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Habituation to repeated painful and non-painful cutaneous stimuli: a quantitative psychophysical study*

R.J. Milne[1], N.E. Kay[1], and R.J. Irwin[2]

Departments of Physiology[1] and Psychology[2], University of Auckland, New Zealand

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Summary. Repeated stimuli elicit progressively smaller responses and elevated sensory and/or pain thresholds (habituation). The present experiments were designed to determine the rate of habituation of perceptual responses to supraliminal painful and non-painful cutaneous stimuli. Changes in the perceived intensity of electrical stimuli applied to the digital nerves of the index finger were determined by a matching procedure in which subjects set the current applied to the index finger of one hand to match the perceived intensity of a stimulus train (5 pulses at 20 Hz) applied to the other index finger. Twenty-five volunteers took part in 7 experiments in which both non-painful (2.5 times the sensory threshold T_s) and painful (1.2 times the pain threshold T_p) stimulus trains were presented. Subjects were required to match the stimuli at 30 s intervals over a period of 7.5 min. The percentage change in matching current (Y) was fitted by the function $Y = -20.7*[1-\exp(-0.56*t)]$ for both painful and non-painful stimuli repeated at 2 Hz. Responses recovered completely within 2 min of cessation of the stimulation. The degree of habituation increased or decreased with the rate of stimulus presentation. These results did not depend on changes in afferent fibre recruitment or fatigue because the afferent volley on the median nerve remained constant throughout the period of stimulation. Thus perceptual responses to the perceived intensity of supraliminal painful and non-painful stimuli delivered to the index finger habituate to the same extent, and the extent of the habituation is a function of the frequency of presentation of the stimulus.

Key words: Cutaneous sensation – Stimulus matching – Habituation – Pain – Human

Introduction

In many systems, repeated stimuli elicit progressively smaller responses. This phenomenon has been defined operationally as 'habituation' (Glaser 1966). Habituation is said to have the following properties (Thompson and Spencer 1966): repeated applications give reduced responses; weaker stimuli give more rapid habituation; the response recovers after the stimulus is withheld; the phenomenon is a function of the frequency of the applied stimulus; extraneous stimuli may result in recovery of the attenuated response (dishabituation). Habituation has been described in spinal reflexes in man (Dimitrijevic et al. 1972); the human blink reflex (Duranti et al. 1983); the electroencephalogram in the cat (Sharpless and Jasper 1956) and in man (Sokolov 1975; Thompson and Spencer 1966; Bromm and Scharein 1982; Condes-Lara et al. 1981); the somato-sensory evoked potential in the rat (Dowman and Rosenfeld 1985) and in man (Jacobson et al. 1985); the dental and auditory evoked response in man (Chapman et al. 1981; Ohman and Lader 1972) and pain thresholds in the rat (Gamble and Milne 1989; Milne and Gamble 1989; Milne et al. 1989). Since the extent and time course of habituation differs from system to system, it seems likely that more than one process may be operating.

In the study of habituation to painful stimulation, most human research has been devoted to the study of subjective changes or changes in thresholds (e.g., Dallenbach 1939; Ernst et al. 1986). In this report we describe a relatively simple method of measuring changes in the perceived magnitude of responses to painful and non-painful electrical stimuli applied to the digits of one hand. The method relies upon comparisons of the perceived intensity of stimuli applied concurrently to homologous sites on each side of the body. We have used this method to characterise the time course of decrements in response to stimuli applied at different frequencies and

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Offprint requests to: R.J. Milne, Adis International Ltd, Private Bag, Mairangi Bay, Auckland, New Zealand

intensities ranging from non-painful to moderately painful.

Our results show that the rate of decrement of the perceived response depends upon the rate but not upon the intensity of the applied stimulus, within the range of intensities tested.

Methods

Subjects

A total of 25 normal volunteers (16 men and 9 women) aged from 15 to 59 years served in the experiments. They were all reportedly in good health.

Experimental environment

The subject was seated comfortably in a quiet room free from interruptions. The forearms rested on two small tables whose heights were adjusted so that each forearm was supported comfortably in a horizontal position. The subject was asked to clench each fist lightly, leaving the index fingers extended. Pairs of electrodes were then applied to the index finger of each hand.

Electrical stimulation

After thorough cleaning of the skin of the index finger with acetone, pairs of ring electrodes saturated with normal saline and covered with a layer of conductive gel were placed midway between the proximal and distal interphalangeal joint, and midway between the proximal interphalangeal and metacarpophalangeal joints. The electrodes were approximately 25 mm apart. Care was taken to ensure that the area between the electrodes was free of gel. In some experiments, in addition to the reference and matching electrodes, a second pair of electrodes was applied to the right index finger, distal to the original pair. The more distal of these two electrodes was placed on the finger tip. The stimulus was provided by an isolated constant-voltage stimulator controlled by solid-state timers. The voltage across a 100 ohm resistor in series with each electrode was measured and displayed on an oscilloscope. Typical electrode impedance was in the range 1200–1500 ohms. Results were discarded if the electrode impedance changed significantly during the experiment. In general, only small random variations in electrode impedance were observed. Each 'stimulus' consisted of a 200 ms train of five pulses (0.2 ms pulse width, 50 ms interval between pulses).

Threshold measurements

Both the absolute sensory threshold (T_s) and the pain threshold (T_p) were determined for the reference stimulus by the method of limits. In determining these thresholds, only ascending series of intensities were presented, to avoid the need for highly painful stimulation. The starting intensity of each ascending series was varied in an unpredictable way, and the series were repeated until three consecutive threshold estimates that were within 5% of one another were obtained. The mean of these three estimates was taken as the threshold value. On average the pain threshold was 4.6 times greater than the sensory threshold. Most subjects reported that stimuli greater than $1.5*T_p$ were very uncomfortable. (By contrast, Rollman and Harris (1987) found the pain threshold was about twice the sensation threshold, and tolerance about three times the pain threshold. They stimulated the volar surface of the forearm with a 40-pulse train, so the difference may stem from differences in either the site of stimulation or the stimulus parameters.)

Matching measurements

The method consisted of requiring the subject to decide whether a stimulus presented to the right (reference) side was greater than or less than a stimulus applied to the left (matching) side. Stimuli were applied to the right (reference) index finger at intensities that were either a little below the pain threshold ($2.5*T_s$) or moderately painful ($1.2*T_p$). Stimuli were delivered to each index finger simultaneously and the subject was instructed to say whether the stimulus to the left (matching) finger should be increased or decreased to match the perceived intensity of the stimulus applied to the right (reference) finger. A range of stimuli both greater than and less than the reference stimulus were applied to the matching finger.

The intensity of the matching stimulus started at zero and was adjusted by steadily turning a potentiometer with the experimenter blind to the dial reading. Subjects instructed the experimenter to turn the stimulus up until they judged it exceeded a match, then down, and so on until they reported a match. Subjects were encouraged to make their judgements quickly and decisively. In general, subjects made their decision in less than 5 s. In effect, this is the psychophysical method of adjustment with the adjustments being made by the experimenter in response to instructions of the subject (Milne et al. 1988).

Experimental design

Each session comprised three phases:

1. *Baseline.* The subject made three matches to the reference stimulus at times zero, 2 min, and 4 min. The average matching current on these three trials served as a baseline to which other matches could be compared. During matching, the 200 ms pulse train was always presented at 2 Hz.

2. *Experimental.* The subject made 15 matches at 0.5 min intervals for 7.5 min. The subject was alerted immediately prior to each impending matching requirement.

3. *Post-experimental.* After a 2 min rest, the subject made three more matches at 2 min intervals.

Afferent volley

In addition to the usual stimulating electrodes that were applied to the left index finger, a pair of silver disc recording electrodes (0.9 mm diameter) were placed 20 mm apart on the ventral surface of the wrist overlying the median nerve that provides the afferent supply of the finger (Gray 1973). The skin at the recording electrode sites was carefully cleaned and roughened, and conductive gel was applied to the electrodes.

The recorded signals of the afferent nerve stimulation were amplified, filtered (bandwidth 50 to 5000 Hz), and averaged over 255 sweeps with respect to the instant of electrical stimulation by a Neurolog hardwired averager.

Statistical analysis

Data were analysed from a split plot or a randomised block factorial design as appropriate. A two-sided Student's t-test was used in some instances and Tukey's post-hoc HSD test was used for further analysis of main and interaction effects. All statistical analysis was performed on an IBM mainframe using the SAS statistical package. A 1% significance level was adopted throughout these analyses. In all illustrations, vertical lines represent 95% confidence intervals. Smooth curves were fitted using a general non-linear least squares method.

All experiments were approved by the appropriate institutional human subjects ethics committee.

Results

Short term stability of matching

The purpose of the first experiment was to determine whether subjects could reliably and reproducibly match stimuli over a 7.5 min period without any other experimental intervention.

Ten subjects were randomly assigned to two groups of 5 subjects. Each group received both non-painful and painful stimulation of the reference finger. One group received non-painful stimuli ($2.5*T_s$) first, and the other group received painful stimuli ($1.2*T_p$) first. After the matches to the first reference stimulus level were completed, the electrodes were removed and the subjects rested for 15 min before the second level of stimulation was presented. In order to determine a match, the reference pulse train was presented at 2 Hz for up to 5 s (usually less, see Methods) or until a match was made. This measurement was repeated at 30 s intervals.

There was a large spread of matching currents among subjects, reflecting different sensory and pain thresholds. The results of this experiment showed no significant change in matching current during the course of the experiment and are shown as the control data in Fig. 1 (below).

Effects of repeated stimulation upon matching currents

Twenty volunteers were randomly assigned to two groups of ten subjects each. One group received non-painful stimulation to the reference finger ($2.5*T_s$) first, and the other group received painful reference stimulation ($1.2*T_p$) first. The same three phases (baseline, experimental, and post-experimental) studied in the first experiment on the stability of matching were employed in this experiment. Here, however, the three phases were presented twice in succession. On the first presentation, the reference stimuli were presented three times at 2 min intervals ('baseline'), then they were presented at 500 ms intervals for 7.5 min (the 'experimental phase'), and then, after a 2 min pause, they were presented three times at 2 min intervals (the 'post-experimental' phase). This three-phase sequence was then repeated, again after a 2 min pause, at the same intensity (the second presentation).

The electrodes were then removed and the subject rested for 15 min. Electrodes were then replaced and the complete experiment was repeated at the second stimulus intensity. During the experimental phase, all subjects reported verbally that the intensity of the stimulus, whether painful or non-painful, appeared to have diminished. For some subjects the non-painful stimulus appeared to become very faint. Most subjects reported that the 'bite' in the painful stimulus disappeared after about two minutes of continuous stimulation, but they continued to report that the stimulus remained unpleasant.

For statistical analysis, the final three measurements of matching current taken during the period of stimulation were compared with the average of the three baseline and with the three post-experimental values. Randomized block and split-plot ANOVAs showed: – (1) at both painful and non-painful levels of stimulation, the matching currents were lower during the 'experimental' period than either before or after this period (for the two repetitions of the experiment, $F_{(2,9)}=81.0$ and 120.1 for one group, and $F_{(2,9)}=74.8$ and 59.2 for the other group, $P<0.01$ for all comparisons); (2) as expected, the matching currents were higher for the painful than for the non-painful stimulation (for the two repetitions, $F_{(1,9)}=71.7$ and 82.4 for one group, and $F_{(1,9)}=36.5$ and 38.5 for the other group, $P<0.01$ for all comparisons); (3) the matching currents set by the two groups of subjects did not differ from each other [$F_{(1,18)}=2.6$, n.s.]; (4) the percentage decrease in matching current for the painful and non-painful stimuli did not differ [$F_{(1,18)}<1$, n.s.]; and (5) the percentage decrease on the first presentation was greater than on the second [$F_{(1,18)}=9.1$, $P<0.01$].

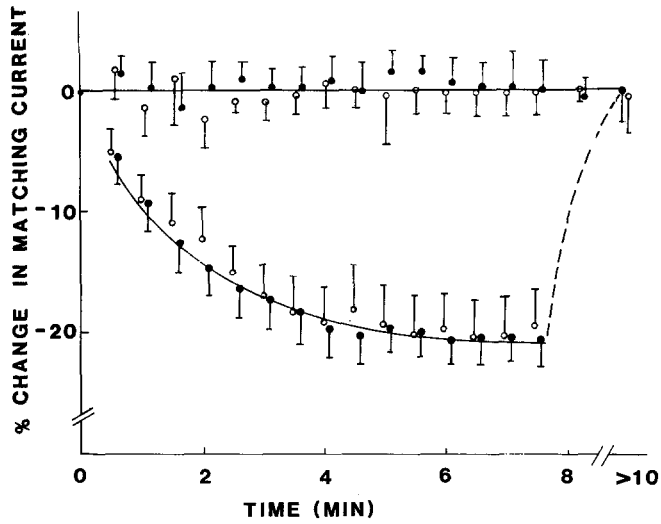

Fig. 1. Percentage changes in matching current at non-painful *(open circles)* and painful *(closed circles)* stimulus intensities. Results are taken from two different experiments. Control experiments ($n=10$) were performed using a stimulus frequency close to 0 Hz (test stimuli repeated at 30 s intervals). The remaining experiments ($n=20$) were performed at 2 Hz. The fitted curve is given by: $Y = -20.7*[1-\exp(-0.56*t)]$

Figure 1 shows the percentage change (relative to baseline) of the matching current, along with the control data described above. Results from groups receiving their first presentation of either painful or non-painful stimuli have been pooled and fitted to the function $Y=-20.7[1-\exp(-0.56*t)$; $\eta=0.92]$. Slightly smaller final values were obtained in response to the second presentation of the stimulus (not illustrated). Under the conditions of these experiments, repeated stimulation caused a decrement of about 20% in the perceived intensity of both painful and non-painful stimuli. As indicated in the figure, the matching currents returned to the initial levels after a two-minute rest.

Long term stability of matching

The purpose of this experiment was to determine whether matching was stable across serially repeated recording

Table 1. Percentage decrease in matching current on separate days. Differences were not statistically significant

Day	Pain	Non-Pain
1	20.0±4.2	22.0±6.2
2	17.2±2.2	18.4±2.4

sessions. We chose to repeat identical experiments one after another, then again after a period of at least one week, with the same subjects. Stimulating electrodes were re-fitted between the two presentations separated by the longer period.

Ten of the 20 subjects who took part in the second experiment were used in this experiment. Subjects were divided at random into two groups with counterbalanced orders of presentation of the two levels of the reference stimulus. Table 1 shows the percentage decrease of matching current to both the painful and non-painful stimuli on two separate days (with consequent re-fitting of the electrodes). Analysis revealed no statistical difference between these changes on either occasion [$F_{(1,9)} = 3.4$; n.s.].

Dependence on stimulus presentation frequency

The difference between control and experimental results shown in Fig. 1 could lie in the frequency of presentation of the reference stimulus (0 and 2 Hz respectively). The purpose of the next experiment was to study other frequencies of presentation to determine more systematically the effects of this variable. Therefore two additional frequencies of stimulus presentation, 1 Hz and 4 Hz, were studied.

Eight volunteers, all of whom had previously participated in earlier experiments, were used. In the experimental phase, the reference stimulus was presented at either 1 Hz or 4 Hz and a match was made once every 30 s as before. During the 5 s matching period, the frequency of presentation of the reference stimulus reverted to the standard 2 Hz, to standardise the conditions under which matches were made. Both the non-painful intensity ($2.5*T_s$) and the painful intensity ($1.2*T_p$) were studied at the 1 Hz presentation frequency, but to minimise discomfort to the subjects only the non-painful stimulus was studied at 4 Hz. A group of five subjects (who had also taken part in the earlier experiments) received the 1 Hz presentation, and another group of five (not all of whom had taken part in the earlier experiments) received the 4 Hz presentation.

Figure 2 shows the time course of habituation of the responses to stimulation frequencies of 0, 1, and 2 Hz. The data for 2 Hz are from an earlier experiment, and the data for 4 Hz, which were not significantly different from those for 2 Hz, have been omitted for clarity. Both non-painful (open symbols) and painful (filled symbols) are shown. The smooth curves represent exponential functions, with time constants of 0.9 min^{-1} and 0.5 min^{-1} for 1 Hz and 2 Hz repetition rates respectively. Clearly, the frequency of presentation had a substantial effect on

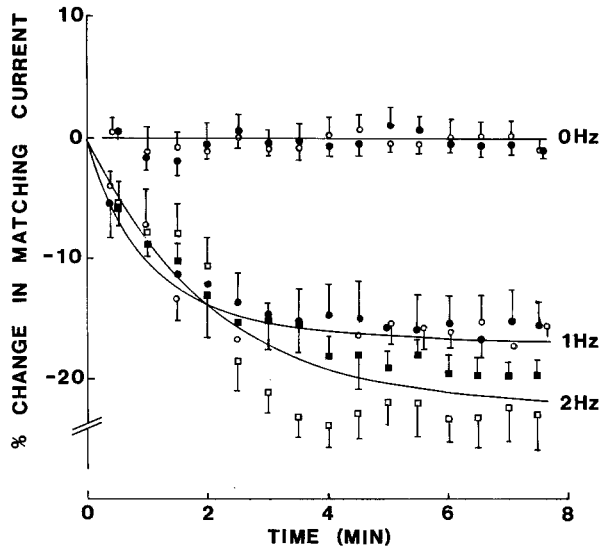

Fig. 2. Percentage change in matching current at non-painful *(open symbols)* and painful *(filled symbols)* stimulus intensities for three different stimulus repetition rates. The fitted curves are as follows:
1 Hz stimulation: $Y = -16.4*[1-\exp(-0.9*t)]$; $\eta = 0.92$]
2 Hz stimulation: $Y = -22.4*[1-\exp(-0.5*t)]$; $\eta = 0.92$]

Table 2. Percentage decrease in matching current as a function of stimulus frequency (non-painful stimulation only)

Stimulus Frequency (Hz)	Decrease
0.0	0.3±0.3
1.0	15.1±1.5
2.0	21.0±2.0
4.0	24.5±5.5

the final amount of habituation, in the expected direction. We were surprised to find that habituation appeared to occur faster with the lower frequency of stimulation, however this difference might perhaps be a result of the forced fit to an exponential function rather than a psychophysical difference.

The mean percentage decrease in matching current for the last five settings was analyzed according to a randomised blocks factorial design. The analysis for the subjects who experienced frequencies of 0, 1, and 2 Hz showed a significant effect of frequency [$F_{(2,8)} = 56.2$; $P < 0.01$], and a Tukey post-hoc test showed all three means to be significantly different from each other. There was no significant difference in the percentage change associated with the two intensities of stimulation. A paired t-test for the five subjects who received both 2 Hz and 4 Hz presentations showed no significant difference between the two frequencies ($t_4 = 1.15$, n.s.) Table 2 summarizes the effects on habituation of the four frequencies studied in these experiments. Since data were not available for 4 Hz at painful stimulus intensities, only responses to non-painful stimuli were analysed.

Control for electrode polarisation

Another experiment was undertaken to exclude the possibility that habituation might result from electrode

polarization or increased resistance at the electrode site. This was done by introducing a second pair of stimulating electrodes through which the stimulation could be delivered during the habituation phase. The original electrodes were then used only to provide the reference stimuli for matching purposes. If the cause of the decrease in matching current found in earlier experiments stemmed from changes in polarization or resistance that accompanied repeated stimulation at the reference site, then no such decrease in matching current should occur in this experiment.

During the experimental phase, stimulation was applied through this distal pair, except for a 5 s matching period which occurred every 30 s. Two intensities ($2.5*T_s$ and $1.2*T_p$) at 2 Hz were again presented, their order being random for each subject.

Experiments were conducted with five subjects. The mean percentage decrease over the last five matches was compared with the results for the same subjects from the second experiment (second presentation). A randomized blocks analysis showed no significant difference between the two experiments [$F_{(1,4)}=0.4$, n.s.], or between the two intensities of stimulation [$F_{(1,4)}=0.4$, n.s.]. Hence the habituation observed in the earlier experiments cannot be attributed to changes in electrode polarization or resistance at the site of the reference electrodes.

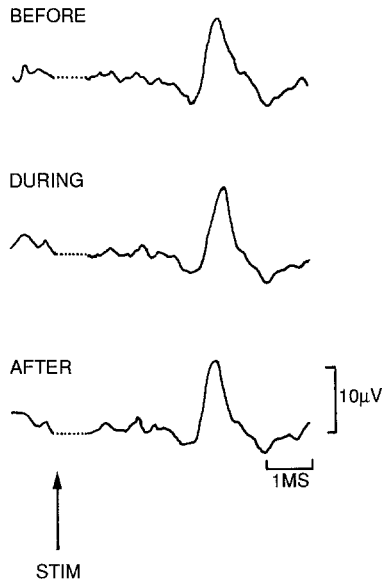

Fig. 3. Typical averaged afferent response to intense but non-painful digital nerve stimulation recorded using surface electrodes at the wrist. *Upper:* average afferent response to 52 stimulus trains (each 5 pulses in 200 ms) presented at 30 s intervals. *Middle:* average afferent response to 52 identical stimulus trains presented at 0.5 s intervals during the final 26 s of 7.5 min of stimulation. *Lower:* average afferent response to 52 stimuli presented at 30 s intervals after a 5 min rest period

Absence of habituation of primary afferents: the afferent volley

The purpose of this experiment was to provide further information upon whether the decline in perceived intensity observed in the earlier experiments could be attributed to a decrease in the degree of afferent fibre recruitment. Such a decrease might result from changes at the electrode site during the course of the experiment. If these changes reduced the flow of current to the afferent nerve, then the observed decrease in matching current could be attributed to changes in the properties of the stimulus rather than to habituation of the subject. One way of examining this possibility is to measure the response of the afferent nerve itself.

Responses of the median nerve of seven subjects to stimulation of the digital nerves on the right index finger was measured before, during, and after repeated electrical stimulation of the same finger through the same electrodes. The intensity of stimulation was set slightly below the threshold of pain. Before the 'experimental' phase of stimulation, the nerve's response was measured by presenting 51 stimulus trains at 25 s intervals. Each stimulus train consisted of 5 pulses at 20 Hz as in earlier experiments. During the next (experimental) phase the finger was stimulated with identical trains of pulses repeated at 2 Hz for 8 min and the afferent volley was recorded over the final 26 s of this period (51 stimulus trains repeated at 0.5 s intervals). The final recording, obtained after a 5 minute rest period, was a repeat of the baseline phase. A typical example of three averaged responses from one subject is shown in Fig. 3. Across all seven subjects, randomised blocks ANOVA of the peak amplitudes showed there were no significant differences in afferent nerve response over the three time periods [$F_{(2,12)}=2.5$; n.s.]. These results show that the habituation observed in earlier experiments cannot be attributed to changes in fibre recruitment in the afferent nerves due to changes at the electrode site.

Discussion

In the experiments reported in this paper we have assessed the effects of repeated stimulation on the perceived intensity of cutaneous stimuli, using a sensitive new method which allows comparisons at any stimulus level in the range threshold to very painful. We chose to use stimuli which were intermediate between the cutaneous sensory threshold and the pain threshold, and stimuli which were between the pain threshold and pain tolerance. The habituation effects observed in these experiments, whether for painful or non-painful stimulation, were shown not to result from certain artifacts. Thus one experiment ruled out the possibility that progressive polarisation of the stimulating electrodes during the 'habituation' phase of the main experiments reduced the level of effective stimulating current. Since the size of the afferent volley produced by the electrical stimulation did not appear to have decreased during 7 min stimulation with the usual stimulus parameters, our results cannot be explained by changes in recruitment of primary afferents at the stimulation sites. Fatigue of the afferent fibres is unlikely for the same reason, and also because the rate of stimulation was well below that which induces fatigue in A fibres (Törebjork and Hallin 1974).

Our experiments show that the perceived intensity of both painful and non-painful electrical stimulation can show considerable reduction over a period of a few minutes as a result of repeated stimulation. The habituation observed was about 20% when measured by the reduction in the current which was matched by the subject. The concept of habituation when applied to the perception of pain has been controversial, but the experiments reported here show habituation at supraliminal levels of stimulation, and thus extend the findings of others who have used threshold methods. Ernst et al. (1986) showed that repeated stimulation of tooth pulp at both non-painful and painful intensities results in significant and long lasting decrements in both detection threshold and pain threshold. In their experiments the habituation was much more pronounced and took about 60 minutes to develop fully. The differences between our findings and theirs might be explained partly by the stimulus parameters, since Ernst et al. used 600 ms trains of 100 pulses compared to the 200 ms trains of 5 pulses which were used in our experiments. The higher frequency stimuli may recruit more slowly acting central mechanisms (Ernst et al. 1986). Another possible source of difference was the site stimulated, since tooth pulp is deficient in Aβ fibres (Lisney 1978) which probably constituted the bulk of the fibre population in our experiments on the index finger which is well endowed with mechanoreceptors (Willis and Coggeshall 1978).

There is evidence that the degree of habituation of the blink response (Duranti et al. 1983) and of pain-related cerebral evoked potentials (Chapman et al. 1981; Jacobson et al. 1985) depends on the frequency of presentation of the stimulus. We have confirmed that the stimulus repetition rate is a potent factor in determining the degree of habituation of perceptual responses. No habituation was produced at a very low stimulus repetition rate (test stimulus repeated at 30 s intervals) whereas stimuli repeated at 2 Hz or 4 Hz proved equally effective in inducing habituation. A repetition rate of 1 Hz produced a degree of habituation which was somewhat less than that produced by 2 Hz stimulation. The effect of repetition rates between 0 and 1 Hz was not investigated here, although the results in Figure 2 suggest that this region of repetition rate is of importance and needs further investigation.

Both the rate and the extent of habituation over the course of the experimental session were similar for painful and non-painful stimulation under the conditions of our experiments. This result is surprising, in view of other observations that responses to weaker stimuli habituate more strongly than responses to stronger stimuli (Thompson and Spencer 1966; Dennis 1976). One difference between the moderately strong non-painful stimuli ($2.5*T_s$) and the painful stimuli ($1.2*T_p$) lies in recruitment of Aδ afferents, since Aβ afferents appear not to be involved in responses that are reported as painful (Willis and Coggeshall 1978). One interpretation of our results is that the habituation process is independent of afferent fibre type, implying that central adaptive responses to thickly myelinated (Aβ) and thinly myelinated (Aδ) afferent fibres are similar. Alternatively, when matching stimuli, our subjects may have disregarded the aspect of the stimulus generated by the Aδ fibres, presumably its aversive quality. Given the dense innervation of fingertips with mechanoreceptors, and our observation that subjects could still match stimuli reliably at such time as the painful characteristics of the stimuli had disappeared, the latter explanation seems more likely. Thus further work is needed to determine the rate and extent of habituation of perceptual responses to stimulation of the Aδ and C fibres mediating nociception.

Others have discussed the relationship between decreases in central responses to sensory stimuli and changes in arousal (Condes-Lara et al. 1981; Chapman et al. 1981). Our subjects reported their perceptual responses by comparing one index finger with the other, thus it seems unlikely that our findings can be interpreted in terms of global changes in attention or arousal. Further work using electroencephalographic and other measures of arousal are needed to clarify the relationship between the habituation found in our experiments and general changes in levels of arousal.

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