red–standard white flicker condition for observer JS. According to subjective report, this condition produced the most difficult psychophysical judgment as well. The range of the psychophysical judgments is represented by the horizontal bar corresponding to each curve in Fig. 2. The amount and direction of the skewness of psychophysical judgments appears to be well correlated with the bias of the minimum values relative to 0.0 on the abscissa. With the exception of the red–standard white flicker condition for observer JS, the minimum value of each curve in Fig. 2 falls either within, or less than one intensity step (0.07 log unit) outside of the psychophysical range. Examination of these functions also indicates that the ordering on the ordinate of the three curves is different for each observer. The significance of these differences cannot be properly assessed until more data from many wavelength combinations have been collected.

The minimum of the curve for the white–standard white flicker condition in Fig. 2 for observer JS, and that of the curve for red–standard white for observer EB, approach the noise level of the electrophysiological analysis system used. The subjective reports of the observers indicate that there was barely perceptible flicker in the neighborhood of the minimum response. Flicker did not disappear altogether in the white–standard white conditions because of the critical nature of alignment factors under these conditions; however, the alignment was sufficiently good that the magnitude of flicker perceived in this condition was extremely small. The smallest responses obtained were approximately 0.4 μv in amplitude. This indicates that the electrophysiological response can be followed down almost to the perceptual threshold of flicker.

Although the electrophysiological and psychophysical results were compared for conditions in which only white, red, and green stimuli were used, the feasibility of performing flicker photometry by measuring evoked brain potentials is clearly shown (*7*). A comprehensive study covering the entire visible spectrum should also reveal the significance of the individual differences observed and the specific relation between these psychophysical measures and the dimensions of the evoked brain potential. It is quite clear from our study that the evoked brain potential is an extremely sensitive measure of changes in stimulus, and that, when the same rigorous control of stimulus conditions expected in exacting psychophysical experimentation is provided, data of comparable sensitivity are the result.

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Attenuation of Aversive Properties of Peripheral Shock by Hypothalamic Stimulation

Abstract. *Clinical reports of alleviation of pain with positive brain stimulation were investigated experimentally. Rats in a two-compartment testing chamber sought out hypothalamic stimulation and escaped from aversive foot shock delivered through a grid-scrambling device. Animals also sought out paired hypothalamic stimulation and foot shock. Control experiments demonstrating that animals did not discriminate between hypothalamic stimulation and paired hypothalamic stimulation and foot shock supported the view that hypothalamic stimulation attenuates the aversive properties of foot shock.*

There are several reports that brain stimulation modifies aversive states. Heath (*1*), for example, states that patients receiving stimulation of the septal area obtain immediate relief from intractable pain, and Lilly (*2*) comments that positive brain stimulation of monkeys increases the threshold of pain resulting from aversive central stimulation. Until recently there were no quantitative data available on this topic. Valenstein (*3*) reported that animals would seek out aversive stimulation of the dorsomedial tegmentum if it was paired with positive hypothalamic stimulation (*4*). As these tegmental sites receive direct input from the spinothalamic "pain tract" (*5*), it seemed important to determine if hypothalamic stimulation would effectively mask a painful stimulus delivered through peripheral receptors.

Eight albino rats (300 to 400 g) of the Holtzman strain were used. The testing chamber, modified slightly from that described in detail elsewhere (*6*), consisted of a plexiglass chamber (60 by 25 cm and 42.5 cm high) divided into two compartments of equal size. The floor of the chamber was a shock grid constructed of brass rods. Two photoelectric cell assemblies located 3.7 cm above the floor divided each compartment in half. As a rat proceeded halfway into a compartment, the light beam was interrupted and a clock was started. If the rat was in the positive compartment, it received either central or peripheral stimulation or both at a fixed repetition rate. In order to turn off the stimulation or, in later experiments, to change the stimulation conditions, the animal had to break the beam in the compartment opposite the one last entered. A test consisted of either 10 or 20 1-minute periods. The positive compartment was switched on a random sequence which guaranteed that each compartment was positive for half the 1-minute periods during each test. Thus an animal actively seeking out or escaping stimulation could not remain in one compartment. Time in 0.1-second units in the positive and negative compartments was recorded automatically.

Bipolar electrodes, bare only at the cross section, were implanted with the aid of a stereotaxic instrument into the lateral hypothalamus (*7*). The coordinates used were 4.0 mm posterior to bregma, 1.5 mm lateral of the midline, and 8.75 mm below the skull surface. At the completion of the experiment the animals were anesthetized and perfused with saline and formalin. Frozen brain sections, 80 μ thick, were stained with chresylecht violet (*8*). The locations of the electrode tips are illustrated in Fig. 1.

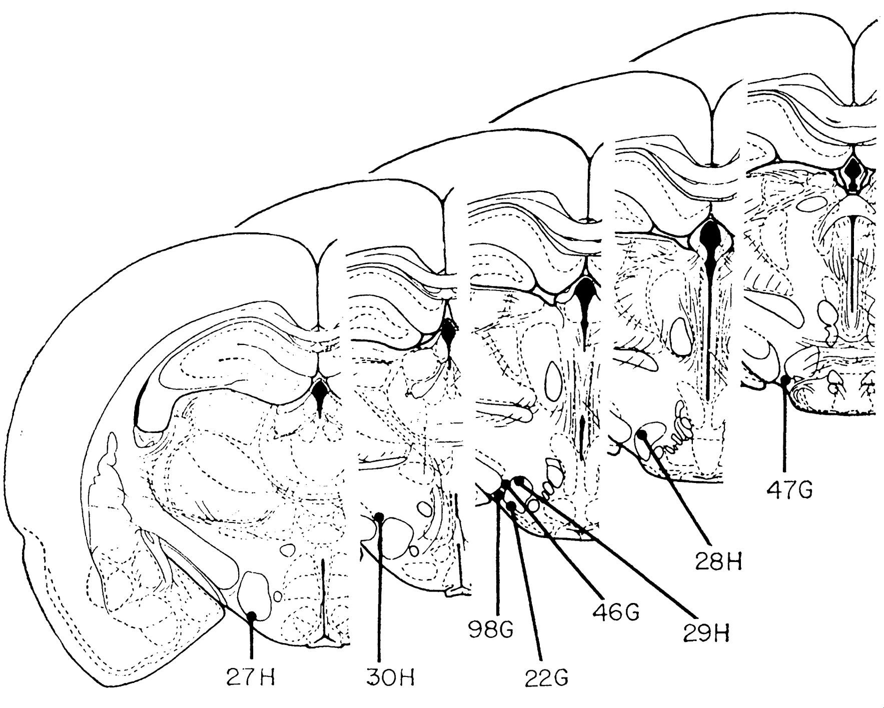
Central stimulation consisted of 0.5-second trains of 100-per-second biphasic rectangular pulses. Positive and negative pulses were 0.2 msec in duration with 0.2-msec intervals between them. Foot shock was delivered through a grid-scrambling device at a peak intensity of 0.68 ma and 270 volts with a train duration of 0.2 second.

To determine the optimum current for hypothalamic stimulation, the rats were given consecutive 20-minute tests until an intensity was found which caused the rats to spend the highest percentage of the time in the positive compartment. After this procedure the stimulation was paired with grid shock (0.68 ma), and the intensity of hypothalamic stimulation was varied until each rat spent the maximum amount of time in the positive compartment. In the experimental sessions, hypothalamic stimulation ranged between 300 and 600 μa (Table 1), and animal impedance averaged 20,000 ohms.

Each animal was subjected to a 13-day sequence of seven different experimental conditions (*9*). Tests during the first 7 days were of 20 minutes' duration. On test days 1 and 2 there were three consecutive tests per day with hypothalamic stimulation alone (H). Three consecutive tests with foot shock alone (S) were administered on day 3. On day 4 the rats were given three tests with 0.5-second hypothalamic stimulation followed immediately by 0.2-second grid shock (H-S); on day 5 three tests with 0.2-second foot shock followed immediately by 0.5-second hypothalamic stimulation (S-H) were provided. On day 6 there were three tests with hypothalamic stimulation alone (H), and on day 7, three tests with foot shock alone (S). All stimulus trains, whether H or S alone or paired, were presented at a repetition rate of one per 1.5 seconds.

Figure 2 shows that when hypothalamic stimulation was presented alone (conditions 1 and 5) or combined with foot shock in either temporal order (conditions 3 and 4) the rats actively sought out the positive compartment. However, when foot shock alone was given (conditions 2 and 6), the rats rapidly escaped stimulation. In Table 1 we present the data for each of these conditions. For six of the rats the data were very consistent, but for two rats (22G and 47G) the data were more variable, exhibiting the least amount of masking of the aversive effects of foot shock. The average amount of masking was slightly less in the S-H than in the H-S tests; with aversive central stimulation the sequence effect has been reported to be considerably more striking (*3*). This difference may reflect the more immediate aversive consequences of central stimulation and therefore the greater difficulty in masking these effects.

Because the first 7 days of testing indicated that hypothalamic stimulation masked the effects of aversive foot shock, additional tests were administered to help clarify the interpretation of these results. On days 8 through 11 a series of forced-choice tests was given in which stimulation was provided in both compartments, and the animal was free only to choose between the two types of stimulation offered. Testing on each of days 8, 9, and 10 consisted of four 10-minute sessions separated by 5-minute rest periods. During the first two sessions, hypothalamic stimulation was presented on both platforms, but the grid-scrambling device was operated, without shock, when the animal was in one of the compartments (H versus H plus grid scrambler). This condition was included to assure that it was the foot shock which was aversive rather than auditory or any other cues associated with the delivery of the shock. The mean percentage of the total time in the grid-scrambler compartment



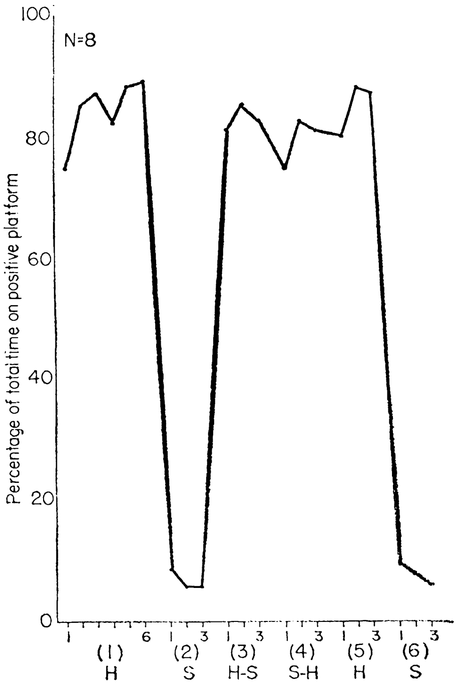


Fig. 1 (left). Schematic presentation of location of electrode tips, after König and Klippel (*17*). Fig. 2 (right). Average percentage of total time on positive platform for first 7 days of testing. Numbers in parentheses indicate conditions: *1*, hypothalamic stimulation alone; *2*, shock alone; *3*, hypothalamic stimulation followed by shock; *4*, shock followed by hypothalamic stimulation; *5*, hypothalamic stimulation alone; *6*, shock alone.

was 47.5. Thus it did not appear that any cues significantly influenced the rats' behavior in the absence of foot shock.

Table 1. Mean percentage of total time spent by rats on the positive platform, and the stimulation intensities and numbers of lever presses per minute.

Animal	Conditions							Current (μa)	Lever presses
	H	H	S	H-S	S-H	H	S		
22G	85.40	87.30	6.87	87.37	66.30	73.43	7.23	600	36.1
27H	79.63	83.37	8.30	76.63	84.57	87.73	10.07	500	67.2
28H	82.33	91.87	6.07	90.70	91.67	89.07	8.10	500	89.5
29H	90.23	94.17	5.27	91.47	91.53	93.77	7.00	300	36.7
30H	78.20	84.43	6.10	88.20	88.03	83.93	8.50	600	41.6
46G	77.37	88.10	5.27	89.90	87.13	91.30	8.20	400	109.3
47G	84.70	79.70	10.03	56.27	48.63	78.90	9.13	500	49.4
98G	86.13	87.87	6.00	89.53	86.23	88.70	5.17	600	67.0

In the third and fourth forced-choice sessions on days 8 through 10, hypothalamic stimulation was presented in one compartment and hypothalamic stimulation followed immediately by foot shock in the other (H versus H-S). By these tests we determined whether the rats were tolerating the foot shock to receive hypothalamic stimulation or whether the stimulation was attenuating the aversive properties of the shock. It will be recalled that Olds (*10*) and Valenstein and Beer (*11*) reported that animals would take avoidable foot shock to obtain hypothalamic stimulation. Our tests then provided the animals with an opportunity to obtain the hypothalamic stimulation without any foot shock. The mean percentage of total time in the H-S compartment was 43.1; however, six of the eight rats spent equal time (50 percent) in each compartment. Subjects 22G and 47G again differed from the rest of the group in that they spent 16.2 percent and 26.9 percent of the time in the H-S compartment, respectively. An analysis of the performance of the animals over the 3 days of testing revealed no trend toward preference for hypothalamic stimulation alone.

Testing on day 11 consisted of four 10-minute forced-choice sessions in which hypothalamic stimulation was delivered in one compartment and foot shock in the other (H versus S). These tests were included to demonstrate that animals were capable of expressing a choice in a procedure which forced them to receive stimulation in either compartment. The mean amount of time spent in the H compartment was 80.5 percent, clearly indicating an ability to express a choice.

Finally, on day 12, the rats were trained to press a lever in order to obtain hypothalamic stimulation. After they pressed the lever 100 times, their self-stimulation rate was recorded for a 30-minute session on each of days 12 and 13. Table 1 presents the mean number of times the lever was pressed during the two self-stimulation sessions. The degree of masking did not appear to bear any systematic relationship to the lever-pressing performance of the rats; however, self-stimulation rate is an unreliable index of reinforcing strength (*12*). On the other hand, a Spearman rank-order correlation (r_s) between the mean percentage of time spent in the positive compartment during all three H conditions and the mean percentage of time spent in the positive compartment during the H-S and S-H conditions yielded an r_s of 88.1. However, we found no relation between the placements of the electrodes in the medial forebrain bundle and the degree of masking.

In addition to the experimental confirmation of reports of attenuation of pain, our results also suggest an alternative interpretation of some results described previously. For example, in studies designed to demonstrate the strength of reinforcing brain stimulation by means of tests requiring animals to take avoidable shocks (*10*), the intensity of the pain caused by the shock may have been reduced. Similarly, in a recent report of a deficit in the passive avoidance of shock during noncontingent septal stimulation, it was suggested that the stimulation was interfering with the inhibition of motor behavior (*13*). In view of our findings, the possibility of an attenuation of aversive effects by reinforcing brain stimulation would also have to be considered.

The results of this experiment and other recent studies (*3, 14, 15*) have generated hypotheses on the interaction between neural systems mediating approach and escape behavior. To date, most of these studies have been concerned with the negatively reinforcing dorsomedial tegmentum and positively reinforcing hypothalamic areas (*16*). Olds and Olds (*14*) suggest that stimulation of the dorsal tegmentum is aversive because it results in an inhibition of spontaneous activity in reinforcing areas. Presumably, stimulation of the hypothalamic areas in our study may have counteracted this inhibitory influence. However, there is little anatomical or physiological support for the position that central and peripheral aversive stimuli inhibit hypothalamic activity.

At this time we prefer to interpret our results in terms of the effect of hypothalamic stimulation on nonreceptive input. Whether hypothalamic stimulation raises the threshold of some area(s), thus mediating the perception of an aversive stimulus, or interferes with the pattern of nerve impulses necessary for information transmission, is not yet evident.

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