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The intensive aspect of information processing in the intradental A-delta system in man — a psychophysiological analysis of sharp dental pain

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The tooth pulp has many attractive features for the study of peripheral pain mechanisms because of its rich innervation, its unique distribution of nerve fibers and its general disposition to give rise to pain upon stimulation. An experimental model has been developed for simultaneous recordings of intradental multi-unit A-delta nerve activity and the subjective intensity and quality of pain evoked by tooth pulp stimulation in conscious, alert humans. The only teeth to be considered for this kind of investigations are those having such a periodontal condition that they have to be extracted. The nerve activity was recorded from two electrodes placed in the dentin on the labial tooth surface, one at the level of the most incisal part of the pulp, and the other as far apically as possible. Brief cold stimulation was produced by using evaporating ethyl chloride administered between the recording electrodes. The magnitude of perceived pain was estimated by means of an intermodal matching technique (finger span) in combination with verbal descriptors. Of three response criteria selected — average response amplitude, peak amplitude and area under the response curve (integral) — for describing the relationship between intradental nerve activity and sharp, shooting pain, the integral yielded the highest mean correlation coefficient.

INTRODUCTION

Sensations, pain included, are set by the integrated mechanisms of the central nervous system and they are only abstractions of the real world[25]. Sensory pain is an experience evoked by bodily damage or by potentially damaging stimuli. It may have different qualities and may also have aversive emotional aspects. Under almost identical stimulation conditions, the subjective intensity of pain may vary considerably from one person to another[24]. Although there is no disagreement about these common observations, it is a long step from peripheral nerves to mind. It is here that the real problems and controversy begin (for review of nociception, see refs. 34, 35).

In his thesis, 'Studies in the sense of pain', the Swedish psychologist Alrutz[7a] asked these questions: 'What mental manifestations should go under the name of pain? What is the reason why some sensations become painful?' Alrutz advanced then the theory that the first sharp and

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the second dull pain evoked by brief noxious stimulation were subserved by two distinguishable categories of peripheral afferents. He noted furthermore that analgesia could exist without anesthesia and vice versa.

Neurophysiological evidence for the existence of cutaneous myelinated A-delta and unmyelinated C-fibers was provided by Zotterman[47–50], who interpreted these observations as experimental proof of Alrutz' concept and as strong support for Bell's and Müller's theory of specificity[8,28]. For 6 decades it has been known[1] that the impulse frequency of a single nerve fiber can signal the intensity of physical stimuli. Despite the success in the application of microneurography in humans (review in ref. 43), it is far from clear how this unitary response can explain the magnitude of the intensive percept.

Since the sensation of pain represents a psychological state of consciousness, it is necessary to use scaling procedures for the assessment of pain and preferably those which have ratio properties[15,16,24]. The magnitude estimation techniques introduced and developed by Stevens[38] to quantify and describe the relation between sensation and stimulus intensity revealed that the psychophysical function conformed to a power law. The internal consistency of sensory scales has been successfully tested by cross-modality matching[40]. However, an internally consistent conceptual-mathematical structure is a necessary but not sufficient condition for accepting the validity of sensory scales.

For the study of peripheral mechanisms of pain the tooth pulp has many attractive features, because of its rich innervation, its unique distribution of nerve fibers and its general disposition to give rise to pain upon stimulation[2–5,27].

The objective of the present investigation was to analyze the functional relationship between the integrated multi-unit peripheral neural output of the pulp and the resultant sensation of pain and to further test the validity of the experimental model developed by Ahlquist et al.[2] for simultaneous recordings of intradental A-delta nerve activity and the subjective intensity and quality of pain evoked by brief cooling of the tooth in conscious, alert humans.

MATERIALS AND METHODS

Subjects

Five healthy volunteers (aged between 43 and 59 years), whose teeth were to be extracted for prosthodontic reasons, participated in parallel neurophysiological and psychophysical experiments. A clinical examination of their teeth prior to the study indicated normal sensitivity to thermal stimulation, no tenderness upon percussion or spontaneous pain.

Two of the subjects took part in one experimental session, two subjects participated in two experiments and one volunteer served as a subject in three full experiments. As a rule one week elapsed between the preparation of a tooth and the actual experiment in order to ascertain full recovery from any sensation of pain caused by the preparatory procedures. The irritation due to cavity preparation may activate axon-reflexes and induce mild neurogenic inflammation. If the neurophysiological recordings are made too early after the preparation, electrical artifacts may be obtained due to the galvanic electromotor force (EMF) between dissimilar metals.

This investigation was approved by the ethics committee of the Huddinge Hospital.

Tooth stimulation

Cooling of the labial tooth surface for 1–2 s by the evaporation of ethyl chloride, in the form of a soaked cotton pellet attached to a non-conducting hand-held rod, was used for stimulation. This procedure produced no electrical interference. The series of roughly graded stimuli, consisting of cotton pellets of different sizes, covered approximately a range of pain intensities between weak and strong on the sensory descriptor scale (see below). Changes in temperature on the tooth surface were monitored by means of a thermistor (Devices Temp. Thermistor 3553) placed at the site of application for the only purpose of indicating the onset and time course of the thermal stimuli. In fact, the stimulus proper is a movement of the fluid contents of the dentinal tubules produced by rapidly cooling the tooth[9,10,20] which preferentially elicits activity in pulpal A-delta nerves[19,29,30].

In a direct test of the hydrodynamic theory of dentin sensitivity performed on humans[7], it was clearly shown that controlled changes in fluid movement evoked a sensation of sharp pain which is consistent with the notion that brief cooling (or heating) of the tooth produces a movement of the contents of the dentinal tubules and that this fluid flow induces a selective activation of the A-delta nerves in healthy tooth pulps.

Thus the adequate, or what Paintal[33] would call the natural stimulus is probably a mechanical deformation of the sensory nerve endings causing the initiation of the propagated neural discharge.

Psychophysics

To estimate the magnitude of perceived pain an intermodal matching technique (finger span) was employed[2,3,13,46]. Finger span was measured using a device consisting of two metal arms of adjustable length attached to a linear potentiometer, whose output voltage was recorded on a polygraph. The metal arms were taped to the thumb and index finger of the subject who was trained to set the distance between the two fingers in proportion to the perceived magnitude of numbers between 0 and 100 read to the subject in a random order before the main experiment. In addition to the cross-modal scaling of pain (proprioceptive analog scale, PAS), the subject was also asked to choose a verbal descriptor (no pain, very very weak, very weak, weak, neither strong nor weak, slightly strong, strong, very strong, very very strong, maximal) that best described the most intense percept experienced during each stimulation. The quality of pulpal pain was determined by the subject's selection of one or more expressions characterizing dental pain from a list presented to the subject after the cold stimulation (Table I).

The schematic diagram of the whole recording system is depicted in Fig. 1.

Neurophysiology

A-delta intradental nerve activity (INA)[2,3,17,18,23] was recorded in combination with simultaneous continuous psychophysical scaling of pain. INA was recorded from two electrodes implanted in deep cavities on the labial surface of the tooth (Fig. 1) and displayed on an oscilloscope (for further details, see ref. 3). The total flux of activity was counted by a spike processor with a bin width of 1.25 s, processed by an integrator (EMG integrator NL 703) with a time constant of 0.5 s, and read out on a polygraph. Repeated stimulations were made during relatively long sessions (2 h) without significantly altering the nervous response pattern. The uncertainty (or error) in the recording system was approximately ± 5%.

TABLE I

The list of qualitative expressions characterizing dental pain presented to the subject after each tooth-pulp stimulation

throbbing (bultande)	dull pain (dov smärta)
quivering (dallrande)	sharp pain (skarp smärta)
pounding (dunkande)	shooting pains (ilning)
pulsing (pulserande)	itching (kliande)
vibrating (vibrerande)	smarting (svidande)
aching (molande)	toothache (tandvärk)
pricking (stickande)	burning (brännande)
dental burr-drill (tandläkarborr)	hot (hett)
splitting (blixtrande)	warm (varmt)
penetrating (genomträngande)	biting cool (isande)
bursting (sprängande)	cold (kallt)
radiating (strålande)	slightly aching (malande)
stinging (bitande)	feeling of pressure (tryckande)
attack of cramp (som kramp)	pulling feeling (som ett drag)
pinching (nypande)	swelling pulp (svällande pulpa)

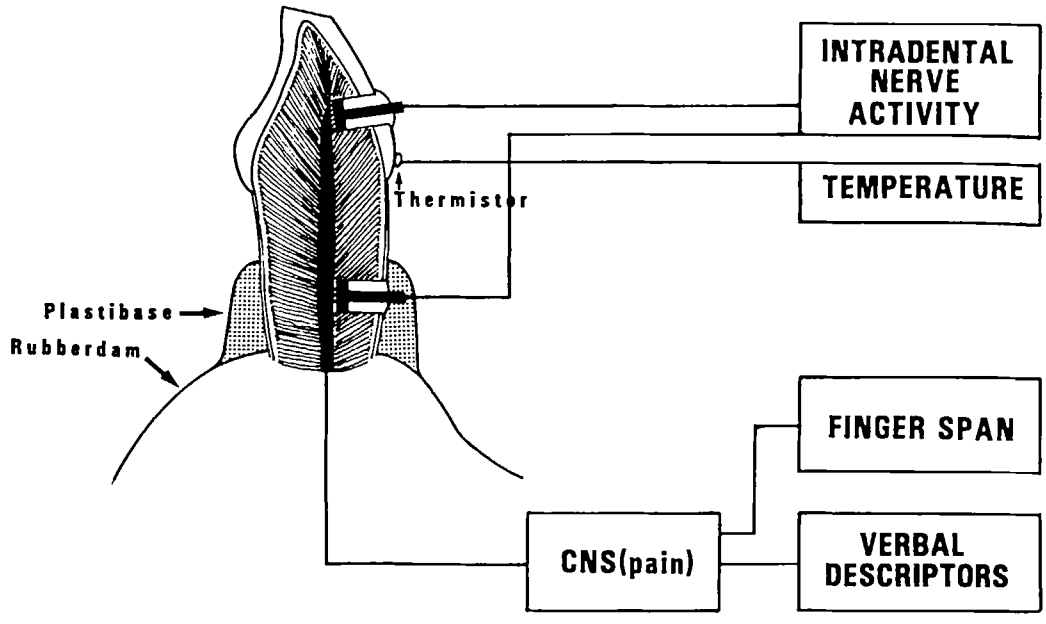


Fig. 1. Schematic diagram of the experimental setup for electrophysiological and psychophysical measurements. The cotton pellet soaked with ethyl chloride was placed between the recording electrodes and in contact with the thermistor.

Analysis of INA and PAS

The data (see Figs. 3 and 4) were analyzed in terms of (1) average response amplitude for the full duration of the perceptual and neural events. This measure corresponds to mean firing rate estimated from spike train data; (2) peak amplitude determined by measuring the response curve from its baseline to its peak; and (3) the area (integral) under the response curves representing the total activity evoked in the neural units. These curves were digitized by means of a Summographics Bit Pad One digitizer and displayed on a graphic terminal, Ramtek 6211. The computer program allowed visual control and thereby minimized errors in the input of the data. Thirty-six (36) points were used to describe each curve and to calculate the area of 35 trapezoids. The sum of these trapezoid values were then computed with an accuracy of 0.01 cm^2 being our final estimate of the total area under the curve from on-set to off-set of INA and PAS.

In congruence with the psychophysical power law of Stevens[38], we assume that equal neural ratios produce equal perceptual ratios, i.e. the sensation magnitude is proportional to the integrated nerve activity raised to a power (exponent), n,

$$P = c \times I^n$$

where P is the magnitude of the percept and I is the integrated neural discharge. This mathematical model will therefore be used for the description of the perceptual-neural relationship. The logarithmic form of a simple power function is a linear equation,

$$\log P = \log c + n \times \log I$$

where log c is the intercept and n is the slope (exponent) of the best fitting function describing the magnitude of the pain percept (P) as a function of the integrated neuronal discharge (I).

All statistical analysis will consequently be conducted on logarithmic coordinates of different response indices.

RESULTS

Four subjects felt sharp and/or shooting pain in 90% of the trials. In one subject (B.L.) pounding, throbbing and/or dull pain was always evoked by the stimulus and it persisted throughout the session. Occasionally, he also experienced shooting pain. In two experimental sessions with

subject B.C. (II and III), he experienced shooting pain that persisted long after the delivery of the cold stimulation. However, this lingering pain was only sensed at the very end of the session. In the first experiment on subject B.C. (I) that took place two weeks earlier, cooling the tooth evoked persistent toothache in 4 out of 6 stimulations. Dull pulsating pain was also experienced between stimulations by subject S.S. in the first session. Only two subjects (P.G.-L. and G.E.) were completely free of any lingering pain after stimulation with ethyl chloride.

The mean of the finger spans assessed by magnitude production was calculated for each subject (Fig. 5a and c). The test-rest reliability of the magnitude production was calculated to be 0.98. The straight line fitted to the data was determined by the method of least squares. The relationship between the number scale and finger span was thus well described by a linear equation with an average regression coefficient of 1.16 and a mean intercept of -8.57. The latter value indicates a somewhat poor proprioceptive resolution at small finger spans with the exception of P.G.-L. and G.E. Because of the very high mean correlation between the finger span settings and the number continuum, $r_{xy} = 0.98$, it seemed unnecessary to make any further scale transformation before comparing the integrated neural output (INA) and the cross-modality matchings of pain intensity as obtained with finger span (PAS).

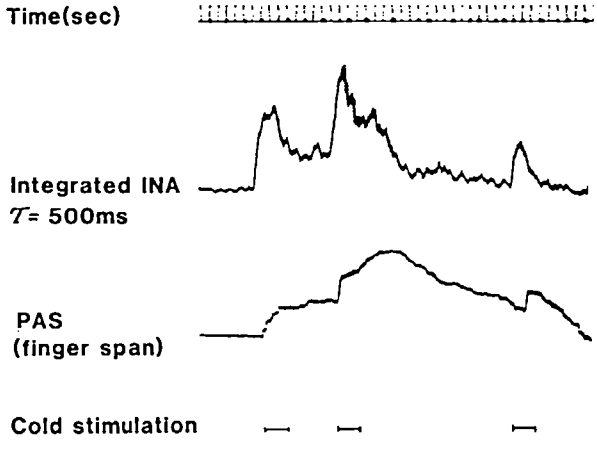


Fig. 2. The result of 3 cold stimuli applied in succession (0 s, 8 s and 25 s) on the tooth surface. The activity evoked by the second and third stimulus was superimposed on an already ongoing neural activity. The subject seemed to respond accurately to these changes in neural input (unpublished observation, 1979).

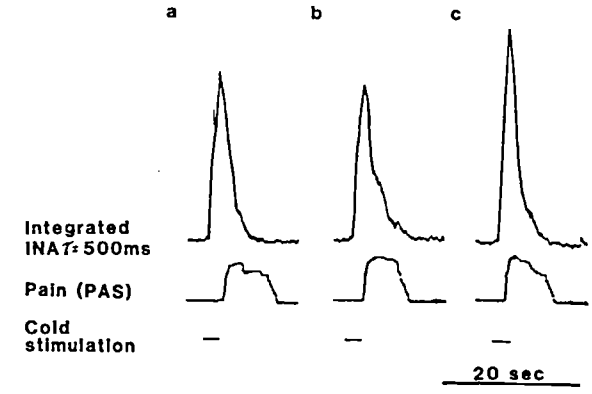


Fig. 3. INA and PAS after 3 cold stimulations in one subject (P.G.-L.). The stimuli were perceived as 'weak' in (a) and (b) and 'neither strong nor weak' in (c). The area under the curves of INA (a–c) was 3.97, 3.77 and 3.97 and under those of PAS (a–c) was 2.04, 1.93 and 2.05, respectively.

Fig. 2 shows the result of one of the first successful experiments, that was encouraging in terms of the quality of the recording and convincing with respect to the agreement between the two response curves. The integrated multi-unit activity in A-delta nerve fibers was elicited by 3 cold stimulations applied in succession as indicated in the graph. The responses evoked by the second and the third cold stimulus were superimposed on an already on-going neural activity and the subject reacted quite accurately to these sudden changes in neural input.

A good reproducibility of the psychophysical–electrophysiological recordings in one subject

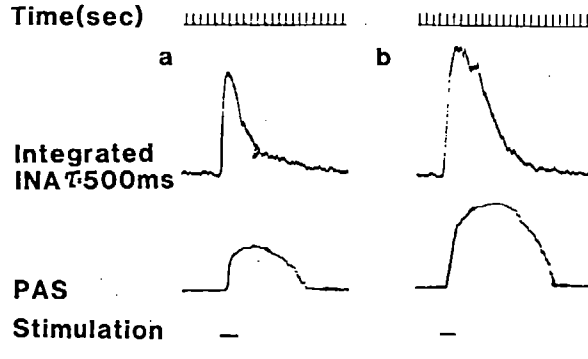


Fig. 4. Responses to two cold stimulations inducing different rates of neural discharge and concomitant changes in perceived pain.

(P.G.-L.) is illustrated in Fig. 3. The multi-unit neural response to cooling always showed a rapid rise to peak amplitude, a short transient and a relatively fast fall to the prestimulus noise level. The sensations following the neural volleys were judged by the subject as 'weak' or 'neither strong nor weak' when she was asked to choose a sensory label to describe her pain.

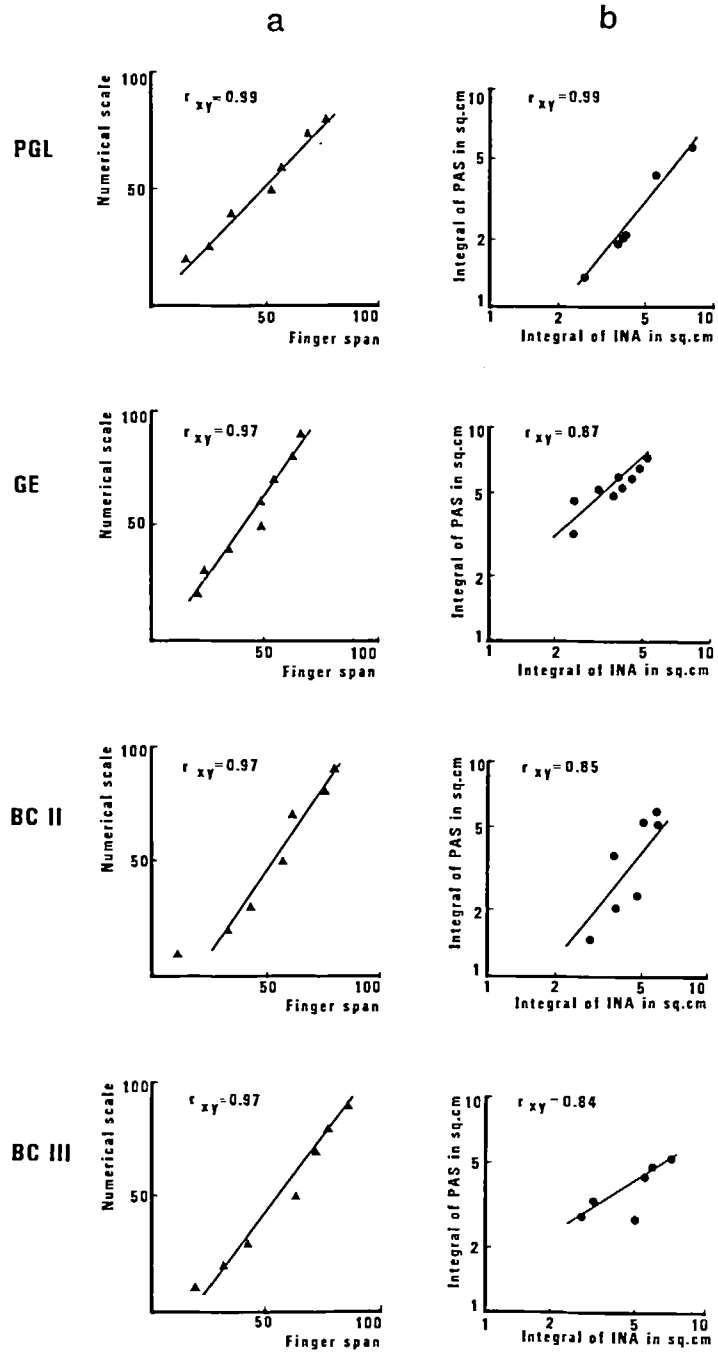
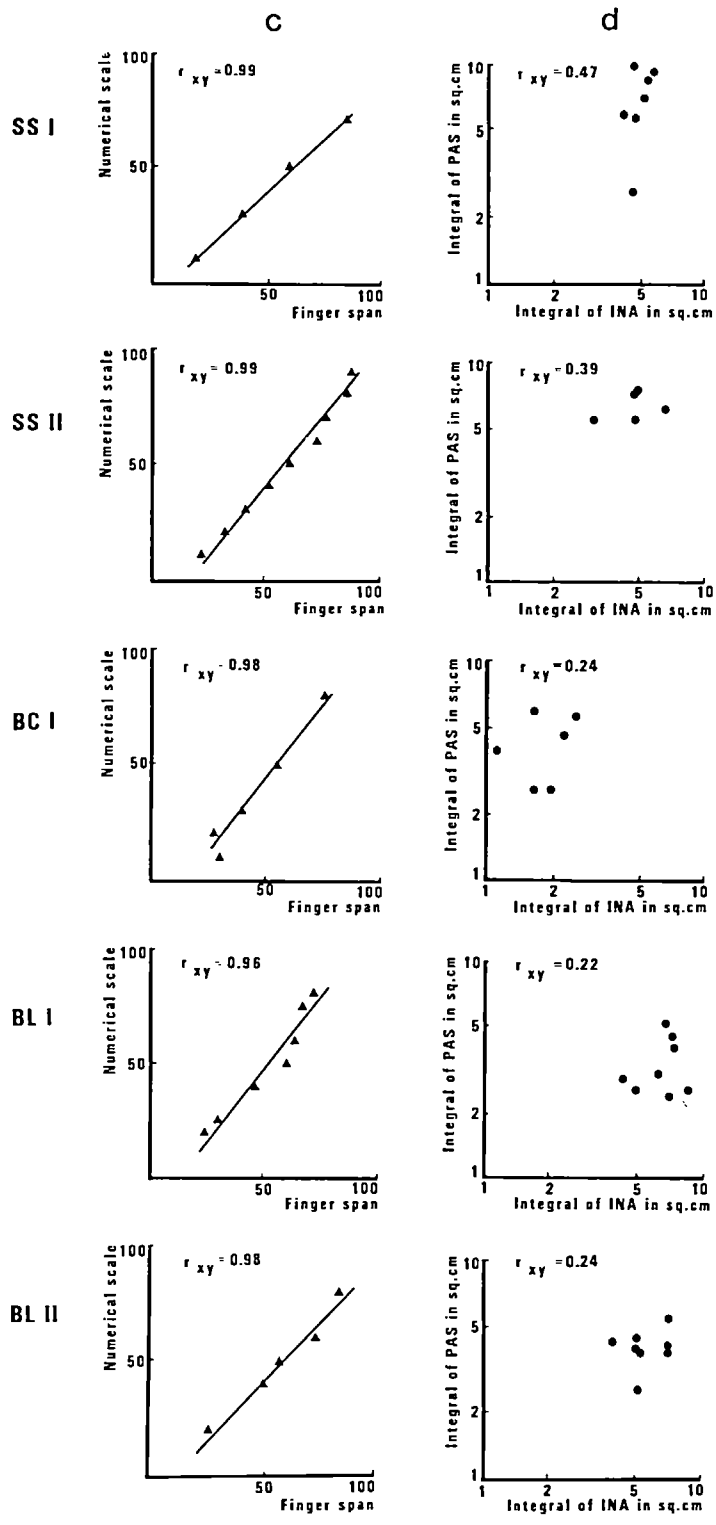


Fig. 5. a: finger span matchings to numbers (numerical scale) read by the experimenter. Finger span was approximately proportional to the subjective impression of the numbers in linear coordinates. b: the integral of INA plotted against the integral of PAS in log–log coordinates. The linear trend of the plots indicates that a power function describes the neural–perceptual relation. The stimuli elicited sharp, shooting pain judged to fall within the range of 'weak' to 'strong' on the descriptor scale.



c: finger span matchings to numbers (numerical state) read by the experimenter. Finger span was approximately proportional to the subjective impression of the numbers in linear coordinates. d: the integral of INA plotted against the integral of PAS in log–log coordinates. In these subjects the cooling stimuli evoked mixed percepts of sharp and dull, throbbing pain, which may explain the apparent inconsistency in the pain estimates and thus the poor correlation between the responses.

The results of two cold stimulations inducing different rates of neural discharge and producing corresponding changes in perceived pain are displayed in Fig. 4. It is obvious that an increment in the neural response is parallelled by an increase in the pain rating. Higher intensities of INA and PAS were usually accompanied by longer durations, ranging from 6 to 16 s for INA and from 6 to 18 s for PAS.

Those subjects (S.S. I, B.C. I, B.L. I and B.L. II) who had either sensations or after-sensation of pounding, throbbing and dull pain were for these reasons excluded from the final quantitative analysis. Moreover, S.S. II was eliminated because of difficulties in determining the offset of his finger span curves. From the 4 sessions carried out on the subjects P.G.-L., G.E. and B.C. (II + III) participating in the main experiment, a total of 28 pairs of neural-perceptual tracings were obtained. We first measured the average response amplitude per second for each pair of records. The Pearson product-moment correlation coefficient, r_{xy}, was then calculated and used as an indicator of the goodness of fit of the measurements of INA and PAS to a straight line determined by the method of least squares. It had an average value of 0.48. The square of the correlation coefficient yields an estimate of the ratio of the predicted variance to the obtained variance. This coefficient of determination, r_{xy}^2, had a value of 0.28, indicating how much the neural response could account for the variance in the perceptual response. Next, the peak amplitude of INA and PAS was computed. This gave a correlation coefficient of 0.67 and the coefficient of determination increased to 0.45. The coefficient of correlation computed for all 28 pairs of integrals (area) had a mean value of 0.90.

The uncertainty in the measurement system of 10% would justify a collapse of adjacent INAs within that bracket, which would reduce the variability and raise the already high correlation.

In Fig. 5b log PAS is plotted as a function of log INA. The regression equation for the relationship between INA and PAS, $\log P = \log c + n \log I$, had a mean regression coefficient (exponent, slope), n, of 1.07 and an intercept, log c, of 0.15. The data points fall close to a straight line indicating that a power function adequately describes the relation between the two response measures. A slope of 1.0 represents direct proportionality between the integral of INA and PAS. Inspection of Fig. 5c and d makes it clear that the inconsistency in the pain estimates in response to changes in the neural discharge cannot be explained by the subjects' inability to perform cross-modality matchings. The neural response range for these subjects is more limited than for those accepted for the final analysis. It is interesting that the subjects who perceived dull, throbbing pain constantly exhibited very low correlations. A general trend appeared to be that the fewer qualitative reports of dull pain after cold stimulation, the greater consistency in the subjects' quantitative estimations.

The displacement of G.E. relative to P.G.-L. along the dimension of PAS reflects differences in the constants of the linear equation. Apparently, G.E. reported more pain than P.G.-L. for the same range of neural input (Fig. 5b). The lowest psychophysical response of P.G.-L. corresponds to the category 'weak' on the verbal descriptor scale and the upper values for G.E. correspond to a feeling of 'strong' pain.

DISCUSSION

The present study provided further evidence that the A-delta barrage from a healthy tooth pulp was highly correlated with a sensation of sharp and/or shooting pain and consequently that the sensation quality was mediated by a labeled line code. Strong support for the labeled line concept was furnished by recent investigations using intraneural microstimulation in awake human subjects[32,41]. Activation of single A-delta fibers was felt as pricking pain and co-activation of several C-fibers evoked a sensation of delayed burning pain. The projected receptive field sizes were smaller for sharp pain than those for dull pain[36].

Since environmental stimulation received by the organism must necessarily produce changes in a large population of nerve cells, we propose that the magnitude of the intensive percept may in general be encoded by a population code, i.e. by

an increase in firing rate of the sensory nerves and/or by recruitment of sensory units with increasing intensity.

It was not self-evident, however, what aspect of the response to select as a candidate for a neural code. That is, which response index of INA — mean response amplitude, peak amplitude or integral of the response curve — would best correlate with the perception of sharp pain. As there was a change not only in amplitude but also in duration of the responses (Fig. 4), one variable might be more important than the other. The time–intensity curves in Fig. 4 raised the fundamental question how to best describe and analyze the relationship between the neural and perceptual responses so they most adequately reflect the information processing of the intensive aspect of sharp dental pain. Measuring the mean response amplitude and peak amplitude of INA and PAS left about 55–70% of the variance unaccounted for. There could be several reasons for this outcome. One is that we did not have the opportunity to repeat an identical stimulus several times which would allow an averaging out of spontaneous fluctuations in the neural and perceptual responses from one presentation to another.

A procedure that disregards moment-to-moment fluctuations in the activity at peripheral and central levels is to calculate the integral (the area under the response curve) of the neural and perceptual events. This stands out as a logical approach, since all sensory systems integrate over space and time[22,26].

The results shown in Fig. 5b indicate that the perceptual–neural relation can be satisfactorily approximated by a simple power function with an average exponent close to unity under the condition that the two separate response measures are appropriately specified. The integrated multiunit A-delta nerve activity appears thus to be not only the neural correlate of perceived pain, but it may in fact constitute the underlying peripheral neurophysiological mechanism of the sensory magnitude of sharp pain.

A mathematical model has been developed[12,37] that describes the transfer function between the neural and the perceptual output and that may be useful for analyzing and determining the relative weight of the intensity and time dimensions of INA for generating a pain percept. There is no antithesis between the complexity of this model and the relative simplicity of the functional relationship of the integral measures obtained in the present study. The two approaches serve different purposes in the search for an understanding of the peripheral-central mechanisms for coding a nociceptive warning message sent over the A-delta system of the trigeminal pathway in order to alert the organism and to initiate appropriate motor behavior. The sensory systems may basically have a surprising simplicity under normal conditions[39].

The circumstance that cooling stimuli could produce sensations and after-sensations of throbbing, pounding and dull pain, which was the case for the subjects B.L., S.S. and B.C. I, may be an indication of pulps in a state of inflammation[11]. These patients may have an elevated pulpal tissue pressure and/or lowered pain threshold which modified their response[42,44]. Indirect electrophysiological evidence of an ongoing pulpal inflammatory process in human teeth having a similar periodontal condition have previously been furnished using heat stimulation[5] and an algogenic agent such as histamine[4,6].

Sustained C-fiber activity as inferred from the quality of the pain percept may have disturbed these subjects' attention to and detrimentally interfered with their perception of the stimulus-evoked A-delta influx resulting in a poor consistency in the psychophysical responses. A lawful relationship might have been obtained if we were able to record from the C-fiber population or some combination of A-delta and C-fibers.

It is known that noxious stimulation exciting somatic and dental A-delta afferents may exert a masking or inhibitory effect on C-fiber activity or C-fiber-related sensations[14,21,45,46]. It remains to explore, though, how an ongoing, concurrent discharge in C-units influences the transformation and the central information processing of the peripheral A-delta input and how such a contextual effect shapes human sensory experience of sharp pain.

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