial radial nerves were isolated and placed on distal recording and proximal stimulating platinum electrodes, 10 cm apart. The nerves were cut distally to obtain a monophasic action potential and were covered with a mixture of mineral oil and petroleum jelly. A bilateral pneumothorax was performed to reduce brain movement. After a transthalamic brain section or decortication was performed, the anesthetic was discontinued. The transthalamic brain section was performed through bilateral trephines placed at Horsley-Clarke coordinates anterior 7.0 to 11.0. An adequate transthalamic brain section was determined grossly in each case when the brain was studied postmortem. Trephine sites were filled with bone wax and the skull openings for recording were filled with 4% agar, to further diminish brain movement. Blood pressure was continuously monitored throughout the experiment on a Sanborn instrument (pressure transducer model 267B, carrier pre-amplifier model 350–3000; write-out on 2-channel recording system

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† Present address: U.C.L.A. School of Medicine, Harbor General Hospital, Torrance, California.
model 296) and animals undergoing decortication received blood transfusions in amounts necessary to maintain normal blood pressure and pulse rate. Body core temperature was maintained between 37° and 39°C.

**Recording System.** Unit responses were recorded with glass-insulated tungsten microelectrodes (tip diameter less than 1 μ), attached to a Bak unity gain pre-amplifier, and led through a Tektronix 2A61 amplifier to a Tektronix 565 dual beam oscilloscope and loudspeaker. The peripheral nerve monophasic action potentials (obtained from the cut distal end) were led through a Tektronix 122 pre-amplifier and Type 2A63 amplifier and also monitored oscilloscopically. Both unit and peripheral nerve responses were recorded on magnetic tape.

**Anatomy.** The region studied extended within these Horsley-Clarke coordinates: anterior 2.0 to 4.0; lateral 1.0 to 2.0; depth 2.0 to −4.0. This included periaqueductal gray and ventral tegmentum (Fig. 1). At the conclusion of the experiment either a DC current or radiofrequency current was passed through the electrode at the estimated Horsley-Clarke coordinates anterior 3.0; lateral 1.0; depth 0.0 in order to verify the electrode positions histologically. Trypan blue was then injected intravenously for easier identification of the electrode tracks and lesion. The animal was killed with an overdose of intravenous sodium pentobarbital, and the brain was perfused with 10% formalin.

**Stimulation.** Supramaximal trains of electric stimuli were applied at 3- to 5-sec intervals to the pads of the forepaws alternately as the electrode was being advanced down a track. Any unit responding to this stimulus was then examined, providing the spike duration was greater than 200 μsec. Stimulation was then applied to the superficial radial nerve, and recordings were obtained in the following manner: 100 consecutive 0.5-msec stimuli just above A-beta (A large), just above A-beta-gamma-delta (A large and small), and just above A + C thresholds were applied at 4.25-sec intervals. The 100 responses of the peripheral nerve and central unit at each level of stimulation were recorded on magnetic tape. Physiological stimulation was usually applied in separate experiments, but occasionally in the same experiment with the distal exposed nerve left intact. Touch and rub were considered non-noxious, while strong electric shock, pinch, and heat were considered noxious. Pinch was applied with a hemostat, and heat was applied with a focused flood lamp. Physio-

![Fig. 1. Electrode tract shown in section at Horsley-Clarke anterior 4.0. The region of periaqueductal gray and ventral tegmentum studied is at the level of the superior colliculus and red nucleus.](image-url)
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logical stimuli were first applied for 2 sec after a 5-sec delay to determine response frequency, and then through 1-min periods for interspike interval analysis.

Data Reduction. The 100 peripheral nerve action potentials at each level of stimulation, recorded on magnetic tape through an FM channel, were added on the CAT (TML model 400) which then displayed these responses in graphic form. The central unit responses were also added on the CAT, and the responses were then further computed and displayed with an IBM 1620.

Results

During the course of the experiments, 400 units were observed. Of these, only 25% did not respond grossly to electrical forepaw pad stimulation, and 45% were not held long enough to perform a complete analysis. Of the remaining 120 units, 65% were analyzed in relation to electrical peripheral nerve stimuli, and 35% with physiological stimuli.

Electrical Stimulation of Peripheral Nerves. Figure 2 is an example of the computer-displayed 100 added action potentials obtained from the superficial radial nerve at each level of stimulation. This provided evidence that we were not stimulating smaller fibers inadvertently. A unit responding to forepaw stimulation on one side almost always responded similarly to stimulation on the opposite side, but the response was generally more intense on one side than the other. The few exceptions to bilateral response came in neurons which responded only to large fiber stimulation, and the responding neuron was usually on the opposite side from the stimulus.

The units responding to peripheral nerve stimulation had characteristic response patterns which could be classified into specific groups: I = response to A-beta alone, short latency (5–10 msec) and short duration (20–50 msec) response (18% of total); II = response to A-beta as in I plus a second response of long duration (350 msec or more) appearing with A-beta-gamma-delta activation (32%); III = no response to A-beta only, but response to A-beta-gamma-delta, long latency (up to 500 msec), very long duration (3–4 sec and longer) (27%); IV = response as in II or III, but when C added, a very late burst of activity from 1.3 to 2.5 sec after the stimulus (13%); V = inhibition of spontaneous activity at A-beta or A-beta-gamma-delta threshold, usually with short latency (10%).

Type I. Figure 3 is an example of a unit in this group, in this instance devoid of spontaneous activity. As 100 responses were averaged, the Y-axis represents number of discharges per stimulus. The three graphs represent the response pattern just above the three different thresholds for A large (A-beta), A (A-beta-gamma-delta) and A + C. With increasing stimulus intensity the response pattern was essentially the same, but the total number of discharges per stimulus increased slightly. The distance between the peripheral stimulating and central recording electrodes was 15 cm. The latency to the first response was 8.75 msec, suggesting that several synapses were crossed before this central neuron was excited. This unit responded only once or twice to each 0.5 msec shock, but most units in this group fired 2 to 4 times to each stimulus.

Type II. Figure 4 shows a unit in this group responding to A-beta with a latency of 6.25 msec. There is a second smaller burst of activity from 42.5 to 55.0 msec after the stimulus at this level. Whether this represents the multiple firing pattern of this unit to A-beta stimulation or whether slower conducting fibers (such as A-gamma) were also stimulated peripherally and caused this later response is not possible to determine. When the peripheral nerve stimulus was raised to bring in A-delta, a prolonged burst of activity resulted, beginning 83.75 msec after the stimulus and lasting out to 390 msec. This prolonged burst of increased firing was not correlated with blood pressure changes.

Type III. Units in this group did not respond to A-beta stimulation, as shown in Fig. 5. At the delta level, in this unit, after a 500-msec delay there is a rather marked progressive increase in firing up to a maximum at 1.2 sec. This continues for 6 sec, after which it slowly declines back to the baseline after 12 sec. In this instance, because of the long duration response at the delta level, only 10 consecutive stimuli were given and analyzed at 35-sec intervals. Blood pressure occasionally rose with a stimulus at the delta level, but there was a delay in blood pressure rise beginning 2 to 3
Fig. 2. Computer displayed example of 100 added action potentials obtained from the superficial radial nerve at each level of stimulation. A large represents A-beta. A represents A-beta-gamma-delta.

Fig. 3. Type I unit (A 4.0, L 1.0, D —0.9). As 100 responses were averaged, the ordinate represents number of discharges per stimulus. The stimulus artifact is represented by the small vertical line at a 10 msec delay. The response pattern is essentially the same with increasing stimulus intensity, but the total number of discharges increases.
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Fig. 4. Type II unit (A 3.0, L 1.0, D -1.1). At A-beta there is an early burst beginning at 6.25 msec and a second smaller burst from 42.5 to 55.0 msec after the stimulus. With stimulation at the delta level, the smaller second burst becomes larger and after an 83.75 msec delay there begins a prolonged burst of increased firing lasting out to 390 msec. The increased base line activity relates in part to the "wind-up" effect described in the text.

see after the stimulus. Furthermore, with this unit, a noxious physiological stimulus to the hind paw which elevated blood pressure did not cause increased firing. It therefore, seems unlikely that the response represents stimulation of the unit by the electrode as a result of increased blood pressure and brain movement. It was also observed that the size of the unit response remained constant during the period of analysis, implying a stable brain preparation. Two other units in this group responded over a very long duration lasting more than 8 sec, and the remainder had increased firing lasting up to 3 to 4 sec. The long delay again suggests that multiple synapses are crossed before the midbrain neuron is stimulated.

Type IV. Within the limits of the technique utilized, the addition of C activation by the peripheral nerve stimulus did not strikingly change the response pattern over that seen with total A fiber activation. Often, however, the total number of discharges increased. In addition, there occasionally occurred a very late burst of activity between 1.3 and 2.6 sec after the stimulus. Figure 6 shows such a unit which, with the addition of C, demonstrated a burst of activity occurring between 2.46 and 2.59 sec. Review of the neural recording on the magnetic tape revealed that this was a definite and repeatable increase in discharge. It remains possible, however, that C fiber stimulation could augment central response more strikingly in a situation of repetitive stimulation.10

Type V. Spontaneous activity of units in this group was inhibited either at A-beta or A-beta-gamma-delta levels of stimulation.

Fig. 5. Type III unit (A 4.0, L 1.5, D -2.5). There is no significant response at A-beta level. At A-beta-gamma-delta there is a marked increase in firing reaching a maximum at 1.2 sec, continuing at this level for 6 sec and declining to the base line after 12 sec. This prolonged response was not correlated with blood pressure.
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FIG. 6. Type IV unit (A 2.5, D --1.9, L 1.0). When C fiber stimulation is brought in there is a very delayed discharge occurring between 2.46 and 2.59 sec. A late discharge between 1.3 and 2.6 sec was seen in 10% of the units analyzed with peripheral nerve electrical stimulation.

These units rapidly and progressively became silent with repeated stimulation and were not subjected to computer analysis.

The pattern of response of neurons to A large and A large plus small fibers was noted to be different in another way. Type I neurons responding only to A-beta did not change their frequency or duration of response with each subsequent stimulus. However, Type II, III, and IV neurons, responding to A-beta-gamma-delta with a prolonged response, often displayed a progressive increase in frequency and duration of response with each subsequent stimulus until the cell would fire continuously at a rate much higher than had occurred spontaneously. This “wind-up” has been described by Mendell in the dorsolateral column of the cat spinal cord with stimulation of C fibers in a peripheral nerve.

Physiological Stimulation. Response patterns to physiologic stimuli often demonstrated similarities to those seen with electrical peripheral nerve stimuli. Those units which responded to non-noxious stimuli (30%) generally had short duration responses with little or no after discharge. When the stimulus became intense, little change was noted in the response. Figure 7 is an example. This is a single 16-sec record and the stimulus, represented by the horizontal line, was applied after a 5-sec delay. There is a short latency increase in firing to a supramaximal 2-sec electric shock to the left forepaw pad. There is no after discharge and, in fact, there is post-stimulus inhibition. Units responding in this fashion (with short latency and no after discharge) characteristically responded identically to a non-noxious stimulus such as touch. If they responded to mechanical noxious stimuli, the pattern was similar. That these units often had wide peripheral fields is demonstrated by the response seen to touch to the left face.

Figure 8 is an interspike interval record of the same unit taken from a 60-sec record of spontaneous activity, of response to heat, and
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Fig. 7. (A 3.5, L 1.0, D —1.7) In this single 16-sec record, stimulation was applied for 2 sec after a 5-sec delay. There is a short latency response with no other discharge to supramaximal electric shock and touch. When these units responded to noxious stimuli, the response pattern was similar. T1 represents number of discharges in the prestimulus period, T2 the stimulus period, and T3 the poststimulus period.

of response to touch. This unit responded both to touch and to heat, but with a shorter mean interval and greater response to touch than to heat. An important criticism to the method of stimulus application here is that the intensity of heat applied over 1 min caused swelling of the limb pad. Mechanoreceptors may have thus been stimulated to influence this response.

In contrast, those units responding primarily to noxious stimuli (60%) demonstrated a prolonged after discharge. Figure 9 is an example. Increased firing to a 2-sec supramaximal electric stimulus lasted longer than 11 sec. In this instance the response onset is of short latency, and a minimal but definite response to touch is also noted. Figure 10 is a unit which also belongs in this category. The long after discharge to a supramaximal electrical stimulus and small response to touch is again noted. Figure 11 is an interspike interval record of this unit. There is a definite increase in firing and shortening of the interspike interval with intense heat, whereas with prolonged touch there is some inhibition as the number of discharges diminished and the mean interval increased. This inhibition of firing with prolonged touch was found in more than 90% of the primarily noxious responding neurons analyzed.

As the experiment progressed, the mode of central response to physiological stimuli could be predicted from the response observed to a 2-sec supramaximal electrical stimulus. Units which responded with a short latency and short duration were primarily touch responders; units responding with short latency and prolonged duration responded both to touch and noxious stimuli, but to noxious stimuli with a prolonged discharge; units responding with long latency and long duration responded mainly to noxious stimuli with a prolonged discharge. Thus physiologic stimuli appeared to exhibit analogous variations in unit response to
those observed in the Type I, II, and III responses to electrical peripheral nerve stimulation.

It was also observed that neurons responding to noxious stimuli with a long duration response would also frequently show the "wind-up" effect with repeated noxious stimuli. Those responding primarily to non-noxious stimuli without an after discharge only rarely showed the "wind-up" with any type of stimulus.

No separate topographical or anatomical organization of differently responding units could be determined in this study. Units demonstrating each major pattern type were found admixed in periaqueductal gray as well as in ventral tegmentum.

Discussion

The classical approach to the problem of correlating electrical activity with sensibility stems from the concept of "specific nerve energies" proposed originally by Müller and expanded by von Frey. According to this theory, stimulation of specific individual cutaneous receptors (which provide sensation for only one modality) results in central conduction of nerve impulses in specific peripheral fibers which project to specific central and anatomically distinct pathways in spinal cord and brain. This concept of a direct telephone line nervous system involving focal modality representation is supported by the fact that, in humans, posterior column lesions may give modality specific deficits in sensory perception, as do more central focal lesions in this lemniscal system in brainstem, in the specific relay nuclei of thalamus, and in the sensory cortex. Not only can focal lesions cause loss of vibratory and proprioceptive sense, but finer discrimination and localization of all sensory modalities are impaired. Furthermore, anterolateral cordotomy can abolish contralateral pain, temperature and itch sensation quite totally for at least many months without effect upon other sensory modalities such as proprioception, touch, and their discrimination.
These anatomical arguments for specificity of modality representation have physiologic support. With increasing strength of electrical stimuli to the exposed and electrically monitored sural nerve in the human, any parameters of stimulation resulting in near maximal but pure large fiber activity never give rise to sensations described as painful. Rather, pain is noted by the patient at the moment delta fiber activity is monitored with increased stimulus. Pain is also experienced with isolated small fiber activation after large fiber activity has been blocked. These data suggest that there is an important relationship between fiber size and the transmission of sensation judged by the organism to be painful.

However, much recent evidence raises doubts concerning the specificity of receptors and of the pathways in the spinal cord and brain. Moreover, certain patterns observed in units provide further contradictions to this concept of fiber and locus specificity.

1. Specific receptors: The human cornea contains only fine free nerve endings, morphologically indistinguishable from each other. Yet the human witness can distinguish warmth, cold, touch, and pain when the cornea is appropriately stimulated. Of further interest is that the unmyelinated C fibers (0.5–1.5 μ in diameter), originally considered along with the smaller myelinated delta axons to be pain fibers, have been shown to have a variety of receptors specifically and exquisitely sensitive to cold, or to warmth or to touch. It thus appears that the large number of unmyelinated fibers (which in cutaneous nerves outnumber myelinated fibers 3 to 12 times) subserve various modalities just as do the myelinated fibers. Indeed, only a limited number of individual C fibers investigated have had very high thresholds suggesting specificity for pain only, and even these were usually modality specific (mechanoreceptors, cold or warmth receptor).

2. Pathways in cord. Recent studies have
demonstrated that there occurs convergence of both myelinated and unmyelinated peripheral axons upon a single secondary sensory neuron in the spinal cord.\(^7\) It has been shown that a single axon in the dorsolateral column of cat may respond to both A fiber stimulation and C fiber stimulation, and to each in a very different way. Thus the cable theory becomes immediately suspect as soon as peripheral neural impulses are transmitted across the first central synapse. Furthermore, as reported above, this present study demonstrates certain single midbrain neurons responsive to both large and small fiber stimulation, and this has also been observed by Amassian and DeVito.\(^2\)

Other important interrelationships between the large fiber system and smaller fiber system have been demonstrated. It has been suggested that the large fiber system has an inhibiting effect on the smaller fiber system, and a theory of pain mechanisms has been presented based on these concepts.\(^5,26\) This theory states that large fiber sensory input has an inhibiting effect, beginning at the first central synapse, upon the small fiber system. This concept has been used to explain pain problems such as postherpetic neuralgia and tabes dorsalis, where large fibers have been damaged out of proportion to small fibers.\(^9\) Moreover, although anterolateral cordotomy in man can at first cause total loss of pain perception in a body area, recovery may take place in time.\(^31\) Indeed, from what we know of other sensory and motor systems, plasticity is the rule, and extensive lesions are often followed by partial recovery.\(^11,19-21\)

3. **Pathways in brain.** Although stimulation of specific areas in brain such as sensory cortex or main sensory nucleus of the thalamus will result in a focal contralateral conscious sensation (usually described as numbness or tingling), no evidence of zonal localization of pain has been obtained. Above the level of the foramen magnus a focal lesion
in stem, mesencephalon, thalamus, or cortex may alter pain perception in a body area, but by no means abolish it, even with unilateral hemispherectomy and thalamectomy. Whether or not claims for partial pain relief following focal lesions in thalamus and cortex become further substantiated, the inability to secure an absolute blockade to pain transmission by a focal lesion above the cord level suggests a widely diffusing system of projection for this sensation at stem and higher levels.

In summary, there can be no doubt that small fibers in nerve and in the anterolateral spinal cord are important in the recognition of noxious stimuli. But the problem remains that small fibers in the anterolateral system subserve non-noxious sensations as well, so that their activity may not signal pain. Rather, we must look for a pattern or code within this system that relates to pain perception.

Considering pain to be a modality like vision or audition leads to much confusion in investigating the physiological mechanisms involved. Rather, pain should be defined as an intensity phenomenon.

Since pain is a word used by humans to cover a multitude of intense sensations, it is unreasonable that we should find fixed loci in the nervous system which subserve its perception. Mechanisms must exist by which all organisms can recognize potentially damaging stimuli. Since the dorsal column lemniscal system is the more recent phylogenetic acquisition, it follows that the rest of the cord should be more important for the recognition of noxious stimuli. The fact that anterolateral cordotomy can stop this recognition for long periods of time only to have it return implies that ability to recognize noxious stimulation can be re-learned. This has been suggested by Melzack. Therefore, unlike vision and audition, pain does not appear to have a unique receptor, pathway, and termination, nor does it have a unique adequate stimulus.

4. Patterns of unit responses. The larger A fibers have been shown to respond to innocuous mechanical stimuli at their receptor site. Of importance is the fact that the discharge rate in a single fiber increases progressively as mechanical deformation of its receptor is increased, and this has been defined by a power function. This suggests, at least, that information about the intensity of this particular stimulus is being transmitted centrally as a function of frequency of discharge in large peripheral fibers rather than merely as a place phenomenon. The finely graded profile of activity set up in a population of neural elements may thus be of importance in sensory discrimination.

We have shown that moderately distinctive types of response to intense electrical stimulation can be demonstrated in single neurons in the medial mesencephalon and that natural or physiological stimuli that we would judge to be painful or noxious give similar responses. Mendell has described similar prolonged responses to A + C fiber stimulation in the dorsolateral column of the cat. He did not, however, subdivide the A fiber input, and in our study stimulation of A-delta fibers appeared responsible for this mode of central response. Although the duration of the delayed response at C fiber threshold in the cord in the report of Mendell was shorter than those observed in the midbrain in this study, it is noteworthy that it is seen centrally in the spinal cord. Indeed, a prolonged after discharge in medial spinal cord, as well as in medial caudal medulla and midbrain of cat, to intense stimuli has been described in experiments employing macroelectrodes.

In this study our principal interest was in determining the response patterns to the differential peripheral stimuli described, and thus to identify central coding as possibly related to stimulus intensity. In view of the similarity of the prolonged responses found to nerve stimuli above delta threshold and to noxious physiological stimuli, it is tempting to consider this as a neural response to pain. This possibility becomes more intriguing when we consider the evidence that pain experience occurs in man when the peripheral nerve fiber diameters being stimulated include the smaller gamma-delta group. One might theorize that the prolonged and intense response of multiple units in this region and perhaps in others might signal to the animal that the stimulus is noxious, that pain perception may be related to intensity of neuronal responses, and pain is signaled when this quantitative response reaches a certain level. The "wind-up" effect or in-
creasing central response noted to repeated intense stimuli may relate to this quantitative mechanism.

This concept that pain has no specific receptors, but is produced in the nervous system as a result of summation of impulses excited by intense stimuli is not new. It was suggested by Goldscheider in 1898 and by Sherrington in 1900. However, as pointed out by Sinclair, since the paper of Aehelis in 1936, little has been heard of the summation theory of pain. This may relate in large part to the fact that this theory was based on clinical intuition without direct neurophysiological evidence. Our findings of long duration responses and summation of central responses to intense and repeated stimuli provide new support of this theory of central pain mechanisms.

We must conclude with the reservation that demonstrating differential responses in neural units to differential peripheral stimulation is not equivalent to the demonstration that this change has a particular significance to the organism. One cannot necessarily equate central activity upon peripheral small fiber stimulation with pain because small fibers carry other information. Moreover, central activity in this particular locus may be related to an alerting phenomenon or an autonomic response. The meaning of a specific neural response pattern to an organism is difficult to understand, but psychophysical correlations relating animal behavior to neuronal responses will be relevant.

Summary

The response patterns of single units in periaqueductal gray and mesencephalic tegmentum to differential peripheral nerve stimuli and physiological stimuli have been studied. This was done in the hope of determining a central code or mechanism relating to type or intensity of stimulus.

We found evidence suggesting a convergence of both the large and small fiber systems on units in this region. Units responding primarilv to stimulation which activated small fibers or was noxious, characteristically showed a very prolonged response. In addition, these units often demonstrated a summation effect with repeated intense stimuli.

The results suggest that the summation of peripheral stimuli into a prolonged and increasing central response is one of the characteristics of reaction to stimuli of sufficient intensity to be noxious.

The difficulties involved in studying pain as a specific modality transmitted in specific loci have been reviewed. We believe an alternative concept of response pattern, dependent upon stimulus intensity and summation, can contribute much to understanding the physiology of pain.

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References


