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Correlation of Subjective Pain Experience with Cerebral Evoked Responses to Noxious Thermal Stimulations

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Summary. The relationships between different parameters of the evoked cerebral response to noxious thermal stimulation, stimulus intensity, and subjective pain were investigated in seven normal human volunteers. The evoked response was characterized by late events: a small negative peak at 164–180 ms, followed by a high amplitude positive peak at 372–391 ms. The only correlation found in this study was between the amplitude of the positive component and the qualitative and quantitative aspects of the verbal report of pain. This was manifested by a linear trend of association: an increase in the evoked response amplitude was accompanied by an increase in the magnitude of the subjective sensation. The findings suggest that the evoked response to noxious heat reflects not a mere transduction of the physical parameters of the stimulus, but rather a complex interpretative action at the cerebral level.

Key words: Pain – Heat – Evoked response.

Measurements of sensitivity to, and perception of, pain are probably among the most complicated in sensory psychophysiology, since the subjective qualities of the pain experience interfere with the establishment of objective parameters of sensitivity to noxious stimulation. Several psychophysical methods were proposed therefore to circumvent the subjective variables involved in these measurements, yet none were completely successful in neutralizing the subjective connotation of the pain report. An alternative and potentially more appropriate solution could be attained by substituting the subjective report with an objective, quantifiable, physiological response which will reflect parametrically the sensitivity to noxious stimulation. We, as others (Chatrian et al., 1975; Stowell, 1975), have tried to use the cerebral evoked response as an

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objective measure of pain (Carmon et al., 1976a). The evoked response to noxious stimuli is characterized by late, high amplitude waveforms augmented by an increase in noxious intensity (Harkins and Chapman, 1978; Stowell, 1977). However, the feasibility of the cerebral evoked response as a substitute for the verbal report cannot be completely determined if correlation of the electrical response is done only with respect to the stimulus intensity. It can be established only if the evoked response reflects the perceptual experience which is influenced by attention and motivation, rather than simply transducing the physical magnitude of the stimulus.

In the present study we have tried to investigate the evoked cerebral response generated to painful stimuli, not only in relation to the stimulus strength but mainly with respect to the subjective perception of pain. The experimental paradigm permitted separate correlations of the averaged cerebral evoked response with both the stimulus intensity and the level of the verbal response. The experimental procedure was designed to test for a possible trend of association between the level of subjective and the parameters of objective responses to painful stimulation. A further aim of the experiment was to see whether different stimulus-response combinations correlated with specific spatiotemporal features (e.g., locus, latency, or specific components) of the cerebral evoked response, and in what way. Such analysis could contribute toward the understanding of the physiological nature of pain.

Methods

The method of noxious heat stimulation was described elsewhere (Mor and Carmon, 1975; Carmon et al., 1976a, Carmon et al., 1976b). A brief pulse of long wave length infra-red (10.6 μ) laser energy was the stimulus. The pulse of heat, monitored by a series of shutters, was delivered to the lateral side of the forearm of seven healthy young subjects. Each subject received 200 stimulations: 100 at an intensity which was initially calibrated by the subject as painful, and 100 at an intensity which was formerly evaluated by him as nonpainful. The subjective threshold was determined by a series of 100–200 stimulations delivered in different intensities along ascending and descending scales. The intensities of the two experimental stimuli were then selected on the basis of stimulus durations to which approximately 75% of the responses were painful (strong stimulus) or nonpainful (weak stimulus). The subjects described the nonpainful sensation as a circumscribed tactile sensation, sometimes experienced as that of a sharp object. Pain was described as a brief insect bite, and when it was more marked, as being accompanied by a lasting after-sensation of burning. Following the initial threshold determinations, the 200 stimulations on which the experiment was based were delivered in 10 blocks of twenty stimuli interspaced by 5 s between consecutive stimuli, with the order of strong and weak stimuli pseudorandomized for each block. The interval between consecutive blocks was approximately 1 min. The durations of these stimuli ranged between 8 and 30 ms, depending on the sensitivity of the subject. The stimulus diameter was 0.6 mm and its physical value was calculated in terms of the total heat flux per area. These values, which differed for various subjects, ranged between 90–160 mCal/cm^2 for the weak, nonpainful stimulus and 240–350 mCal/cm^2 for the painful, strong stimulus.

The subjects sat in an isolated, partially soundproofed room – the laser beam emerging from an adjoining room through a small hole in the wall and the subject resting his forearm across this hole; in this way the noise associated with the pulse-forming mechanical shutters was completely eliminated. Subjective responses were given about 3 sec after stimulation and were recorded separately for each trial. Subjects responded by defining their subjective sensation on a 10-point scale; nonpainful sensations were scaled on ascending degrees from 1 to 5 and painful sensations were scaled from 6 to 10, with 10 bordering on intolerance.

The electrical activity was picked up from the scalp by silver/silver chloride cup electrodes, and amplified on Beckman amplifiers at a gain of 20,000. Low frequency cutoff was 0.16 Hz and high frequency cutoff 30 Hz. The band pass filter was chosen on the basis of prior experiments which failed to show relevant and consistent components faster than 10–15 Hz. The electrodes were placed in the following locations (derived according to the 10–20 system): C_z, P_z, C_3, P_3, C_4, and P_4 which correspond to the vertex and the ipsilateral and contralateral somatosensory projection areas. The electrodes were selected after initial testing which showed that in other locations, e.g., frontal, temporal, and occipital, no consistently measurable responses were recorded. Reference was to A_1–A_2. The nose bridge served for grounding. In several instances another recording electrode was connected to the forearm or arm in order to see whether the recorded response was not due to volume conduction or whether any muscular artifacts were introduced into the measurement. These artifacts were ruled out. Beside the six EEG inputs, an additional channel was used to monitor gross eye movement in excess of 150 microvolts in order to eliminate bias due to such movements. The EEG signal was transmitted directly to a PDP 11/45 computer, and the inputs were digitized and averaged on-line. Data was sampled 500 ms before stimulation at a rate of 100 Hz, and during 800 ms following stimulus onset at a rate of 250 Hz.

The computer program was structured so as to compute independently averaged evoked responses for each of the stimuli, each of the subjective responses, and each of the four stimulus-response (S-R) combinations (i.e., combinations of weak and strong stimuli with nonpainful and painful sensations), as well as to collect and average separately trials in which no subjective response was given. The numerical values of the subjective responses served for additional analysis.

Results

The shape of the evoked responses to noxious thermal stimuli obtained in the present experiment was very similar to the shape reported by us earlier (Carmon et al., 1976a, b). This evoked response is characterized by two late components, without any consistent traceable activity preceding the first 150 ms after stimulation. The first of these components was a relatively short, negative deflection (N_1) ranging from 2 to 6 μV and with a peak latency of 164–180 ms. The second component (P_1) was a positive wide deflection ranging from 23 to 30 μV and with a peak latency of 370–390 ms. The base line of the EEG, recorded for 500 ms before each trial, did not show any trend of DC shift.

The highest amplitude of the response was observed over the midline electrodes. There was no significant asymmetry in the amplitude when the ipsilateral and contralateral responses were compared, nor did the latency of either peak vary significantly with respect to the location of the recording. Table 1 depicts the range and amplitude of the two components with respect to the six recording electrodes locations, irrespective of the stimulis intensity or the verbal response level.

Both parameters, the latency and amplitude, were then evaluated in each recording channel in relation to stimulus strength, type of response, and S-R combinations. Figure 1 is an example of the computer output for channel C_z, including the eight averaged evoked responses used for the various evaluations.

The four values extracted from each average, i.e., the latency and amplitude of the negative and positive components, were subjected to analysis of variance in order to determine the effect of the stimulation strength or the type of response on these values. The total amplitude of the averaged evoked response was larger in those trials in which the subject indicated that he felt pain (P) than

Table 1. Amplitudes and Latencies of Cerebral Evoked Responses to Noxious Thermal Stimuli (mean values are in italics, ranges are in brackets)

	N_1		P_1	
	Amplitude (μV)	Latency (ms)	Amplitude (μV)	Latency (ms)
Electrode Location				
Vertex C (C_z)	*–5.4* (1.0–13.0)	*174* (144–188)	*30.7* (17.1–49.4)	*372* (334–438)
Vertex P (P_z)	*–2.4* (1.0–9.7)	*166* (136–190)	*29.1* (17.2–38.9)	*384* (340–446)
Contralateral C ($C_{3,4}$)	*–6.2* (1.0–10.1)	*180* (156–192)	*23.3* (10.5–40.0)	*379* (336–450)
Ipsilateral C ($C_{3,4}$)	*–4.4* (1.0–11.0)	*178* (140–196)	*23.8* (12.2–40.1)	*382* (338–460)
Contralateral P ($P_{3,4}$)	*–4.0* (1.0–9.5)	*164* (146–194)	*23.2* (12.5–39.0)	*391* (334–450)
Ipsilateral P ($P_{3,4}$)	*–4.2* (1.1–10.5)	*176* (150–220)	*25.5* (14.5–36.8)	*388* (336–446)

in the trials where the subject did not feel pain (NP). The amplitude of the response was higher when the subject received the strong stimulation (S) as compared to trials with the weak one (W). The statistical analysis showed, however, that only the type of subjective response significantly affected the amplitude of the averaged evoked response. A significant effect of the response type on the evoked response amplitude ($p<0.01$) was obtained in all channels examined. Only in location P_z did the stimulus effect approach the 0.05 level of significance.

The negative and positive components of the evoked response were treated separately in subsequent analysis. The effect of the response was found to be due mainly to the increase in the amplitude of the positive late wave of the evoked response when pain was reported. The amplitude of the negative component did not show significant variation associated with the type of response or with the stimulus strength (cf. Fig. 2). The latencies of the evoked responses did not co-vary significantly with either the stimulus or the verbal response.

In order to further evaluate the validity of the association between the subjective sensation and the amplitude of the late positive component of the evoked response, the scaled subjective responses and their relation to this amplitude were examined. Both the "pain" as well as the "no pain" responses were based on several degrees of subjectively scaled reports, and thus each carried different weights in different subjects. A weighted score was therefore computed for each combination in the stimulus-response matrix. This score, $\bar{S}_i$, was the proportion of the specific scaled subjective response [P (S_i)] multiplied by the numerical scale value N_i, i.e., $\bar{S}_i = P(S_i)N_i$.

The four $\bar{S}$ values were quite similar among the subjects for the given stimulus-response combinations. These values ranged as follows: "Pain" response to strong stimulus 7.61–6.33; "Pain" response to weak stimulus 7.54–6.00; "No Pain" response to strong stimulus 4.50–2.78; and "No Pain" response to weak stimulus 4.29–2.19. The $\bar{S}$ values were then correlated with a standardized amplitude of the positive component of the evoked response, using the mean amplitude as a zero point and computing the deviation of the

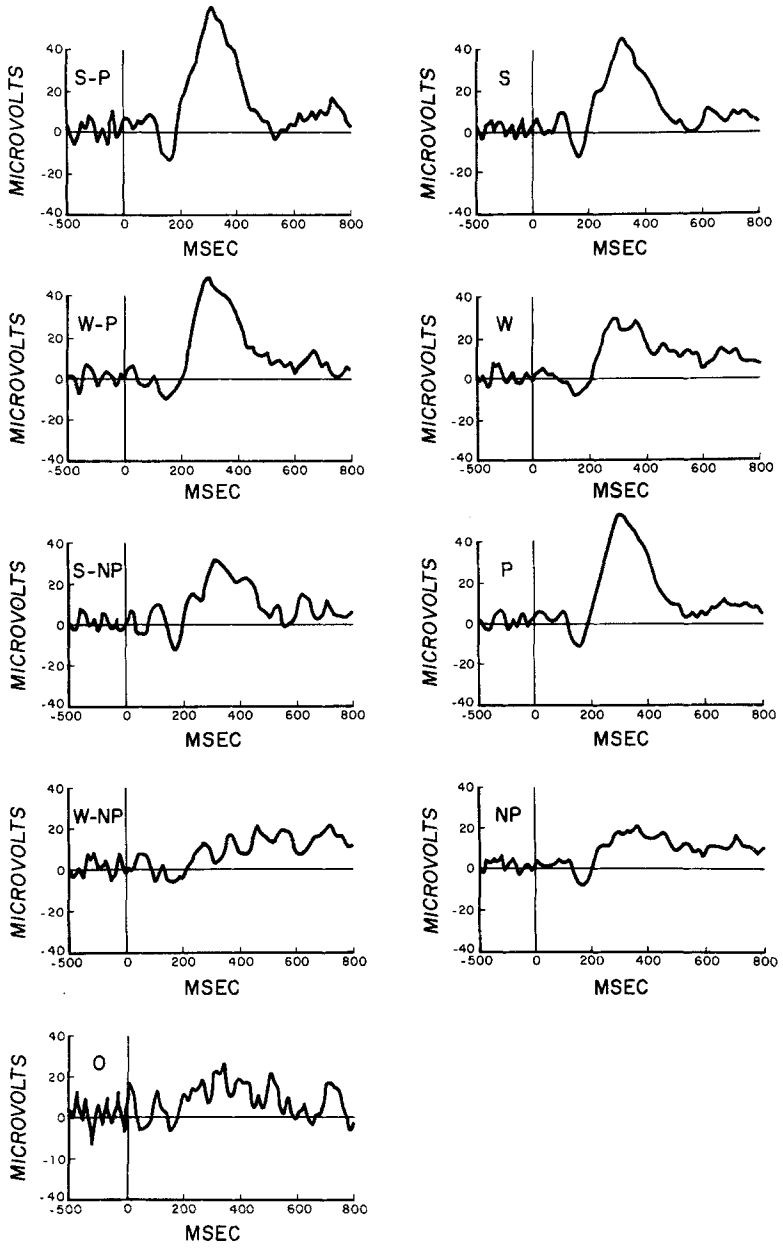

Fig. 1. Form of the evoked responses to noxious thermal stimuli (channel C_z of one subject), obtained under different stimulus and response conditions. S = strong stimulus; W = weak stimulus; P = pain response; NP = no pain response; 0 = no response at all

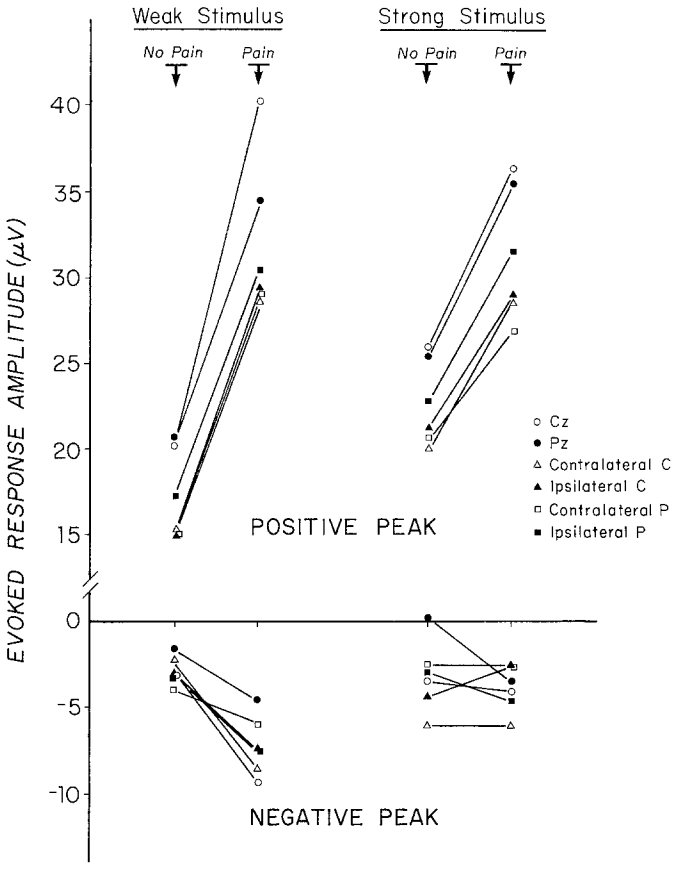

Fig. 2. Amplitude measurements of the late positive and negative components of the evoked response to noxious thermal stimuli under different stimulus-response combinations

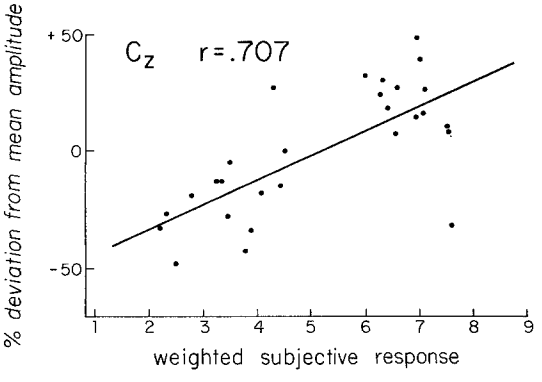

Fig. 3. Correlation between standardized amplitude of evoked response and weighted subjective responses

amplitude in percents. The correlations ranged between 0.67 and 0.77 ($p < 0.01$) in the six channels.

An example of the scatter diagrams for channel C_z (Fig. 3) shows two distinct aggregates which reflect the strong association between the evoked response and the subjective response. The lower aggregate is composed of amplitudes obtained for "No Pain" responses, while the upper aggregate is composed of amplitudes associated with the "pain" responses.

Finally, in some trials no response was given by the subjects. This occurred rarely when the stimulation was strong, but was more frequent (up to 20%) when a weak stimulus was applied. No consistent evoked response was observed in these trials in any of the subjects.

Discussion

Evoked responses to different modes of noxious stimulations share in common the late, high amplitude events. Similar late components, but less conspicuous, were recorded also during non-noxious somatosensory stimulation (Goff et al., 1969). Thus, for example, a recent study of evoked response to non-noxious thermal stimulation (Chatt and Kenshalo, 1977) demonstrated a positive, high amplitude, late wave at somewhat earlier latency (<280 ms) but of significant lower amplitude (<10 μV) than observed by us.

The late components of the somatosensory evoked response differ generally from the earlier ones in their cortical representation. In contrast to the lateralization of the earlier wave forms, components that are later than 120 ms are generally present bilaterally when the stimulation is unilateral (Johnson et al., 1975). The maximal amplitude of the late components is observed at the vertex (Goff et al., 1969). This distribution might suggest that late components of the somatosensory response originate from deep midline structures. The possible origin can be deduced also from studies in which the late components of the evoked response were found to be attenuated by thalamic lesions (Velasco et al., 1975). Such symmetry and vertex accentuation are typical also to noxious stimulation (Chatrian et al., 1975; Carmon et al., 1976a). As the late events amplitude is augmented by an increase in stimulus intensity (Johnson et al., 1975), they should be more apparent when stimulation is increased to noxious levels. It is therefore logical to assume that, when stimulus intensity is gradually increased to achieve progressive levels of pain, the evoked response amplitude will show, being a function of stimulus intensity, correlation with the degree of the subjective feeling of pain. The question is then, which parameter correlates better with the evoked response amplitude – stimulus intensity or subjective experience?

The case of thermal stimulation is most suited to answer this question, since the evoked response contains only the relevant, late events which are manipulated by stimulus intensity.

The results of the present study confirmed and strengthened the initial impression (Carmon et al., 1976a) that the amplitude of the late positive component of the cerebral evoked response to noxious thermal stimulation is

correlated best with the subjective sensation of pain. In the earlier report, however, no attempt was made to study this finding systematically.

The relations of the evoked response to the stimulus intensity and to the subjective experience were investigated more closely in the present study by comparing the verbal scales and the electrophysiological responses. The amplitude of the late positive wave of the evoked response was more prominent when the subject perceived pain than when he felt only a sharp touch, even if this painful sensation occurred at an intensity which generally did not elicit pain. Furthermore, a relative independence of the evoked response amplitude from the stimulus intensity was also observed. This independence is probably limited to situations in which the stimuli are relatively close together on the intensity dimension and thus result in difficult discernibility. It can be expected that two very distinct stimuli will result in distinct subjective sensations as well as generate distinct evoked response amplitudes. Recent studies by Harkins and Chapman (1978) and by Stowell (1977) showed that stimuli which were subjectively distinct from each other generated significant amplitude differences in the evoked responses. However, these authors did not analyze the data on the basis of individual subjective responses, but assumed that a given intensity generated always the same pain experience. Thus, their conclusions could not be applied separately to either the stimulus intensity or the response generated by the subjects, a feature possible in the present experiment.

In a former study (Carmon et al., 1976a) we reported that the latency of the negative component was influenced by stimulus intensity. This finding was not corroborated in the present experiment. The discrepancy may be due ot the reduction of the stimulated area by a factor of 10^2, a change which clearly affected the evoked response latencies.

The correlation of the physiological event with the subjective experience might point out that not only peripheral events but also higher interpretive processes influence the overall physiological reaction to pain. Therefore, if the evoked response reflects not only the sensitivity to a stimulus but also a higher level of discriminability which is manifested in contextual interpretation, it can serve as a substitute for the subjective response.

The importance of this proposition is stressed by the current state of the art of psychophysical research of nociception. There is a constant search for a suitable objective measure of pain which will reflect not only the sensory function but will also demonstrate the evaluation process of sensation. A physiological measure, which can be calibrated objectively, should not be biased by additional sociocultural variables which make the verbal report of pain difficult for interpretation. Such a measure could be of use in evaluation of analgesic agents, as well as in general experimentation of pain.

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