Effects of competitive cutaneous stimuli on pain thresholds in the monkey*

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In the late 1920s Bishop and Erlanger[1] performed a series of experiments which suggested that pain could be diverted or occluded by competing nervous system activity. In an ingenious series of experiments performed on peripheral nerves they concluded that pain could be diminished by the peripheral occlusion of nerve impulses arising at a great distance from the brain. A more recent conceptual model of the competitive inhibition of pain stimuli suggested by Melzack and Wall[2] is known as the Gate Control Theory of Pain. Although there has been extensive theoretical analysis of this system, the physiologic and behavioral evidence for its actual functioning presence in animals or man has not been forthcoming.[3–5] Lack of physiologic proof, however, has not prevented the system from being employed in methods of treating pain.[6, 7] An industry has sprung up over the past 10 years which claims to use the gate theory as a means of alleviating chronic, intractable pain with the use of electrical stimulators to deliver "pain-ablating" impulses to the skin or deep structures to render certain synaptic junctions unavailable for the transmission of pain impulses. When the use of the skin stimulation systems has been put to controlled clinical test-

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ing, stimulation pairing has not uniformly been found to decrease pain perception.[8, 9]

The present study employs behavioral experimentation to test the implications of the gate control mechanism for the behavioral response to noxious stimulation. Briefly, the gate theory states that if large fiber input predominates at synaptic gates such as the substantia gelatinosa, noxious information will be prevented from reaching central mechanisms for perception and response. In human studies, Nathan and Rudge[9] found that pairing C-fiber stimuli with A-fiber stimuli in man did nothing to increase thresholds at which pain was perceived from a variety of electrical and thermal stimuli. On the other hand, Campbell and Taub,[8] using pinprick stimuli, found that pain thresholds were elevated by electrical stimuli which appeared to produce selective small fiber blockade. The mechanism of pain relief under such conditions was thought to result from blockade or occlusion of peripheral nerve activity in small diameter fibers, particularly the A-delta fibers.

In the present study we conditioned stumptail macaques to respond to noxious electrical stimulation and to ignore stimulation at nonnoxious levels. These stimuli were then paired in an effort to see whether large fiber stimuli could raise the threshold of a conditioned noxious response within the same spinal segment, in a contralateral spinal segment at the same level, or at the peripheral nerve level.

Methods

Subjects for this study were adolescent female stumptail macaques (*Macaca arctoides*) trained to press a bar to reduce the intensity of an electrical stimulus applied either to the skin or directly to peripheral nerve. Operant conditioning of the bar-press response provided a behavioral index of the animal's annoyance or pain threshold. After several days of habituation to the primate chair and experimental room, the bar-press training was begun with a food reward. Variable ratio schedules were increased until the monkey pressed an average of 20 times for each reward. Reinforcement was next shifted to termination of an electrical stimulus applied through surface electrodes on the skin of the foot in the S1 dermatome. The final step in training consisted of shifting the reinforcement to reduction of the stimulus intensity by about 0.1 ma for each bar-press, so that the monkey must press repeatedly to reduce the stimulus. The animal's pain threshold was then analyzed according to the "staircase" variant of Fechner's method of limits.[10]

The noxious electrical stimulus (SI) was provided by a variable amplitude, constant current stimulator with output level regulated by a stepping motor driven by a Lab K logic controller (Digital Equipment Corporation). Timing pulses incremented the stimulus intensity every 2 seconds, while each bar-press response by the monkey reduced the current 0.1 ma. Maximum intensity was set at 22 ma. Each SI stimulus was a 200-msec train of 0.5-msec rectangular pulses at 50 Hz. Trains were delivered once per second. A multichannel chart recorder was used to obtain a permanent record of stimulus intensity and bar-press behavior for statistical analysis. To obtain the annoyance threshold, we averaged 20

stimulus intensity values sampled every 12 seconds over 4 minutes of stable response behavior.

Two latter phases of the study investigated the effect upon footshock annoyance threshold of adding a second electrical stimulus of non-noxious intensity at the popliteal fossa (SII). The animal did not press the bar in an attempt to terminate this stimulus. In general, 4 to 8 volts applied to the skin of the popliteal fossa would elicit an escape response. When SII was used to attempt to produce blocking of the conditioned response to SI, its value was decreased to the 2- to 3-volt range.

In half the trials, the popliteal stimulus was applied ipsilateral to the footshock, and in the remainder of the trials it was applied to the contralateral homologous location. The dermatome location was in the S1 segment in each instance. This study investigated the effect of adding a non-noxious electrical stimulus to another part of the same dermatome, either contralateral or ipsilateral, and looking at the effect of this paired stimulation upon annoyance threshold for footshock within that dermatome.

A bipolar platinum leaf electrode was also implanted on the right sciatic nerve in one animal, with leads run under the skin of the back to a plug bolted to the skull. When the incrementing stimulus current was applied to this electrode, the monkey immediately pressed the bar to control the stimulus level in the same manner as when it was delivered to the skin of the foot. Single 0.5-msec pulses delivered once per second were used instead of trains. The non-noxious stimulus (SII) was then applied to the ipsilateral or contralateral popliteal fossa proximal to the site of nerve stimulation to determine the effects of paired stimulation upon annoyance threshold for sciatic nerve stimulation. In this portion of the study the nerve stimulus was the one capable of eliciting a conditioned avoidance response.

Behavioral study of these monkeys has been ongoing for nearly 3 years. To maintain the animal's cooperation for this aversive task, a second bar was introduced which the monkey pressed to obtain a highly desirable food reward on a variable ratio schedule from an automatic feeder. The footshock annoyance threshold is determined with one bar, and the food delivery system is manipulated by a similar bar employing the use of a contralateral hand. The animals quickly learned how to handle the tests simultaneously by using one hand on each bar, as shown in *Figure*.

Statistics

Each phase of this study can be represented as a factorial design in which all treatment combinations were given to a single subject. On each day of testing, observations were taken at only one level of variable A (SII site or SII site order), while all levels of the second variable (SII voltage level or SII site) were presented. Since each experimental phase lasted several months, providing a minimum of 15 days of observations, "observation days" rather than subjects were considered as the elements of each sample. Thus each analysis involves independent samples of "observation days" for variable A (SII site or SII site order), and repeated observations on variable B (SII DC level or SII site). In all cases the basic observation was the mean SI

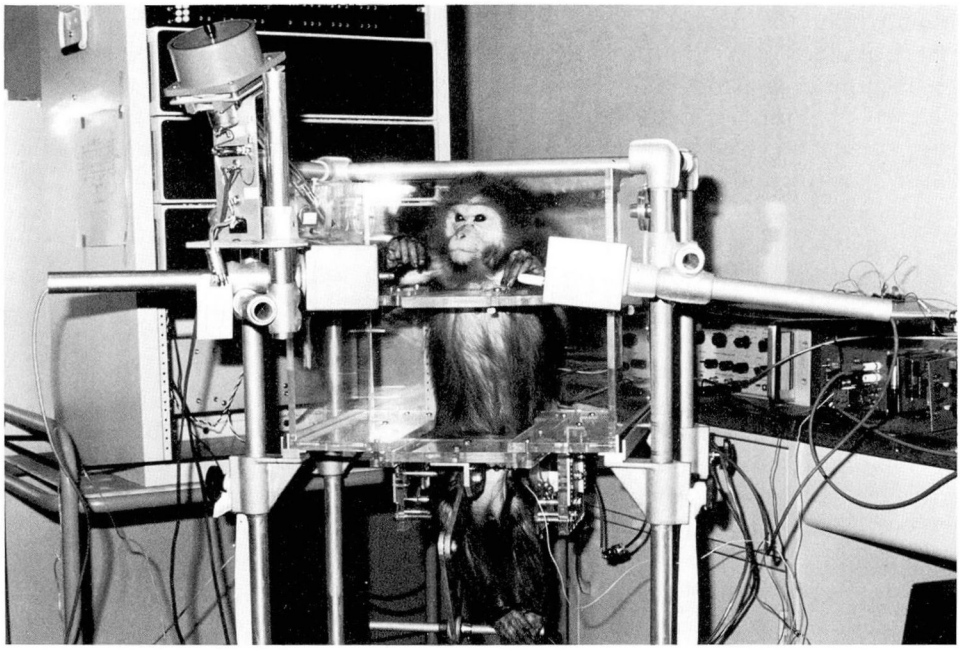

Figure. A female stumptail macaque (*Macaca arctoides*) is seated in the behavioral testing apparatus. The animal's right hand is operating a lever controlling the delivery of a food reward on a variable ratio schedule while the left hand operates a lever which modulates the intensity of noxious stimulation being delivered to the left leg.

pain threshold calculated from 20 samples of each SI current level taken every 12 seconds over 4 minutes of stable threshold performance according to the "staircase" method.

In the first phase of the studies of the effects of popliteal SII on threshold for SI applied to the skin of the foot, a 2 × 3 factorial design was used for each animal with independent observations on SII site and repeated measures on SI DC level. In the latter two phases, analysis of variance was done on independent observations of SII site order and repeated observations of SII site itself. Then the second observation of SI threshold alone taken between the two observations of SII effects was added to allow an analysis of covariance, with SII site as the experimental variable and SI threshold as the covariate. This analysis tests the significance of the differences in effect of SII ipsilateral vs SII contralateral on SI threshold with any linear effects of SI threshold itself removed. If the differences in effect of the two SII popliteal sites are either masked by a linear regression with SI threshold or inflated by such a relation, comparison of the unadjusted analysis of variance for SII site with the analysis after covariance adjustments will reveal these biasing effects. The data for Subject 2 on the effects of SII popliteal stimulation on threshold for SI applied directly to the sciatic nerve were subjected to the same type of analysis of variance and covariance as described above for the second and third phases of SI applied cutaneously. All

computations were done according to the methods given by Winer.[11]

Results

Initial determinations of the bar-press threshold for pain over more than a year indicated that the values were quite stable. *Table 1* shows the threshold for each animal on 5 days selected at random from a month's records. The aversive stimulus was delivered to the left foot throughout the study. Threshold standard deviation is 0.42 ma for both animals. Mean threshold is 4.41 ma for Subject 1 and 3.32 for Subject 2 ($t_8 = 3.67$, $p < .01$). Footshock thresholds were both stable and characteristic of each animal; Subject 2 maintained a significantly lower pain threshold than did Subject 1.

In the first evaluation of paired stimulation, a DC current at either 2 or 3 volts was applied to the popliteal fossa. This non-noxious stimulus was a continuous DC level applied throughout the 4-minute duration of each SI pain threshold determination. On each day of testing the DC voltages (SII) were applied to only one fossa, and the order of the levels (0, 2, and 3 volts) was randomized. On successive test days the placement of SII ipsilateral or contralateral to the left footshock (SI) was randomized. Five test days were chosen at random for each SII site. None of the F tests for SII site or SII voltage level were significant for each animal.

To provide a positive motivation to stabilize performance in the experimental sessions, a second bar was added which delivered banana pellets on a variable ratio schedule. This modification did not result in elevation of the annoyance threshold. Footshock pain thresholds were determined concurrently with the original bar. Subject 1 was further evaluated for the effects of SII at the popliteal fossa on SI pain threshold. The testing session was extended to five threshold measures each day, with the laterality of order of SII location randomized. A two-way analysis of variance with repeated measures on SII site produced no significant F tests, confirming the results of the first phase of this study. To determine whether differences in the effects of ipsilateral vs contralateral SII placement on SI pain threshold were being masked by variations in the SI threshold itself, an analysis of covariance was performed and revealed no significant F values.

A final study of the effects of SII on footshock pain thresholds employed the same 200-msec trains of 0.5-msec pulses at 50 Hz as are used for SI, rather than continuous DC

Table 1. Cutaneous footshock thresholds

	Date					
	7-9-74 ma	7-12-74 ma	7-16-74 ma	7-22-74 ma	7-25-74 ma	Mean threshold, ma
Subject 1	4.33 ±.79	3.84 ±.47	5.02 ±.39	4.36 ±.59	4.52 ±.51	4.41 ±.42 $t_8 = 3.67$, $p < .01$
Subject 2	3.27 ±.62	3.05 ±.43	2.80 ±.70	3.62 ±.53	3.85 ±.61	3.32 ±.42

levels. The amplitude of the SII pulses was again set at 3 volts to preserve its non-noxious character. The same arrangement of five trials per test day and randomized SII site order described above was followed (*Tables 2 and 3*). The F tests revealed no effect of either SII site on SI pain threshold. There is a tendency for lower SI thresholds overall on the SII ipsilateral first days compared to the SII contralateral first days ($F_{1, 10} = 2.27$, $.10 < p < .25$). There is an indication of interaction between SII site order and the SI thresholds seen for the different SII sites ($F_{2, 20} = 2.82$, $.05 < p < .10$). Analysis of covariance also produced no significant F values.

While Subject 2 had the bipolar electrode implanted on the right sciatic nerve we investigated the effects of a 3-volt DC current (SII) applied to the ipsilateral or contralateral popliteal fossa upon pain threshold for direct sciatic nerve stimulation (SI). The schedule of five threshold trials a day with SII order randomization on successive days was employed. The simple analysis of variance (*Tables 4 and 5*) gives no significant F values, but there is a tendency for SII ipsilateral to affect the SI pain threshold differently than SII at the contralateral fossa ($F_{2, 16} =$

Table 2. Mean SI pain thresholds (Subject 1)

	SII site		
	None	Ipsilateral	Contralateral
SII site order			
Ipsilateral first	2.49 ±3.23	3.35 ±1.33	4.21 ±4.50
Contralateral first	7.16 ±5.95	7.42 ±4.22	5.72 ±4.37

Table 3. Analysis of variance summary table (Subject 1)

Source	SS	df	MS	F
A. SII site order	104.90	1	104.90	2.27*
Days within groups	462.52	10	46.25	
B. SII site	1.97	2	0.99	0.33†
AB interaction	17.03	2	8.52	2.82‡
Bx days within groups	60.40	20	3.02	
Total	646.82	35		

* $.10 < p < .25$.
† $.05 < p < .10$.
‡ Not significant.

Table 4. Mean pain thresholds for SI applied directly to sciatic nerve (Subject 2)

	SII site		
	None	Ipsilateral	Contralateral
SII site order			
Ipsilateral first	1.25 ±1.01	2.04 ±.85	1.52 ±.70
Contralateral first	1.61 ±1.05	1.80 ±.77	1.44 ±.83

Table 5. Analysis of variance summary table (Subject 2)

Source	SS	df	MS	F
A. SII site order	0.001	1	0.001	0.0007*
Days within groups	12.01	8	1.50	
B. SII site	1.46	2	0.73	1.78†
AB interaction	0.48	2	0.24	0.59*
Bx days within groups	6.55	16	0.41	
Total	20.50	29		

* Not significant.
† $.10 < p < .25$.

Table 6. Mean sciatic nerve SI pain thresholds (Subject 2)

SII site			
Ipsilateral		Contralateral	
SI alone	SI and SII (3 V)	SI alone	SI and SII (3 V)
1.25 ±1.01	2.04 ±.85	1.70 ±.85	1.52 ±.70
1.60 ±.71	1.80 ±.77	1.61 ±1.05	1.44 ±.83

1.78, $.10 < p < .25$): SII ipsilateral raises the SI pain threshold in comparison to SII contralateral or the SI control threshold. Analysis of covariance to control for the influence of SI threshold itself provides stronger confirmation for the tendency of SII ipsilateral to raise the SI pain threshold (*Tables 6–8*). The adjusted value falls considerably beyond the .05 level of significance ($F_{1,7} = 7.75$; $p = .05$ for $F_{1,7} = 5.59$), indicating that the effects of SI pain threshold variations were masking the differences between SII at the ipsilateral vs. the contralateral popliteal fossa. SII applied to the ipsilateral popliteal fossa raises the pain threshold for SI applied to the sciatic nerve in comparison with SII contralateral or the SI alone controls.

The lack of any competitive effect when SII was applied contralaterally suggests that the effect of the SII stimulus was specific. SII was only effective in raising the threshold of behavioral responses in the nerve-skin stimulus pairings when applied in the same limb and dermatome. No segmental contralateral interaction effects were demonstrated. These findings do not give clues as to whether the interactive site lies in the peripheral nerve or its central connections.

Discussion

These studies indicate that non-noxious stimulation of skin in a portion of a dermatome has no effect upon the behavioral response of a monkey to aversive stimulation of skin in another part of the same dermatome. According to Melzack and Wall's[2] gate control theory, the non-noxious SII stimulus should activate only large diameter cutaneous afferents and, when applied ipsilateral to the SI aversive footshock stimulus, should elevate the SI pain threshold. Thus the results of these investigations of paired skin stimulation are inconsistent with the theory. In comparing our study with other reported studies, it must be noted that we have developed an animal model for the behavioral assessment of pain threshold, while related investigations have employed human subjects. The advantage of the animal model comprises its freedom from such biasing influences as suggestion, cueing, and

Table 7. Analysis of variance summary table (Subject 2)

Source	SS	df	MS	F
A. SII site order	0.13	1	0.13	0.12*
Days within groups	8.58	8	1.07	
B. SII site	0.97	1	0.97	5.24†
AB interaction	0.02	1	0.02	0.11*
Bx days within groups	1.48	8	0.19	
Total	11.18	19		

* Not significant.
†$.05 < p < .10$.

Table 8. Analysis of covariance summary table (Subject 2)

Source	SS	df	MS	F
A. SII site order	0.26	1	0.26	0.30*
Days within groups	6.15	7	0.88	
B. SII site	1.24	1	1.24	7.75†
A′B′ interaction	0.09	1	0.09	0.56*
B′× days within groups	1.09	7	0.16	
Total	8.83	17		

* Not significant.
† $.001 < p < .05$.

other verbal and nonverbal interactions between experimenter and subject.

Previous studies have employed a wide variety of aversive and non-noxious stimuli, so that comparison among them and with the present study is limited. A number of investigators have shown that tactile[12] or vibratory[13, 14] stimulation of the skin elevates the threshold for mild electrical or radiant heat pain in the same skin region. Melzack et al[13] and Sullivan[14] found that vibration decreased the pain tolerance level, while Higgins et al[12] showed that brief light touch raised pain tolerance threshold. Campbell and Taub[8] and Nathan and Rudge[9] both looked at the effects of electrical skin stimulation upon pain threshold. The stimuli used by Campbell and Taub[8] ranged from 10 to 22 volts, much greater than the 2 to 3 volts employed in the present study. At 10 volts they reported elevation only of stimulus detection threshold, but not for pain; at 22 volts both thresholds were elevated. Their finding that a 10-volt stimulus failed to raise pain threshold is consistent with the absence of pain threshold elevation by a 3-volt stimulus in the present study. Although electrical parameters of the stimuli used by Nathan and Rudge[9] were not specified, the stimulation was adjusted to be non-noxious. Their report that innocuous stimulation has no effect upon pain thresholds parallels the results of this investigation. Satran and Goldstein[15] employed a 25-volt train of pulses preceding determination of pain tolerance threshold. Although they observed elevation of tolerance threshold, the use of a possibly noxious conditioning stimulus and tolerance threshold makes the relevance of their methods to the present study questionable. In summary, studies of the effects of tactile stimulation on mild pain threshold are consistent with the gate

control model, but none of the investigations using non-noxious electrical stimulation, including the present study of footshock pain, support Melzack and Wall's[2] theory.

In contrast to the results for footshock pain threshold, non-noxious electrical skin stimulation was found to elevate the monkey's behavioral threshold for pain resulting from direct stimulation of the ipsilateral sciatic nerve. Certainly, direct nerve stimulation produces a much more intense perception of pain than does skin stimulation, so that the threshold measured in this phase of the study was more likely pain tolerance than pain detection. The observed threshold elevation corresponds to the results of Higgins et al[12] and Satran and Goldstein,[15] demonstrating that tactile or electrical stimulation raises the threshold for pain tolerance. The distinction between pain detection and pain tolerance is relevant and clinically important. Studies of electrical skin stimulation by electronic devices in order to produce analgesia have shown such treatment to be effective in some patients with chronic pain from a variety of causes. Many patients with a demonstrated physical cause for pain have been shown to experience some degree of relief, whereas those with psychogenic pain syndromes are unrelieved by electrical cutaneous stimulation.[16] Our behavioral test of the gate theory did not include the condition of chronic pain, nor did other work already cited study humans with chronic pain. It is possible that chronic pain is a necessary condition to demonstrate functional gate control, and that the mechanism influences pain tolerance but not pain detection threshold.

Summary

This study employed a behavioral index of pain threshold in the monkey to test some implications of Melzack and Wall's[2] gate control theory of pain. The theory predicts that non-noxious skin stimulation will activate large diameter cutaneous afferents whose inputs to the spinal cord will block the input from small fibers generated by noxious stimulation, thus elevating the pain threshold. Operant conditioning was used to train stumptail macaques to respond to noxious stimulation and to ignore non-noxious stimulation of skin or peripheral nerve. These stimuli were then paired to determine whether a non-noxious stimulus would elevate the threshold of a conditioned noxious response within the same spinal segment, in the contralateral homologous segment, or at the level of peripheral nerve. Three successive evaluations over several years demonstrated that non-noxious stimulation of the S1 dermatome at ipsilateral or contralateral popliteal fossa does not raise the pain threshold for noxious skin stimulation of the foot in the S1 dermatome. In contrast, a non-noxious popliteal skin stimulus does elevate the pain threshold for ipsilateral stimulation of sciatic nerve; the response to contralateral nerve stimulation is not altered. These findings are discussed in relation to the results of other reported studies, and their implications for the gate control theory of pain are considered.

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