Short Title

INDIVIDUAL DIFFERENCES IN EFFECT OF SEPTAL STIMULATION ON ESCAPE

Ph. D. PSYCHOLOGY

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A test of preference for accepting or rejecting electrical stimulation of the rat's septal area revealed individual differences: "positive" reactors sought the stimulation; "negative" reactors escaped from it.

All animals escaped from electrical stimulation of the dorsal tegmental area. Rapidity of this escape reaction was altered by concurrent low level septal stimulation. Animals previously classified as "positive" reactors to septal stimulation escaped more slowly; "negative" reactors escaped more quickly. This differentiation did not appear, however, in the reaction to electric shock applied to the feet: with concurrent low level septal stimulation present both types of reactor escaped more quickly. Questions of individual differences in reaction to septal stimulation and of differences in reactions to aversive central and peripheral stimulation are discussed.

Cardiac effects of stimulation in the tegmentum and at the periphery were also studied. Effect of the former stimulation appears to be more complex than that of the latter.

INDIVIDUAL DIFFERENCES IN THE EFFECTS OF SEPTAL STIMULATION ON ESCAPE BEHAVIOUR IN THE RAT

by

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Since 1954, when it was successfully demonstrated that stimulation of different sites within the brain could serve as reward (Olds & Milner, 1954), or punishment (Delgado, Roberts, & Miller, 1954) in learning situations, a considerable number of studies investigating these phenomena have been reported. Olds and his associates, in particular, and others, using stimulation and lesioning or ablation techniques, have investigated relations between various structures of the brain and learning and retention.

Dual effects of stimulation

At first the approach seems to have been to treat particular structures as though they had but one valence: that is, as though stimulation within these structures would have either rewarding or punishing effects on behaviour (Olds, 1956a; 1956b; Delgado, et al., 1956). However in 1958 Roberts (1958a) showed that this was not always the case; stimulation of the same structure could have both positive and negative reinforcing effects on behaviour.

Duration of Stimulation. In an earlier study Roberts (1958b) had found that, with stimulation in the lateral and posterior hypothalamus, he could elicit in rats very adequate escape behaviour, but no avoidance behaviour. In an

attempt to find the reason for this, Roberts (1958a) also in rats, investigated the possibility that onset of stimulation in these areas was rewarding, but that when prolonged, the same stimulation became aversive. In this experiment, Roberts tested 14 different points in the lateral and posterior hypothalamus. First the animals were tested in a bar-press situation in which they learned to press for food on a variable interval (VI) schedule. Next they were put on a schedule of alternating periods of extinction and VI food reinforcement. The extinction periods were either of the usual type, or each bar-press during this period resulted in a 0.5 sec. burst of brain stimulation. Nine of the 14 animals showed a higher than normal rate of pressing during these stimulated extinction periods; five showed a lower than normal rate during these periods. All 14 animals learned to escape in a one-way shuttle box situation or a T-maze situation in which the animals had to go into the correct arm of the maze to escape or avoid stimulation. None of the animals learned to avoid. Roberts suggested that a possible reason for these results might be that two overlapping neuronal systems having different recruiting or fatigue rates were involved. Why the five animals who appeared to find stimulation in the bar-press situation aversive did not learn to avoid he does not explain.

He notes that in other animals placements almost identical to these "aversive" ones produced positive reinforcement of behaviour when stimulated.

Again in 1958, Bower and Miller, this time stimulating in the anterior portion of the medial forebrain bundle and using the same T-maze avoidance situation as Roberts', found that the rats also learned to escape, but not avoid, stimulation. Both Bower and Miller and Roberts interpreted their results as showing that while stimulation of brief duration appeared to be rewarding, prolonged stimulation in these structures was aversive. Bower and Miller suggested that the reason the animals did not learn to avoid was that the aversive phase of the stimulation was too long in coming. In a second part of their study they found some support for this hypothesis. In a one-way shuttle box avoidance situation, where brief stimulation of the brain was followed immediately by shock to the feet, no avoidance was obtained if the intensity of the shock was raised from a fairly low level to a fairly high level over a 3 sec. period; however, if the shock was raised by the same amount over a 1 sec. period, avoidance was obtained.

Brown and Cohen (1959) tried to show that the dual effects obtained by stimulation of the same structure of the

brain were due to environmental differences. They used rats with lateral hypothalamic placements. Their animals were trained to run down an alley to obtain 0.3 sec. of brain stimulation, or, in a two-way shuttle box situation, to avoid stimulation. In the avoidance situation, the mean duration of the stimulation was 0.3 sec. per trial. They found that the animals would traverse the alley with increasing speed to receive stimulation, but that they would also learn to avoid the stimulation in the shuttle box situation. They interpreted their results as showing that stimulation in the hypothalamus "acts as an energizing, drive arousing operation to produce both approach and avoidance learning." It has no rewarding or punishing properties of its own: these are provided by the situation in which the animal finds himself. However, in the avoidance situation in this experiment the stimulation was in fact left on until the animal escaped, so that the two situations were not really comparable. The animal's experience was that if he did not escape or avoid, the stimulation would remain on and become aversive. Thus Roberts' (1958a) explanation probably fits their data better than their own. Why Roberts could not obtain avoidance when Brown and Cohen succeeded in doing so is not clear. In view

of Bower and Miller's results with the brain stimulation and foot shock, it may have been due to the fact that Brown and Cohen used higher levels of stimulation.

Stein (1962) reported a study which investigated the duration of stimulation preferred when rats were stimulated in hypothalamic, ventral tegmental, and septal reward areas. In this experiment the animals received stimulation as long as they held down a bar in a one-bar Skinner box type of apparatus. Stein found that the animals with septal placements tended to hold the bar down longer than did those animals with the hypothalamic and ventral tegmental placements. He also found that, as the intensity of the stimulation was increased, the hypothalamic and ventral tegmental animals would terminate the stimulation sooner, while the septal animals would hold the bar down longer. He suggested that, in the case of the hypothalamus and ventral tegmentum, prolonged stimulation was actually punishing. The effect of prolonging the stimulation was to activate neighbouring aversive systems. In the case of the septal area, however, stimulation becomes less rewarding through "adaptation" to the stimulation, rather than because it becomes aversive.

Intensity of Stimulation. Reynolds (1958), using rats in a bar-press situation, reported that with stimulation in

the ventromedial region of the anterior hypothalamus, the intensity of the stimulation was an important parameter. Up to a certain current level the rate of pressing to obtain stimulation increased and other behaviours, such as exploring, decreased. Above that level, however, the rate of pressing fell off and withdrawal responses began to appear with the extent of retreat increasing with current level increase. While these high current levels were available, the animals did return every now and then to press the bar. It is possible, of course, that the stimulation was still rewarding at these high levels, but only if there was a long interval between stimulations.

Frequency of Stimulation. Olds (1960) reported a study in which frequency of stimulation did seem to be important. His electrodes were implanted in the "mid-lateral" hypothalamus of the rat. In this case durations of the stimulating trains were identical and the current levels used were the same for approach and escape, but in the escape bar-press situation, the trains occurred at the rate of 1 per sec. until the bar was depressed, at which point the trains would be halted for a 4 sec. period. In the approach situation, where the animal was free to stimulate himself whenever he wished, he did so at the rate of about 1 press every 2 sec.

On this basis Olds concluded that frequency of stimulation was here the important parameter in determining whether approach or escape would be obtained.

Environmental Conditions? The above studies have been concerned with the dual effects of stimulation within the hypothalamac complex. However, moving on to another structure, the thalamus, dual effects are also to be found. Kopa, Szabo, and Grastyan (1962) report such effects with stimulation in the region of the centrum medianum and habenulo-peduncular tract in cat. In this study the animals were first trained to escape foot shock by jumping off an electrified grid onto a wooden platform where they were never shocked. Then the animals were placed either on the nonelectrified grid floor or on the "safe" plaform and were stimulated in the thalamus. The authors found that if the animals were placed on the grid floor, they would quickly jump up onto the "safe" plaform when stimulated in the thalamus. However, if they were on the "safe" platform when stimulated, they would lie down, purr, and in general show clear signs of contentment. This pattern changed immediately to alertness, getting up, and perhaps even getting down off the platform when stimulation was terminated. The authors reported not being able to obtain these dual effects when stimulating other sites within the thalamus. With stimulation of these other points

they could obtain only the escape response pattern.

Kopa et al. have in this study reported data which might be thought to provide evidence for the kind of concept which Brown and Cohen (1959) formulated. However, they prefer to interpret their results in terms more like those suggested by Roberts (1958a) and Stein (1962); that is, in terms of the existence of two, perhaps antagonistic, neural systems which overlap in this region of the brain. The effect of the environment on the animal renders one system or the other more likely to be activated. In support of such an interpretation they cite evidence reported by Monnier and his associates (Monnier, et al., 1960) that there is electrophysiological evidence for two such "reciprocally interconnected neural systems" in this area of the cat thalamus. The two systems are the thalamic extension of the reticular system and the intralaminary recruiting system. The two were judged to be opposite in effect, and possibly antagonistic, because stimulant drugs increased the excitability, as judged by EEG response to stimulation, of the thalamic reticular system, but depressed the excitability of the thalamic recruiting system. Depressant drugs had the reverse effect on the two systems. Decerebration at the intercollicular level decreased the excitability of

reticular system, but increased that of the recruiting system. And finally, stimulation of the reticular system resulted in increased activity of single cells at various points in the cortex, while stimulation of the recruiting system inhibited the activity of these same units.

Olds also has noted different effects of stimulation in this same general area of the thalamus. In 1960, Olds, Travis, and Schwing reported that stimulation of the anterior and instralaminary nucleus areas of the thalamus proved to be rewarding in a situation in which the rats were pressing a bar in order to obtain stimulation. In this study they were not given the opportunity to escape the stimulation. In 1963, Olds and Olds reported the anterior thalamus to be an area of negative reinforcement in the rat. In this latter study the animals were tested in both approach and escape bar-press situations. The authors report that the animals showed no tendency to approach the stimulation. They suggest that the explanation of Kopa et al. likely accounts for their divergent results. What was different about the two approach situations they do not explain.

The studies just reviewed all show that stimulation of certain structures in the brain can yield both rewarding and punishing effects on behaviour. In all these studies the

differences were attributed to some variation in the experimental conditions, whether duration, intensity, or frequency of stimulation; or differences in the environmental conditions. The tendency seems to have been to try to explain this phenomenon in terms of the involvement of other, perhaps antagonistic, neural systems which pass through the same structures. It might be noted here that Valenstein (1964) suggested caution in making such complex interpretations before seeking a simpler solution. He suggested that the answer to the problem may often lie in the method by which the rewarding properties of a structure are ascertained. For instance, he cites evidence (Valenstein & Valenstein, 1963) that where rats were required to hold a bar down in order to continue stimulation of the hypothalamus, the preferred duration was significantly shorter than in the situation in which the animals were required to press one bar to turn the stimulation on and another to turn it off. The differences could not be accounted for merely by the additional time required to get from one bar to the other. He suggested that the motoric effects of the stimulation itself forced the animals off the bar, thus producing the bar presses of brief duration. Valenstein further noted that while the idea of temporal summation, in the case of such duration effects, in the activation of a

in the activation of a neighbouring aversive system might be applicable where preferred durations are of approximately 1 sec. (the one-bar situation), it is very unlikely that it can be applied when the durations are of the order of 10 sec. or more (the two-bar situation).

Dual effects of stimulation within the septum

Another structure which appears to show dual effects of stimulation is the septum. References to such dual effects can be found in the literature, though in most instances these findings have received relatively little attention.

Location within the Septum. Bursten and Delgado (1958) reported an experiment in which they were investigating the reinforcing potential of various structures of the brain in monkeys. The apparatus was a rectangular "table". If the animals went to one end of the table they would receive stimulation in 0.34 sec. bursts every 3.46 sec. as long as they remained at that end of the table. If they went to the other end of the apparatus they received no stimulation. The end on which the stimulation could be obtained varied randomly. Among the areas tested was the septum. In the discussion they make this comment:

> "Regarding the septal area we have found positive results from stimulation of the

> lateral septal nucleus, but not from stimulation of the medial septal nucleus. This suggests that reference merely to the septal area (without specifying the particular nuclear groups) may be masking differences to be found within this region." (p.9)

In this study the medial septal animals could have escaped the stimulation had they wished, but they for the most part did not either seek or escape it to any significant degree suggesting that the stimulation had essentially neutral effects.

Olds, Travis, and Schwing (1960) reported both "square" and "undulating" functions when stimulating within the septum. By "square" functions they meant that raising the intensity of the stimulation increased the bar-pressing rate up to a point beyond which further increases did not increase the rate, but did not cause it to decrease either. "Undulation" referred to the situation in which increasing the intensity of the stimulation was matched by an increase in rate up to a point, with further increases resulting in reduction of the pressing rate. This latter pattern resembles that described by Reynolds (1958) for the ventromedial region of the anterior hypothalamus. The "square" functions appeared to be associated

with stimulation of the more dorsal and lateral areas of the septum, while the "undulating" functions, or no stimulation effect, appeared to be associated with the medial, more ventral, area.

Newman (1961) reported an experiment in which rats were tested in an alley and two different bar-press situations for reward effects of stimulation in the septum. Various temporal stimulation parameters were investigated. She found that the rewarding effect of the stimulation was shown more clearly in the bar-press situation than in the alley situation. However, she notes that, in the alley test, placements in the supracommissural septal area 250 to 750 micra anterior to the anterior commissure produced strong reward effects, while placements more rostral to this appeared to impair performance in the alley, suggesting that stimulation in this area was "noxious or punishing rather than rewarding."

Individual differences in response to stimulation

In the preceding studies, differing responses to stimulation have been attributed to differences in the experimental conditions or to differences in the location of the electrodes. However, there seem to be cases in which stimulation of identical, or nearly identical, sites have, in different animals, produced different effects on behaviour.

First, in an area other than the septum, Roberts (1958a), it may be remembered, mentioned five animals who extinguished more quickly than normal, suggesting that, for these particular animals, even brief stimulation of these sites in the hypothalamus produced aversive effects. However, he also notes that other animals with those same placements under the same conditions responded to the stimulation as though it was rewarding.

In studying the septum Newman (1961) noted that in the alley task one animal (no.1) with an electrode placement in the region of the diagonal band of Broca and the medial septal nucleus, responded to stimulation as though it were clearly rewarding, but another animal (no.9) with the same placement "did not indicate by its performance that the conditions were reinforcing."

Asdourian (1962) reported an experiment with rats which was designed to determine the effect of rewarding brain stimulation on intake of palatable and unpalatable solutions. His electrode placements were scattered throughout the septal area. The animals were initially screened in a bar-press situation and, of the 26 animals used in the experiment, 12 proved to have rewarding placements and 14 to have nonrewarding placements. Results of the histological analysis showed

the 26 placements to be all within the septal area, with no particular area in the septum appearing to have exclusively one effect or the other. In some instances the same placements in different animals seemed to have different effects. At one location, for instance, there is a cluster of 9 points; 4 were rewarding, and 5 were nonrewarding (personal communication). In the experiment proper, when paired with an unpalatable solution the rewarding stimulation did not enhance the acceptability of that solution; i.e. the animals would not drink more than they normally did. However, when this stimulation was paired with a 9% sucrose solution, which the animals like anyway, they drank more of it then they would normally. In the case of the nonrewarding stimulation, when the animals were given a choice between a 9% sucrose solution paired with stimulation and a 4% sucrose solution not paired with stimulation, the animals chose the 4% solution. This is of interest since the 9% concentration is normally preferred; and indeed when the nonreward stimulation was paired with both concentrations the preference for the higher concentration returned. Asdourian commented:

> "The behavior of the nonresponse group clearly indicates that the brain shock

> was an aversive stimulus and that the designation neutral for a brain shock that does not alter operant levels of bar pressing may be a misnomer resulting from failure to use a wide enough spectrum of test situations." (p.689)

Malmo (personal communication) has provided further data indicating that there are individual differences in the rewarding properties of stimulation of highly circumscribed areas within the septum of the rat. These are unpublished bar-pressing data from Experiment 2 in Malmo (1965). Histological analysis showed that, of the 21 animals used in the experiment, 17 had placements clearly within the septal area (see Malmo, 1965; Fig.1). In the case of animals 12 and 25, the electrode tips were on the border of the septum and the caudate nucleus and it was probable that the caudate nucleus was also stimulated. Adopting a criterion of 400 responses per hour in classifying the animals as responders or nonresponders, 12 were classified as responders, 5 as nonresponders. The 12 responders were animals; 1, 2, 7, 9, 11, 15, 16, 17, 18, 21, 22, and 24. The nonresponders were animals; 5, 8, 10, 13, and 20. It can be seen from the Figure that the electrode placements for all 5 nonresponders

were the same as those for responders 7, 11, 16, and 18. To illustrate the great difference in bar pressing rates obtained for animals with the same placement: animal 8 had a pressing rate of only 78 responses per hour; animal 11 had a rate of 762 responses per hour.

It is apparent, then, that stimulation within the septum does not have only positively reinforcing effects on behaviour. It would also appear that there may be some individual differences with respect to response to this stimulation since stimulation of very similar (or even identical) sites, under the same conditions, seems to produce quite different effects on behaviour. It has also been suggested that for nonresponders the stimulation may not be just neutral, but in fact aversive (Newman, 1961; Asdourian, 1962).

The present problem

The previously cited evidence suggests that stimulation within the same area of the brain may produce different behavioural effects. It also suggests that, at least with regard to the septal area, there may be individual differences in this respect since seemingly identical placements produced differing behavioural effects. If this is so, the question arises as to whether these individual differences will show up in other situations. That is, will septal stimulation have

but one effect on behaviour motivated by other stimuli, despite the individual differences, or will there be some correlation between these differences and the effect of septal stimulation on these other behaviours? Asdourian's study (1962), mentioned earlier, suggested that there is such a correlation where behaviour motivated by peripheral stimuli is concerned.

Another test would be to see whether there is any correlation between these differences and the interaction of septal stimulation with stimulation of some other area of the brain which has but one valence, or effect, with regard to reinforcement of behaviour. One such univalent area seems to be the dorsal portion of the midbrain tegmentum. This area encompasses the dorsal part of the periaqueductal grey substance, the dorsal tegmental region, and the region of the superior colliculi. Olds and Olds (1963) have classified it as one producing only negative reinforcement in a bar-press test situation. Valenstein (1965) noted that tegmental placements which consistently yielded better than 90% efficiency of escape in a two-way shuttle box type of apparatus were all located in the region of the dorsal periaqueductal grey substance, the superior colliculi, and the posterior commissure.

Routtenberg and Olds (1963; personal communication) have reported briefly on the effects of rewarding septal stimulation on escape behaviour motivated by stimulation of this dorsal tegmental area in rat. Three animals were trained to escape, by pressing a bar, 0.5 sec. trains of tegmental stimulation, delivered at the rate of one train per sec. This response delayed the stimulation trains for a 6 sec. period. When stable escape pressing rates had been attained, below reward intensity, continuous, noncontingent septal stimulation was introduced into the escape situation. This continuous stimulation was present during the whole half-hour escape session on alternate days. The authors found that when the low level stimulation was present the escape pressing rate declined. They also noted that the effect of the septal stimulation seemed to decrease with repeated tests. Data for one animal who did not have a rewarding septal placement indicated that, for this animal, the presence of the continuous septal stimulation did not alter his escape pressing rate. All septal placements were extremely rostral.

It has been suggested that rate of pressing a bar is not a particularly sensitive measure of the reinforcing properties of brain stimulation (Hodos & Valenstein, 1962;

Valenstein & Beer, 1962; Meyers & Valenstein, 1964). For example Hodos and Valenstein (1962) showed that, when given a choice, animals may select stimulation at intensities or of neural sites which support the lesser response rate. Valenstein and Meyers (1964; Meyers & Valenstein, 1964) have developed a method which seems to provide a more reliable and sensitive measure of the reinforcing consequences of brain stimulation. The apparatus used is a form of two-way shuttle box. The measures taken are the amount of time spent accepting stimulation and the number of times the animal crosses from one side of the box to the other in order to turn the stimulation on or off. The side on which the stimulation can be obtained shifts from side to side so that the animal is forced to move about.

The main purpose of the present study was to investigate further, using this more sensitive technique developed by Valenstein and Meyers, the effects of the differences of response to septal stimulation. To be more specific, the question was raised as to whether some correlation would be found to exist between response to septal stimulation and the effect which stimulation of these same septal sites would have on behaviour motivated by other stimuli. The behaviour studied was escape, on one hand motivated by stimulation within the univalent dorsal tegmental area of the brain, and on

the other by peripheral foot shock. Heart rate was also recorded for some of the animals.

Method

Subjects

The subjects were 25 naive male hooded rats from the Quebec Breeding Farm. In 15 of these animals (to be referred to as tegmental animals) two electrodes were implanted: one aimed at the septal area, the other at the dorsal tegmental region. Ten of these 15 animals were used in the test for the effect of septal stimulation on escape from aversive stimulation in the tegmentum. Of the remaining five animals, three did not have "septal" electrodes which terminated in the septum, and two were used only in the screening portion of the study (see Table 1a). In the other 10 of the 25 animals (to be referred to as peripheral animals), one septal and one peripheral electrode were implanted. Seven of these 10 animals were used in the test for the effect of septal stimulation on escape from aversive stimulation at the periphery. Of the remaining three animals, two did not learn the escape task adequately, and one was used only in the screening tests (see Table 1b). EKG records were taken for five of the tegmental animals and three of the peripheral animals (see Tables 1a and 1b).

Apparatus

Figure 1 is a sketch of the two-way shuttle box used

throughout these experiments. It was adapted from the apparatus described by Valenstein and Meyers (1964). A green gelatin filter which covered the plexiglass window served to make it a one-way vision screen since the house light inside the box, set just above the window, was white while the light in the room outside the box was red.

The interior of the box was divided into two compartments by a 1 in. high hurdle. The floor of each compartment consisted of a wire mesh platform, pivoted at the center of the box, and balanced by a counterweight. The outer edge of each platform operated a microswitch which closed when the animal crossed onto that side, thereby turning a stimulating current on or off depending upon whether or not that microswitch was connected into the stimulation circuit. The stimulation source was a Grass S4 stimulator (Stimulator 1). The two switches were alternately connected into the stimulation circuit by activation of two Hunter Decade timers (Model 111-C): when one timer timed out it activated the second one, which when it timed out, reactivated the first one. The house light in the box also blinked off for 0.1 sec. at the time of alternation.

The stimulation circuit described above was used during screening and escape training. During testing, an

additional continuous source of stimulation was provided by a second Grass S4 stimulator (Stimulator 2). The two stimulators were synchronized by connecting the synchronization output of Stimulator 1 to the synchronization input of Stimulator 2. By appropriate adjustment of the pulse delays, the pulse trains from the two stimulators were interdigitated. That is, pulses were delivered alternately by the stimulators such that the two pulse trains were 0.005 sec. out of phase; and thus the two sites of stimulation were never both receiving a pulse at the same instant.

The outputs of the two stimulators were modified to increase accuracy of current intensity measurement. This was done by:

> "...equalizing the capacitance of the electrode-electrolyte combination with an inductance connected in series into the (stimulation) circuit. ...the output capabilities of the stimulator are only slightly reduced. With proper adjustment the original rectangular shape of the pulse is reasonably restored, simplifying monitoring of stimulation current." (Mundl, in press b.)

Two Fairchild 704 oscilloscopes were used to monitor current

levels at all times.

An attempt was made to minimize any electrical crosstalk between the two electrodes implanted in the same animal (Schwartzbaum & Donovick, 1965; Valenstein, 1964). This was done by "...minimizing ground and stray capacitances, minimizing resistive ground paths ..., and in reducing the high frequency components of stimulation pulses." (Mundl, in press a.) The crosstalk, or induced, current in the electrode circuits was measured, using an oscilloscope, "as a function of potential difference across (a) 1K resistor inserted into the shorted leads of (the) electrode." (Mundl, in press a.) The maximum amount of induced current was measured in the circuit providing stimulation to the periphery, due to stimulation of the septum, amounted to an extra, nonadditive (i.e. interdigitated), high frequency spike of not more than 1/150 the value of the peripheral stimulation. In the other direction (i.e. the current induced in the septal stimulation circuit by stimulation of the periphery) this value was not more than 1/20 the value of the septal stimulation. In the case of the crosstalk between the tegmental and septal stimulation circuits, the value amounted to not more than 1/50 the value of the stimulation proper.

For certain animals the EKG was taken continuously during all training and testing sessions. Cardiotachograms and print-out records of the interval between heart beats, recorded in milliseconds, were also taken (see Mundl, 1965). Interbeat intervals were printed out three at a time and with each print a mark was automatically made on the graphic record indicating which beats on that record corresponded to those on the print-out tape. The graphic records were taken on a Grass Model 5 polygraph, at a paper speed of 25 mm. per sec.

All stimulating and recording leads were connected through a swivel device which allowed the animal complete freedom of movement about the box. White noise was present at all times to mask any extraneous sounds.

Surgical technique

The animals were anesthetized with Nembutal (Abbott - 6% solution, 0.09 cc./100 gm. body weight) and placed in a Stoelting stereotaxic instrument. The anterior (septal) brain electrode was implanted first using the co-ordinates +2, ½, 5 (i.e. 2 mm. anterior to bregma, ½ mm. to the right of the saggital suture, and 5 mm. below the level of the dura), in the vertical plane of the sterotaxic instrument. The posterior (tegmental) brain electrode co-ordinates used were -7, 1, 5, perpendicular

to the surface of the skull (Olds, 1963). The "peripheral" electrode was placed in the same position on the skull as the tegmental one, but its tip was inserted under the skin of the neck on the left side. For the peripheral animals this neck electrode served as one electrical pole while the wire mesh floor of the apparatus served as the other. Thus the current flow was between the neck and the feet. The animals reacted to this stimulation as though it was most noticeable at the feet.[1] All the electrodes were held in place with Caulk NuWeld which was poured around the base and around jeweler's screws which had been screwed into the skull before the electrodes were lowered into position. The hardened NuWeld also served to seal up the wound.

The electrodes implanted within the brain were bipolar and consisted of two strands of 0.007 in. or 0.01 in. diameter Dyamel coated platinum wire, twisted together, and soldered to 27-9 Amphenol plugs. Only the tips of the wires were bare of the insulation. The peripheral electrodes con-

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[1]An attempt had been made earlier to have both poles located up near the head, but this only resulted in the animals flattening themselves against the floor or occasionally slinking along on it. This behaviour did not get them across the hurdle and they subsequently "froze". Animals who were stimulated with both electrodes elsewhere on the body, instead of escaping, attempted to remove the offending electrodes.

sisted of a Formvar coated strand of 0.01 in. diameter stainless steel wire, doubled over and twisted. One end of this twisted wire was soldered to an Amphenol plug; to the other end was affixed a ball of solder coated with silver paint.

The EKG electrodes were implanted immediately after removing the animal from the stereotaxic instrument. Two 2 in. lengths of #28 B&S Hoskins Chromel "A" resistance wire were used: one placed above the shoulder blade on the right side, the other at the posterior end of the rib cage on the left. The wire was threaded through a 20 guage hypodermic needle inserted subcutaneously, with a distance of about 3/16 in. between insertion and exit. The needle was then withdrawn leaving the wire in its place. The ends were twisted together and cut to leave about a ½ in. length of protruding twisted wire onto which the EKG leads were clipped for recording.

After surgery the animals were injected with 100,000 IU Bicillin 600-LA (Wyeth) to counter any infection, and with 0.5 cc. Megimide (Abbott - 0.05% solution) to shorten the period of anesthesia. They were then allowed 5 or 6 days in which to recover before screening was begun.

Screening

After recovery from surgery, each animal was placed in

the apparatus for a 15 min. "adaptation" period. During this time the septal lead was attached to the animal and, except that the animal did not receive any stimulation, all conditions were the same as they would be during the subsequent screening test sessions. Scoring of the animal's behaviour during this session was carried out as though he could obtain stimulation by depressing one or the other of the platforms. That platform on which he would later be stimulated was designated the "on" platform, and that on which he would not be stimulated the "off" platform. Each platform was alternately the "on" platform for a 30 sec. period (i.e. the intertrial interval (ITI) was 30 sec.). The amount of time spent on the "on" platform and the number of times the animal crossed the hurdle onto the "on" and "off" platforms were recorded. On the second day the animal was again put in the box, but this time he was stimulated to find the lowest current level at which he would show a clear preference for being stimulated or, alternatively, not being stimulated. Stimulation consisted of a 100 pulse per sec. continuous train of biphasic rectangular pulses of 0.5 msec. pulse duration.

On the following two days the animal was given a 15 min. session each day. The current level used was that de-

termined on day 2; the ITI was 30 sec. Again the time spent on the "on" platform (that platform on which the animal could obtain the stimulation) and the number of crossings to obtain and to escape stimulation were recorded. The mean time per session spent on the "on" platform (and by subtraction the mean time spent on the "off" platform), and the mean number of crossings to turn the stimulation on and off are presented in Table 2. On the basis of these results the animals were classified as either "positive" or "negative" reactors to the septal stimulation. A "negative" reactor was one who would, under the above stimulating conditions, tend to escape rather than seek the septal stimulation. This classification of the animals was always carried out prior to initiation of the escape training.

The data presented in Table 2 show quite clearly that the "positive" and "negative" reactors were responding quite differently to the same type of stimulation. The mean intensity of stimulation was about the same for both groups. However, the mean time spent being stimulated was very different for the two groups. While the "positive" reactors took a mean of 9 min. 41 sec. of stimulation during the 15 min. test period, the "negative" reactors took only 4 min 3

sec. of the stimulation. The number of crossings to the "on" and "off" platforms also showed that the groups were different with respect to their preference for the septal stimulation. The "positive" reactors showed a mean of 27 crossings to turn the stimulation on and a mean of 11 crossings to turn it off. The "negative" group, on the other hand, crossed to turn the stimulation on a mean of only 5 times in the 15 min. period, while they turned it off a mean of 31 times in that same period.

Training and testing

The day following the last screening test the animals were again placed in the apparatus but were now trained to escape either central stimulation in the dorsal tegmentum, or peripheral stimulation of the feet. An ITI of approximately 1 min. was used and each daily session consisted of 20 trials. All stimulation parameters, except intensity, were the same as those used during screening. The current level was determined for each animal (see Tables 1a & 1b) during the first few sessions. For the tegmental animals this level ranged from 35 microamp. to 300 microamp. with the median being 65 microamp. For the peripheral animals the range was 0.75 milliamp. to 2 milliamp. and the median was 1.25 milliamp. The stimulation remained on until the

animal escaped, and training was continued until a stable latency of escape had been achieved. The criterion for stability was that the mean trial latencies for three consecutive sessions should have a range of no more than 0.3 sec.

As soon as the animals had achieved this degree of stabilization, low level septal stimulation was introduced into the situation. The current level used was 1/3 the level used during screening. At this intensity, which ranged between 10 microamp. and 30 microamp., the stimulation had no noticeable reinforcing effect on the behaviour of the animals. The other stimulation parameters were the same as those used during screening. Three such test sessions were run with all conditions for the escape task being the same as during training. Then followed three further sessions under conditions which were the same as those during train ing. That is, no low level septal stimulation was present. Three final sessions were then run with the continuous low level septal stimulation again present.

During all sessions the escape latencies were recorded on the Grass polygraph and were later measured to the nearest 0.05 sec.

Histological technique

Following completion of the last test session the animals were killed with ether and perfused with physiological saline followed by 20% formol-saline. The brains were removed and fixed in 10% formalin in tap water. Sections were cut on a freeze-microtome at 40 micra in approximately the DeGroot plane (DeGroot, 1963). In general, every section or every other section was taken throughout the electrode track, depending on how close the angle of cutting was to the angle of the electrode track. All sections were stained with Neutral Red and Luxol Fast Blue stains.

Treatment of data

A t-test for correlated samples was performed for all groups, except one, to test the significance of the difference between mean escape latencies under the two experimental conditions. That one group consisted of the two "negative" reactors tested in the peripheral stimulation escape situation. For these animals a t-test for independent samples was performed for each animal individually since the N in this group was so small.

The EKG records were measured, in millseconds, in groups of three beats. The last 15 beats before onset of stimulation and the first 45 beats following termination of

stimulation were measured for each trial. Thus there were 5 prestimulation and 15 poststimulation units measured per trial. These units were then converted to heart rate in beats per min. Finally a mean prestimulation and a mean poststimulation heart rate value were computed for each animal. These mean values were for 3 sessions, or 60 trials, for each of the tegmental animals and for 20 trials, obtained from 2 or 3 sessions, for the peripheral animals. The relative paucity of trials for the peripheral animals is due to the fact that it is rather difficult to obtain measureable EKG records when using peripheral stimulation. To test the significance of the change in heart rate following aversive stimulation, a Lindquist Type I analysis of variance was performed, (Lindquist, 1953) using the pre- and poststimulation means for the five tegmental and three peripheral animals for whom EKG was recorded.

For three of the tegmental animals, individual beat measurements were made to study in more detail the polyphasic nature of the heart rate response pattern which appeared to follow stimulation in the dorsal tegmentum. This was done for the 8 sec. period following termination of the stimulation. Single beat intervals were also measured at seconds 1, 2, and 3 before onset of stimulation and at seconds

40, 50, and 55 at the end of the trial. Measurements were made for only 1 session, or 20 trials, for each animal because of the time involved in such measurement.

Results

Effect of low level septal stimulation

Table 3a shows that, for the animals who had sought septal stimulation during screening ("positive" reactors), the introduction of continuous low level septal stimulation into the tegmental escape situation resulted in a marked increase in the latency of escape. That is, these animals escaped tegmental stimulation more slowly when the septal stimulation was present. The mean trial latency of escape for the six sessions during which no septal stimulation was present was 1.31 sec. The mean trial latency for those six sessions during which the septal stimulation was present was 2.15 sec. The difference of 0.84 sec. per trial was significant at the .001 level.

Table 3b shows that, for the animals who tended to escape septal stimulation during screening ("negative" reactors), the introduction of continuous low level septal stimulation into the tegmental escape situation had the opposite effect. The latency of escape decreased. When no septal stimulation was present the mean trial latency of escape was 1.97 sec. When the low level stimulation was introduced the mean trial escape latency dropped to 1.44 sec. This decrease of 0.53 sec. per trial was significant at

better than the .01 level.

Table 4a shows the result of introducing low level septal stimulation into the peripheral escape situation for the "positive" reactors. Here the effect of septal stimulation was opposite to what it had been in the case of the "positive" reactors in the tegmental situation. With the low level stimulation present, instead of increasing, the mean trial escape latency decreased from 2.05 sec. to 1.44 sec. This decrease of 0.61 sec. per trial was significant at better than the .01 level.

The two "negative" reactors who were run in the peripheral stimulation escape situation behaved in a manner similar to both the "negative" reactors in the tegmental escape situation and the "positive" reactors in the peripheral escape situation. That is, they too escaped the aversive stimulation faster ($p < .001$ for each animal) when low level septal stimulation was present. Their data are presented in Table 4b.

General behaviour in the escape situation

Reaction to dorsal tegmental stimulation typically consisted of two successive phases. The first phase was a halting or arrest of any ongoing behaviour which occurred with onset of stimulation. This was followed by the second phase

which was a rather sudden jump over the hurdle to the "off" platform. With a relatively high current level, the first phase was very brief and the escape across the hurdle was very quick (having an "explosive" appearance). At the beginning of training, during the period of seeking an optimal intensity for eliciting a definite escape response, the animal's first response, at lower intensities, was the arrest behaviour. Then, as the stimulation current was raised, he would burst into excited, undirected activity and in the course of it cross the hurdle. This activity very quickly became directed toward crossing the hurdle to turn the stimulation off. With relatively more ventral points of stimulation (e.g. Fig.4 - ST IX & ST X), particularly if the stimulation was sufficiently high, the animals showed a tendency to back up, rear up in "defensive" or "fighting" postures, and, with increased stimulation, to turn on their backs. Also with these more ventral placements higher intensities of stimulation seemed required in order to elicit prompt escape than was the case with the more dorsal placements.

It seemed to be impossible to obtain reasonably short and stable latencies with three of the animals with the deeper placements. They appeared not to react at all to lower

levels of stimulation. Higher intensities elicited the retreat and rearing reactions, followed finally by crossing to the "off" platform; but it required 5 to 10 seconds or more for this "escape" response to appear. Two of these animals, ST XI and N, in addition to showing the behaviour patterns described above, developed another curious pattern which appeared to be testing or checking the "on" platform from the "off" side. Typically the animal "gingerly" depressed the "on" platform with one or both front feet until the stimulation came on, and then jumped back releasing the "on" platform and so turning the stimulation off again. When the stimulation switched to the side on which he happened to be, however, he would back off into a corner. After a time he would move again, more backward than forward, and so finally cross to the "off" side. There he would take a short "rest" and then, following a brief restless period, initiate the "testing" behaviour just described.

To test the possibility that the stimulation was rewarding when of short duration, the two animals were put on an intermittent schedule of stimulation such that when they were on the "on" platform they were stimulated for ½ sec. every 2 sec. (i.e. stimulation was on for ½ sec. and off for 1½ sec.). But the behaviour pattern did not change.

ST VIII, the third of the three animals, pulled his tegmental electrode out during his third training session. Since the tegmental electrodes implanted in five of the animals (ST VIII - ST XI, & N) had been 5½ mm. instead of 5 mm. long, it was decided to try to reimplant a shorter (5 mm.) electrode along the same track. When this was done ST VIII's escape latencies at once became more similar to those of the animals having more dorsal placements, though the stimulation level required remained high (see Table 1a). When it became clear that the other two animals (ST XI & N) were not going to improve their escape behaviour, it was decided to try the same experiment with them. The effect of the reimplantation on the escape latencies can be seem from Tables 5a and 5b. The mean trial latency for each of the two animals for 5 sessions before and after reimplantation dropped from 9.83 sec. and 12.98 sec. to 1.30 sec. and 1.73 sec. respectively. The current intensity required also dropped from 125 microamp. and 200 microamp. to 50 microamp. and 45 microamp. respectively.

The second electrode tip for ST VIII proved to be about ½ mm. more dorsal than the first (Fig. 2). For ST XI the difference was about 1½ mm. For N the location of the first electrode tip could not be ascertained with any degree of confidence. The placements shown on the diagrammatic

chart (Fig. 4) are the locations of the tips of the second electrode.

As a group, the tegmental animals were not particularly active during the interval between trials. The animals with the relatively more ventral placements tended to be a little more active than those having the more dorsal placements.

The reaction of the peripheral animals to stimulation was rather different from that of the tegmental animals. With these animals there appeared to be no arrest component to the escape response. During the early training sessions the reaction to the increasing intensity of the stimulation was a gradual increase in activity which appeared to be of the nature of trying to lift the feet, one or two at a time, away from the aversive sensation resulting from contact with the floor. This "dancing" movement eventually resulted in the animal's crossing the hurdle and so turning the stimulation off.

For the peripheral animals the aversive sensation appeared to be definitely localized, which did not seem to be the case for the tegmental animals. As was mentioned earlier (Footnote 1), if the animals were stimulated with both stimulating and indifferent poles located on the head or elsewhere on the body, great difficulty was experienced in getting

them to escape across the hurdle. If both poles were located up near the head, the animals would flatten their heads down on the floor as if trying to duck out from under the stimulation. If no hurdle had been present they might have learned to escape by wriggling across to the other side in this position. As it was, they came up against the hurdle, could not cross it in this posture, and subsequently "froze". If the electrodes were placed elsewhere on the body the animals would spend their time biting at the electrodes and trying to remove them rather than crossing the hurdle, even after having been assisted in crossing several times. Shocking the feet was found to be the most effective method of obtaining prompt escape from aversive electrical stimulation of the periphery. Even so it seemed to require more trials before the peripheral animals would direct their attention mainly toward crossing the hurdle and escaping the situation in general, than were required for the tegmental animals. These latter animals usually "had the concept" within the first 20 trials or less, while the peripheral animals seemed to take several sessions to stop directing most of their attention to their feet. However, once the peripheral animals had learned what to do they seemed to stabilize faster than did the tegmental animals.

Effect of stimulation on heart rate

Table 6a shows the marked increase in heart rate level which appeared following aversive stimulation, whether it was of the dorsal tegmentum or of the periphery. Data are not included for sessions during which low level septal stimulation was present because after some measurement and careful visual inspection of the records, it did not appear to affect the heart rate and the picture was the same whether or not it was present. The results of the analysis of variance are shown in Table 6b. This analysis showed the heart rate increase to be clearly significant ($p < .005$) for both groups, and the effect of the stimulation to be basically the same for both groups. The F values for both group and interaction effects were less than 1.

Figure 6 shows graphically the effect of the aversive stimulation on the heart rate. It also brings out the fact that the heart rate response following tegmental stimulation may be more complex than that following peripheral stimulation. The EKG data for this group were measured in groups of three beats. Figure 7 shows the individual beat EKG data for one session for each of three of the tegmental animals. It illustrates in more detail the polyphasic nature of the heart rate response following stimulation in the dorsal

tegmentum. Animal D_{10} showed the effect to the greatest degree, while D_7 showed it to the least.

Figures 8, 9, and 10 are records of individual trials for the three animals A_4, ST IV, and ST VI. Figure 9 illustrates the prolonged increase in heart rate level which usually followed tegmental stimulation. The heart rate often did not return to prestimulation level until 10 to 15 seconds before the beginning of the next trial. Figures 8, 9, and 10 further illustrate the finding that the immediate heart rate response to tegmental stimulation was not as consistent from animal to animal as the poststimulation effect. Both ST IV and ST VI showed a clear brief slowing response during stimulation, while A_4 showed a heart rate increase.

Histological analysis

Histological verification of the electrode tip placements is shown schematically in Figures 3 and 4. Figure 3 indicates the location of the tip of the septal electrode for all animals except A_4, D_7, and D_{10}. The electrode tip for A_4 terminated in the anterior caudate nucleus; those for D_7 and D_{10} did not penetrate through the corpus callosum in to the septum. As can be seen, all placements were within the septum, regardless of whether the animals turned out to

be "positive" or "negative" reactors to the stimulation of these sites. The apparent dorsal - ventral differentiation of "positive" and "negative" reactors is most likely accidental since, except for ST III and Q, 5½ mm. electrodes happened to be implanted at the same time animals were being screened for "negative" reactors. The placement for animal D was included to show this.

Figure 4 shows the location of the tips of the tegmental electrodes to be in the region of the superior colliculus, periventricular grey substance, and the dorsal portion of the mesencephalic reticular formation.

Figure 5 shows representative examples of a septal (upper) and a tegmental (lower) placement. Figure 2 is a tegmental section from animal ST VIII enlarged to show the location of the original and the second, shorter electrode tips. The open arrow head indicates the tip of the original electrode; the solid arrow head, the tip of the shorter electrode.

Discussion

Behavioural results

The results of the screening test showed that the "positive" reactor group clearly sought the reinforcement-intensity septal stimulation, while the "negative" reactor group appeared to find this stimulation aversive and quickly learned to escape it. The differences demonstrated in this way were confirmed by the differential effect of continuous low level septal stimulation on escape from aversive dorsal tegmental stimulation. The "positive" reactor group escaped the tegmental stimulation more slowly when the low level septal stimulation was present in the escape situation. The "negative" reactor group, on the other hand, escaped the tegmental stimulation more quickly when the low level septal stimulation was present. This kind of differential effect of the septal stimulation was not observed, however, in the peripheral stimulation escape situation. Both "positive" and "negative" reactor groups escaped the peripheral stimulation more quickly when the low level septal stimulation was present.

Response to Reinforcement-Level Stimulation. A major purpose of this investigation was to bring further experimental evidence to bear on the question of the differences

in reaction to septal stimulation. Differences were indeed found, and careful scrutinizing of various alternative possibilities indicated that these differences were not artifacts of the particular experimental conditions employed. First, the differences in the response to reinforcement-intensity septal stimulation cannot be attributed to differences in the parameters of stimulation (Roberts, 1958a; Bower & Miller, 1958; Reynolds, 1958; Stein, 1962; Olds, 1960; and others) since they were constant for all animals. Pulse form and frequency were identical; intensity was at the lowest level required to produce a clear behavioural response of seeking or escaping stimulation. The mean effective intensity was not significantly different for the two groups. Second, these differences cannot be attributed to differences in the environmental conditions (Kopa, et al., 1962; Olds & Olds, 1963) since both groups were tested under the same conditions in the same apparatus.

Figure 3 might suggest that there was a difference between the two groups as to electrode placement. However, this difference can most likely be accounted for, procedurally as follows: as was mentioned earlier, at one point 5½ mm., instead of 5 mm., electrodes were implanted. Except for

animals ST III and Q, the implantation of the longer electrodes coincided with screening for animals who would escape rather than seek the septal stimulation. While it is true that animals ST III and Q did turn out to have more ventral placements, so did animal D. The screening data for this latter animal show that the stimulation was clearly rewarding for him. Thus a dorsal - ventral distinction is probably not valid. A medial - lateral distinction certainly cannot be made since all placements, except perhaps that for animal Q, were either cearly within the lateral nucleus area or on its border. An anterior - posterior distinction cannot be made either since there is obvious overlap of reward and nonreward points in sections A-7.4, A-7.8, and A-8.2 in the Figure.

After excluding these other possibilities, the most reasonable explanation for these differences in the response to reinforcement-level septal stimulation seems to be in terms of individual differences. The precise nature of these differences (e.g. whether structural or otherwise) would of course remain a problem for further investigation. Such a conclusion is supported by the findings of Newman (1961), Asdourian (1962), and Malmo (personal communication) mentioned earlier. In all these studies stimulation of

identical, (Newman, Malmo), or very nearly identical (Asdourian), placements within the septum produced differential effects with regard to the reinforcement of behaviour. The present findings would seem to bear out the suggestion of Newman and Asdourian that nonrewarding septal stimulation may not be merely neutral but in fact aversive. It has been suggested (Kasper, 1965) that this aversiveness of septal stimulation may be related to findings of rage reactions following electrical (Galeano, et al., 1964) and chemical (Hernández-Peón, et al., 1963) stimulation in the septal area.

It seems clear, therefore, that there are individual differences in the reaction to septal stimulation, and from histological analysis it appears that these observed individual differences are not a function of electrode placement. However, these findings do not rule out the possibility that, if one were to place multiple electrodes within the septal area of an individual animal, some electrodes might elicit "positive" reactions and others "negative" reactions. This is an experiment which obviously should be done. The reason for these individual differences is not at all clear at this time. However, it is not really surprising that there are differing effects considering the

complexity of this area (Andy & Stephan, 1964) and the multitude of connections which it has with other parts of the brain (Nauta, 1956; Guillery, 1957; and others). One possibility might be that, whereas the rewarding properties of septal stimulation have been shown to be dependent upon the functioning of the rewarding ventral tegmentum (Schiff, 1964), so perhaps the aversive properties of septal stimulation might in some fashion be dependent upon the functioning of the aversive dorsal tegmentum. Neither lesions (Schiff, 1964) nor chemical stimulation (Routtenberg, 1965) of the dorsal tegmental area appear to affect the rewarding properties of septal stimulation; whether or not they would affect escape from aversive septal stimulation remains to be investigated.

While both descending and ascending neural connections between the septum and the ventral midbrain tegmental area (which includes the ventral portion of the periaqueductal grey substance) have by now been clearly established for the rat (Nauta, 1956; Guillery, 1956; 1957; Morest, 1961; Powell, 1963), information regarding possible neural connections with the dorsal tegmental area comes, as yet, from studies of other species. One descending pathway between the septal area and the dorsal tegmentum has been suggested

by Adey and his co-workers (Adey, 1958; Adey, et al., 1958). In the phalanger (a marsupial), using stimulation and recording techniques, they have traced a pathway which goes up from the septum via the hippocampus and entorhinal cortex to the dorsal tegmentum. On the ascending side, Eidelberg et al. (1959) in the rabbit and Adey (1958) in the phalanger, have suggested that there may be an important ascending system from the dorsal tegmental region which passes through the thalamus into the septum. Certainly in the rat and cat the dorsal longitudinal fasciculus of Schütz, which originates diffusely throughout the midbrain tegmentum and appears to be the first link in the ascending pathways to the septum and hippocampus, projects to the thalamus as well as to more ventral regions (Nauta, 1956; 1958; Guillery, 1957; Morest, 1961).

Effect of Low Level Septal Stimulation. The results obtained with the "positive" reactor group in the tegmental stimulation escape situation agree well with those obtained by Routtenberg and Olds (1963). As was mentioned earlier, they found that their reward septal animals pressed a bar less frequently to terminate the aversive tegmental stimulation when low level septal stimulation was present. However, for their one animal who proved to have a nonrewarding placement, they did not find that the septal stimulation had any

effect on the escape rate. In the present experiment, on the contrary, there was a clear effect in the opposite direction for the "nonreward" animals. It is possible that the present testing situation was more sensitive, as Valenstein and Meyers (1964) have suggested, and therefore the effect appeared where it did not in the Routtenberg and Olds bar-pressing situation. These latter authors also reported that the effect of the low level septal stimulation appeared to be temporary. Such a transient effect of the septal stimulation was not noted in the present study, but the two testing situations were not really comparable. Also it might be that with more extended testing the same effect might have appeared.

In the case of the animals who were trained to escape the aversive peripheral stimulation, as previously explained, no differences were found between the "positive" and "negative" reactor groups in the effect which the low level septal stimulation had on the escape response. Both groups escaped the peripheral stimulation more quickly when the low level stimulation was present. This finding is in agreement with some preliminary unpublished data of Schwartzbaum's (personal communication). He finds that in a shuttle box escape situation his rats seem to escape grid shock more quickly when low level stimulation of the lateral septal

nucleus is present. Stimulation in the medial septal nucleus appears to have no effect on the escape latency.

At this stage it is difficult to know how to explain the present results. It has been suggested that rewarding septal stimulation, at least, has calming effects in animals (Brady, 1958; Brady & Conrad, 1960) and in man (Heath, 1954). It has also been suggested that this stimulation reduces sensitivity to pain (Lilly, 1958; 1960). Then again it has been suggested that stimulation, like lesions, results in a reduction in the ability of the animal to inhibit responses (McCleary, 1961; Schwartzbaum & Spieth, 1964; and others). This last explanation does not seem to fit too well with the present data since it would seem that the "positive" reactors should then have escaped the tegmental stimulation at the same speed or more quickly when the septal stimulation was present, certainly not more slowly. However, the answer may lie in such complex relationships as those described by Tsubokawa and Sutin (1963) who report that stimulation within the dorsal tegmental area increases the response of hypothalamic units to septal stimulation.

It is of interest that the low level stimulation of rewarding septal sites had opposite effects on tegmental and

peripheral escape behaviour in view of the fact that it is to the same dorsal tegmental region as here stimulated that the spino-tectal tract projects and through which the spino-thalamic tract passes. Further, stimulation of this tegmental area produces behaviour which Delgado (1955) in monkeys and Speigel et al. (1954) in cats, have termed "pain suggestive reactions"; i.e. animals exhibit behaviours which closely resemble those they exhibit when they are hurt. Human subjects also report feeling pain when this area is stimulated (Speigel, et al., 1954; Mehler, 1962). Whether either the tegmental or the peripheral stimulation under the conditions of the present experiment was painful is not certain.

It has been suggested (Nauta, personal communication) that the reason for the difference between the effect of the septal stimulation on escape from tegmental stimulation and from peripheral stimulation may be that there is a difference in what is being activated. In the case of stimulation at the periphery, a specific delimited sensory system would presumably be activated, whereas in the case of stimulation within the brain, one might easily be activating more than one system, or portions of other systems. Certainly, observation of the animal's behaviour, as was

noted in some detail earlier, indicates that though in both cases the stimulation was aversive, the resultant behaviours had their differences. In particular, no initial arrest behaviour was noted with the peripheral stimulation. Also it has been noted elsewhere (Olds & Olds, 1963; Stein, 1965) that it is difficult, if not impossible, to obtain avoidance behaviour with dorsal tegmental stimulation, which is not the case with peripheral aversive stimulation.

Heart rate results

The heart rate data showed a clear overall speeding response following both tegmental and peripheral aversive stimulation. But it too revealed differences between effects of tegmental and peripheral stimulation. As Figure 6 shows, the speeding following the peripheral stimulation was immediate, while the full speeding effect following tegmental stimulation was delayed in its appearance for about 2 sec. Also, while the heart rate of the peripheral animals appeared, from visual inspection of the EKG records, to increase with onset of stimulation, that of the tegmental animals appeared most often to show at least a brief slowing.

The finding of cardiac acceleration following aversive electrical stimulation of the periphery agrees with other

reports of such an effect of aversive peripheral stimulation (e.g. Black, 1959; Stern & Word, 1961; Westcott & Huttenlocher, 1961; Fuhrer, 1964). This same type of cardiac response seems to result following presentation of other aversive peripheral stimuli such as a loud sound (Geer, 1964; Fehr & Stern, 1965). It has been suggested that it forms part of the "defense" reflex (Graham & Clifton, personal communication), the response to threatening situations. The course of this cardiac response seems never to have been systematically studied.

The situation regarding the effects of midbrain tegmental stimulation on the cardiovascular system appears to be somewhat in a state of confusion. The role of this area in the control of cardiovascular function has not been extensively studied as Bard (1960) and Uvnäs (1960) have pointed out. In support of the present findings, however, Bard (1960) in cats and McQueen et al. (1954) in dogs have reported heart rate increases to occur with stimulation in the dorsal tegmental area as defined in the present study. More tenuous support comes from studies which report blood pressure increases following stimulation in this area (Danilewsky, 1875; Prus, 1899; McQueen, et al., 1954; Lindgren, 1955). Danilewsky, unlike McQueen, reported cardiac

deceleration to accompany the rise in blood pressure which he observed.

Lindgren (1955), who has reported the most extensive study of the dorsal tegmentum in its relation to cardiovascular function, reported that stimulation in this midbrain region, particularly in the deeper layers of the superior colliculi, produced sympathetic vasodilation in the skeletal musculature, sympathetic vasoconstriction in the skin, and activation of the adrenal medulla. It is possible that the delayed acceleration observed in the present study might be a function of the time required for the effects of the vasodilation and the hormone to effect the heart. That is, as Lindgren suggested, it may be that the dorsal midbrain tegmental area plays its main role in the regulation of vasomotor function rather than of cardiac function.

However, as Oberholzer (1960) in particular, and others, have pointed out, it is very difficult to sort out the direct effects of the brain stimulation from effects due to concommitant behaviour. Thus the difference in the heart rate response to peripheral and tegmental stimulation might also be a function of the fact that the tegmental animals manifested the initial arrest response which the peripheral

animals did not.

To further complicate matters it seems that it is not even clear whether the cardiovascular effects of dorsal tegmental stimulation are due to stimulation of this area or due to stimulation of fibres passing through this area which come from the hypothalamus or still higher up. Oberholzer feels that the dorsal tegmentum plays very little role in cardiovascular control. Lindgren and Uvnäs consider it to play an important integrative role in the control of vasomotor function.

Clearly a good deal of further investigation is required to understand the role played by this midbrain tegmental area in both physiological and behavioural functions. It seems to have been somewhat neglected in the past, perhaps because of its complexity, but it seems clear that it is not merely a relay area or one through which fibres from other areas pass; that is only one of its functions.

Summary

A test of preference for accepting or rejecting electrical stimulation of the rat's septal area revealed individual differences: "positive" reactors sought the stimulation; "negative" reactors escaped from it.

All animals escaped from electrical stimulation of the dorsal tegmental area. Rapidity of this escape reaction was altered by concurrent low level septal stimulation. Animals previously classified as "positive" reactors to septal stimulation escaped more slowly; "negative" reactors escaped more quickly. This differentiation did not appear, however, in the reaction to electric shock applied to the feet: with concurrent low level septal stimulation present both types of reactor escaped more quickly. Questions of individual differences in reaction to septal stimulation and of differences in reactions to aversive central and peripheral stimulation are discussed.

Cardiac effects of stimulation in the tegmentum and at the periphery were also studied. Effect of the former stimulation appears to be more complex than that of the latter.

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Figures and Tables

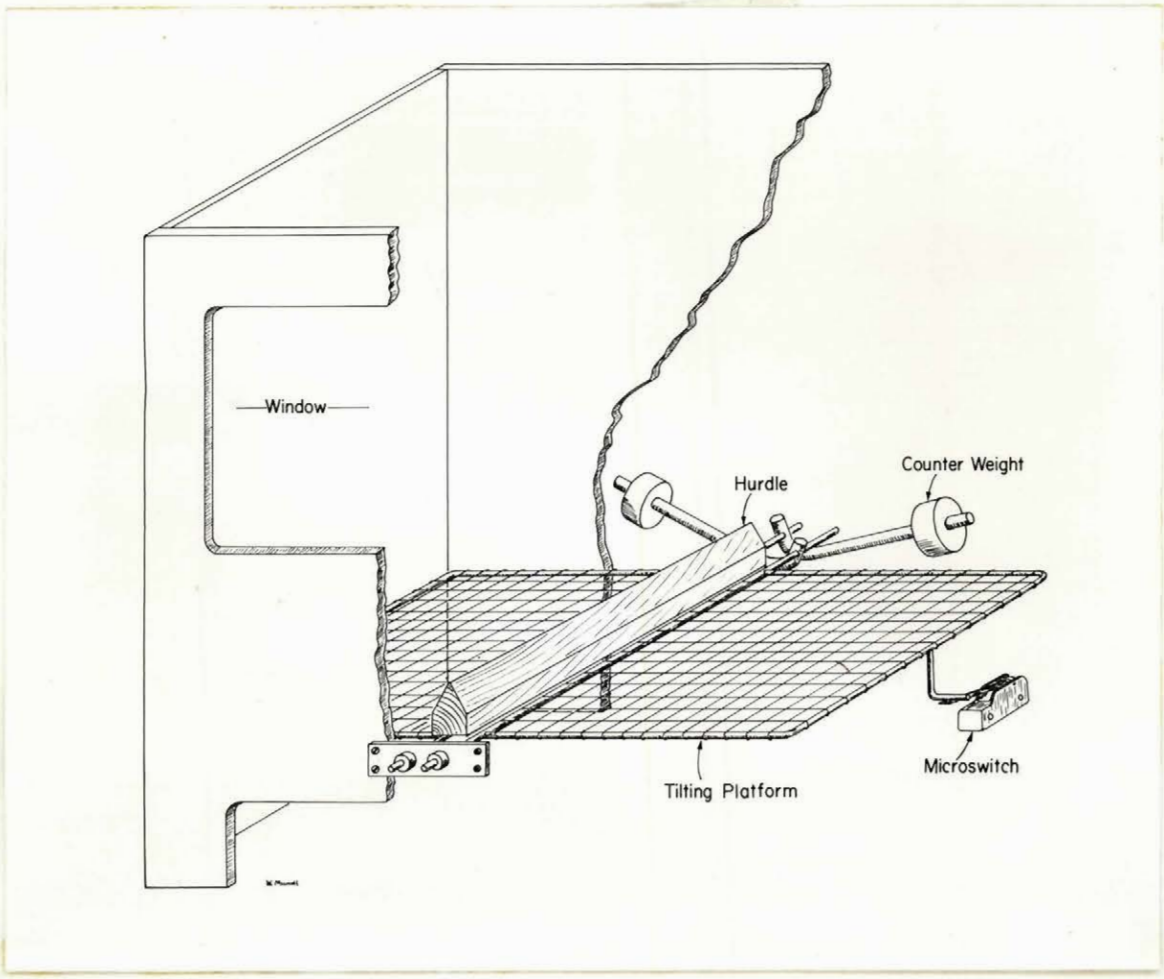

Fig. 1. Diagrammatic representation of the apparatus. Dimensions of the wooden box were 14 x 16 x 10 in. Those of the plexiglass window were 7½ x 15 in.

Fig. 2. Photomicrograph of tegmental section for animal ST VIII enlarged to show location of original and second electrode tips. Open arrow head indicates location of original tip; solid arrow head indicates location of tip of second, shorter electrode.

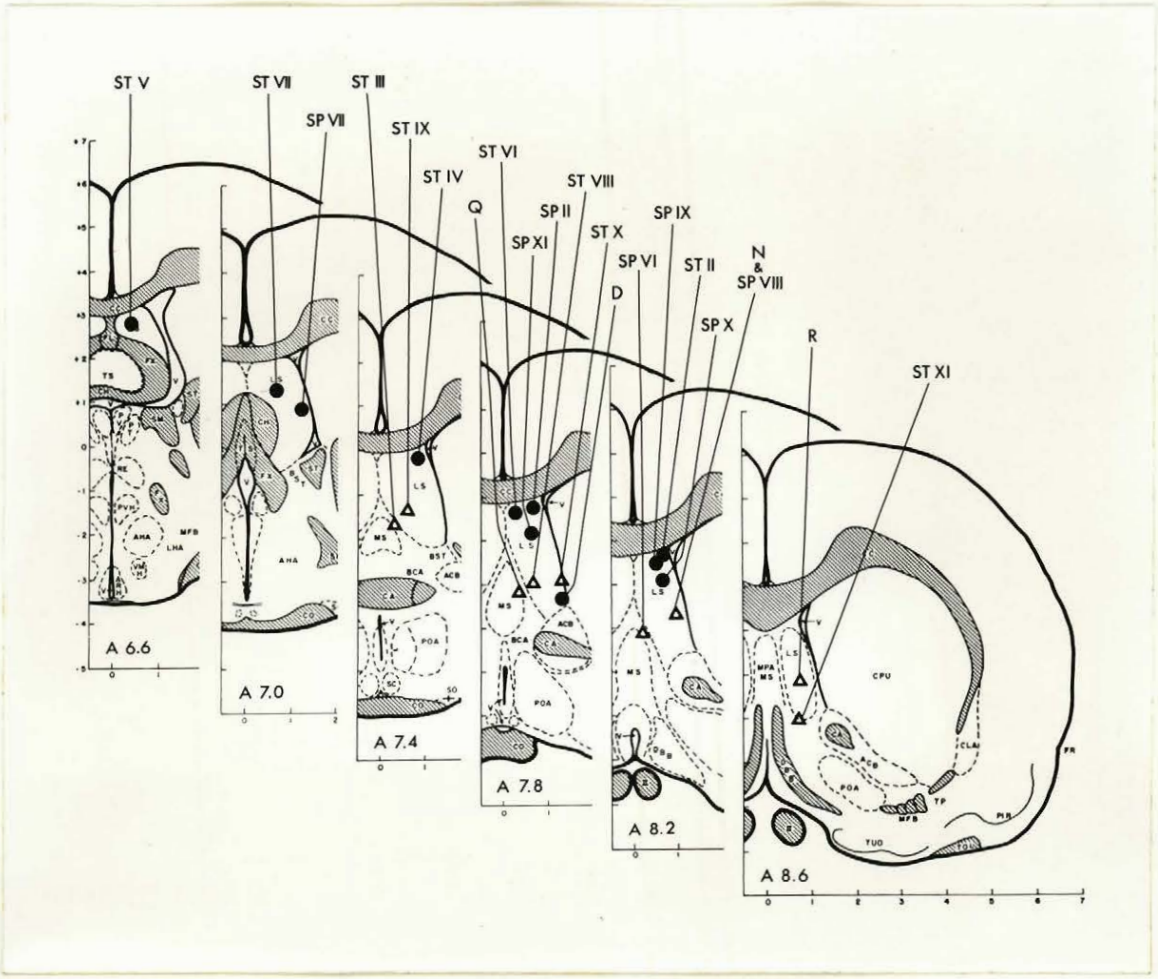

Fig. 3. Schematic representation of sections through the septal area with locations of electrode tips indicated. Solid circles represent placements for "positive" reactors; open triangles represent placements for "negative" reactors. (From DeGroot, 1963.)

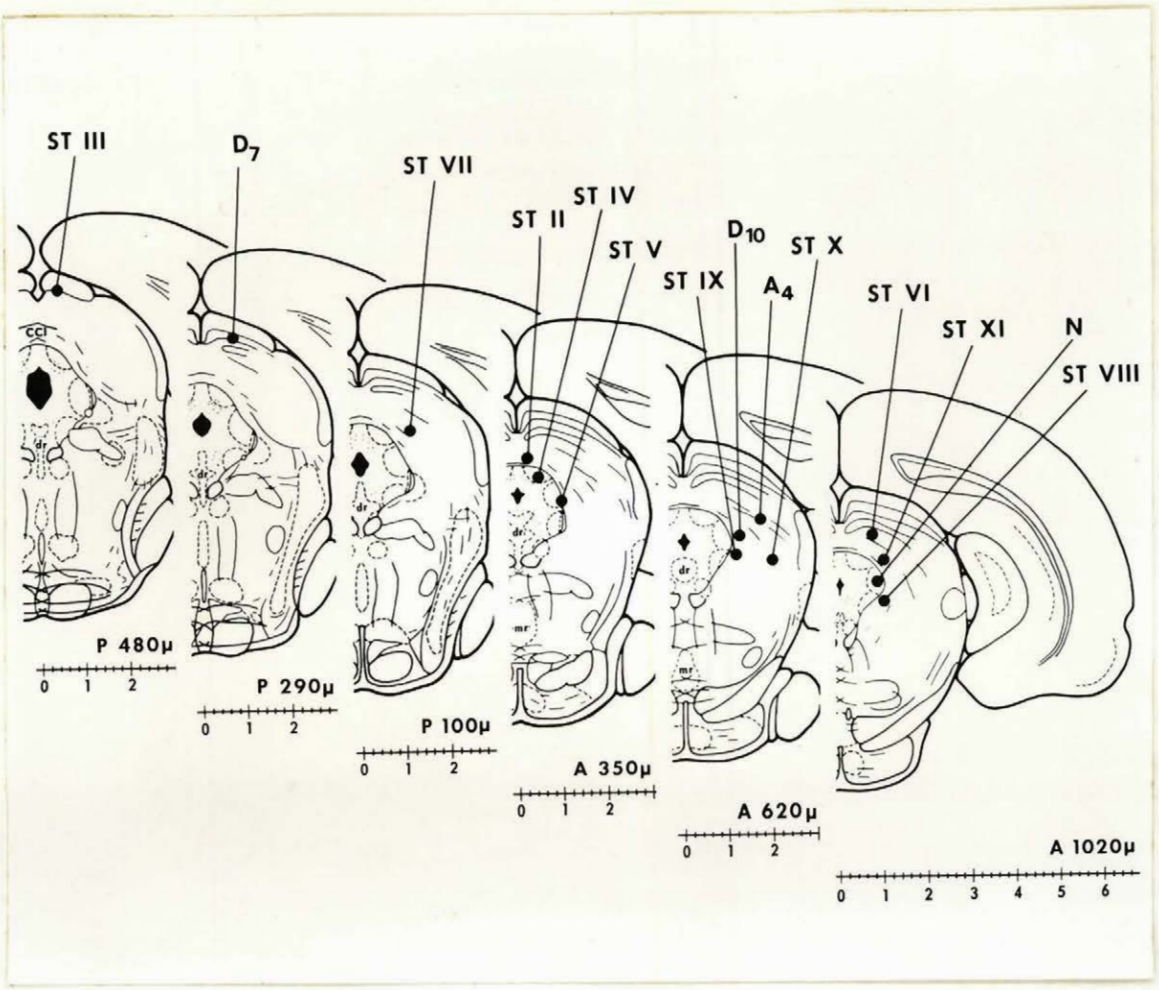

Fig. 4. Schematic representation of sections through the tegmental area with locations of electrode tips indicated. (From König & Klippel, 1963.)

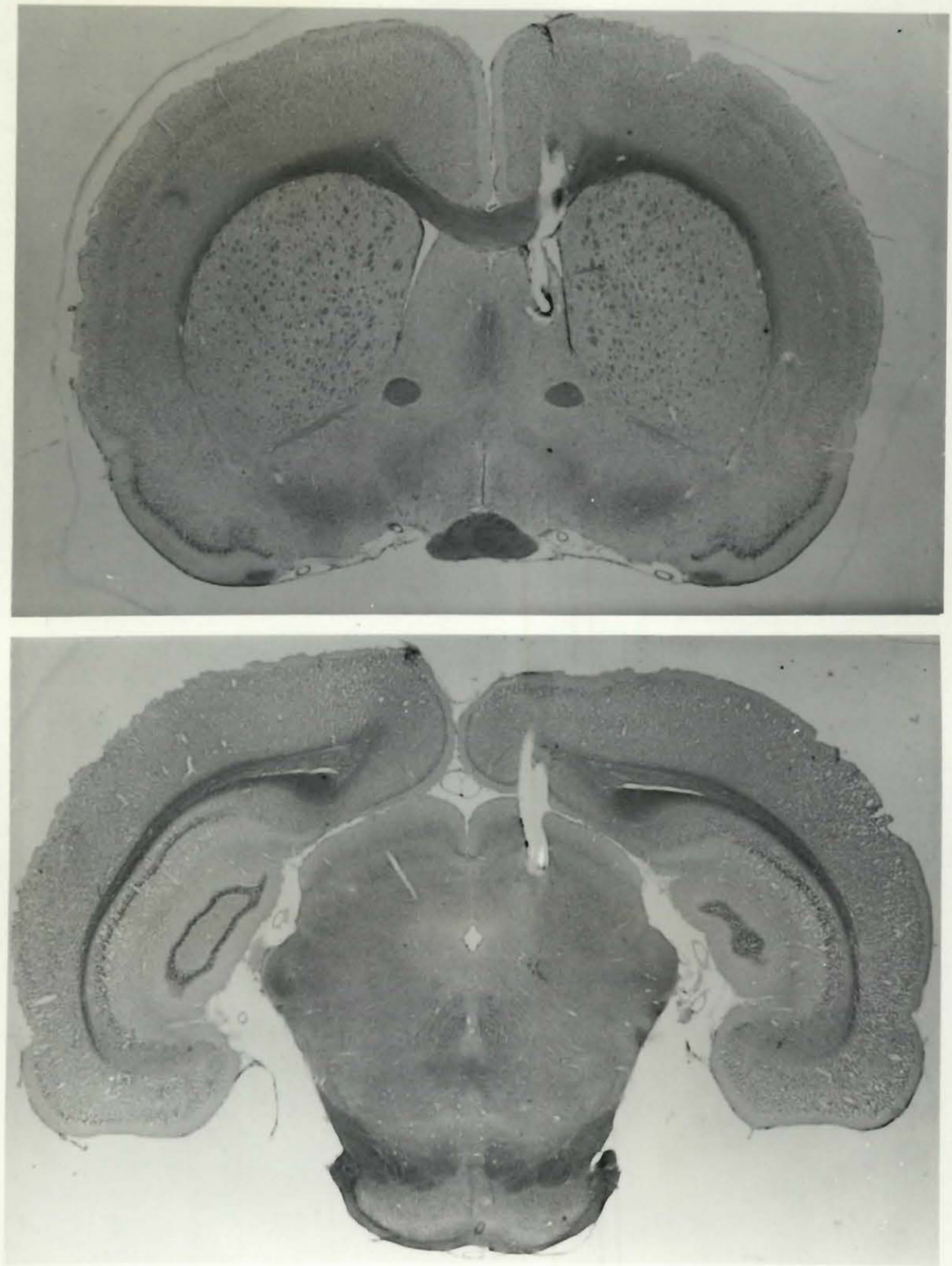

Fig. 5. Photomicrographs of a representative septal (upper) and tegmental (lower) section showing, in each case, location of the electrode tip and part of the electrode track.

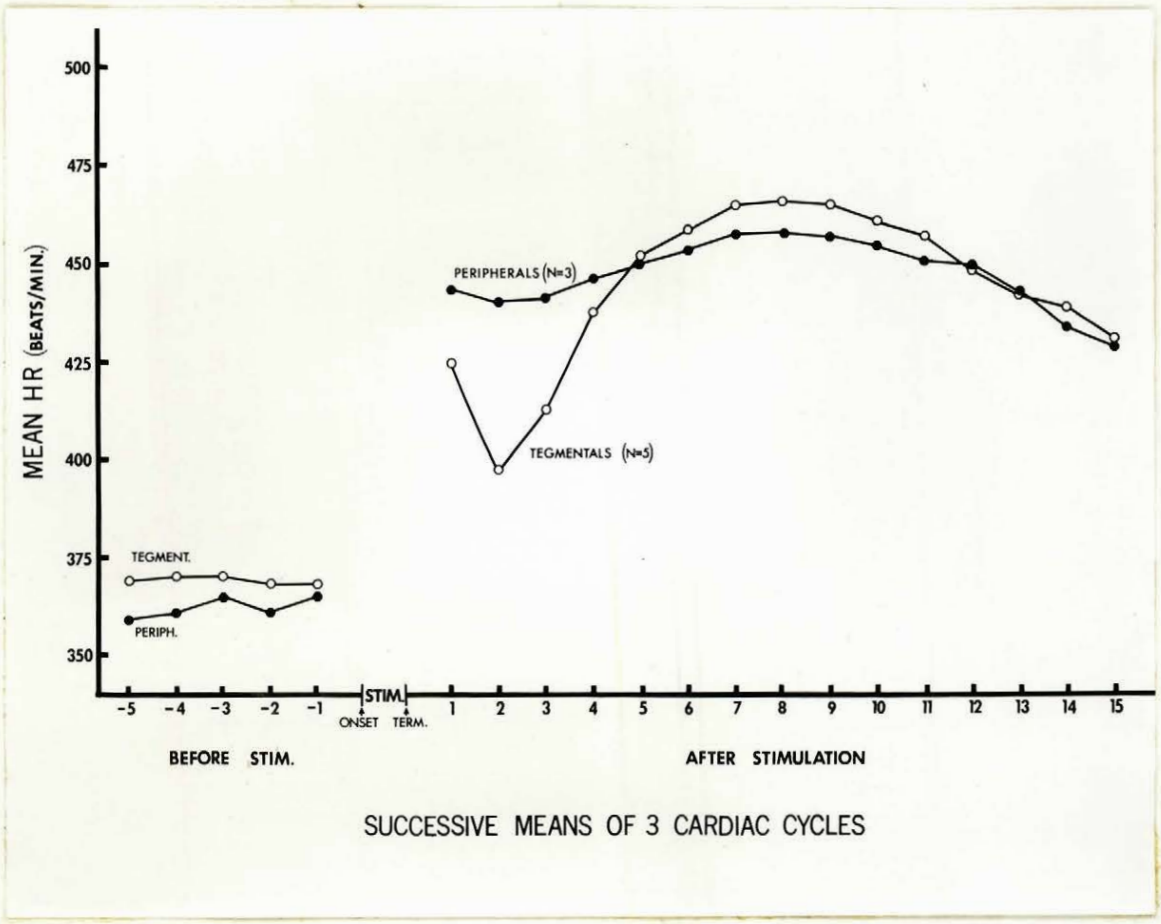

Fig. 6. Comparison of effects on heart rate of stimulating in the dorsal tegmentum with effects of stimulating at the periphery. Each point represents the mean of three beats over 60 trials for the animals stimulated in the tegmentum and over 20 trials for the animals stimulated at the periphery.

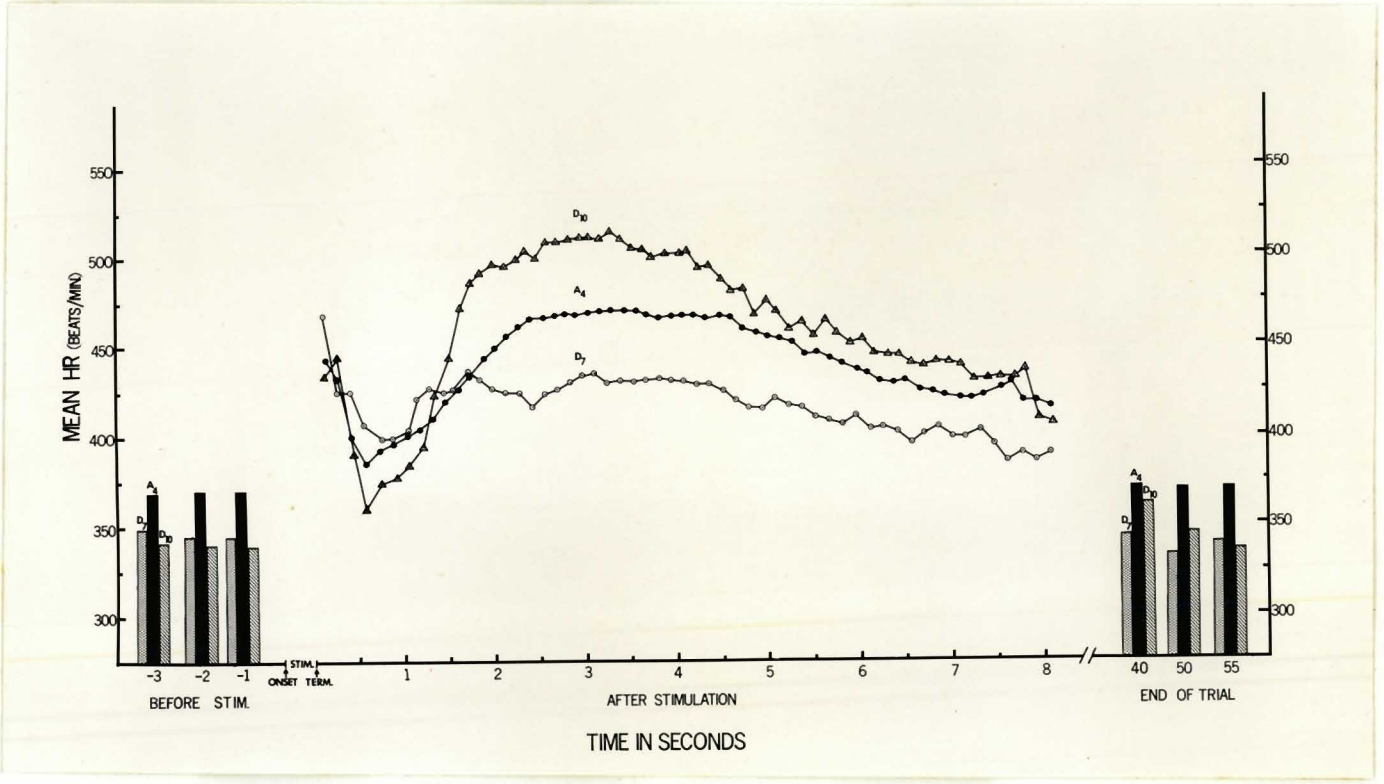

Fig. 7. Beat-by-beat heart rate curves showing effects of stimulating the dorsal tegmental area. (See text for explanation.)

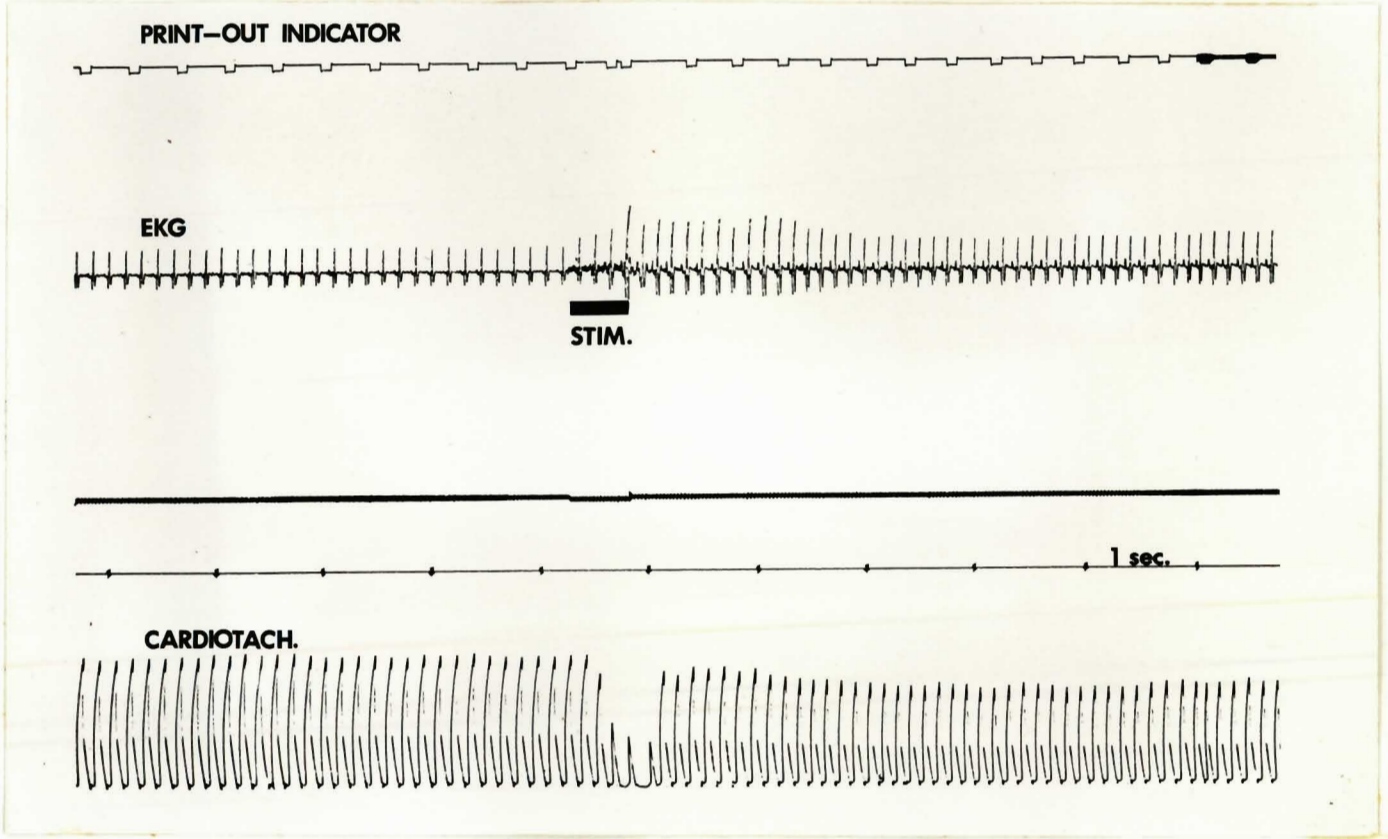

Fig. 8. Representative trial for animal A_4 showing cardiac speeding both during and following stimulation in the dorsal tegmental area. Because of artifacts in the cardiotachogram during stimulation, only the EKG was available for observation during this time.

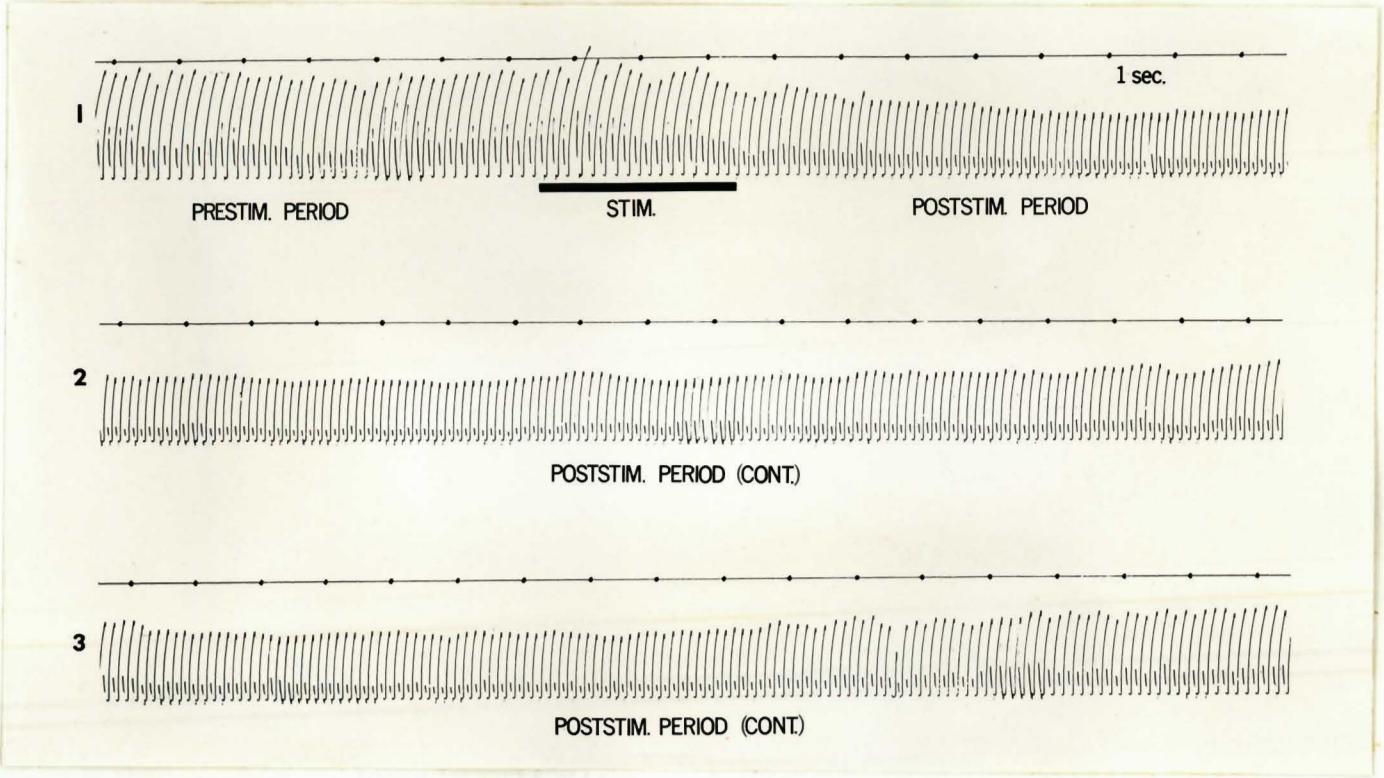

Fig. 9. Representative trial for animal ST IV showing cardiac slowing during, and duration of speeding which followed termination of, stimulation in the dorsal tegmental area.

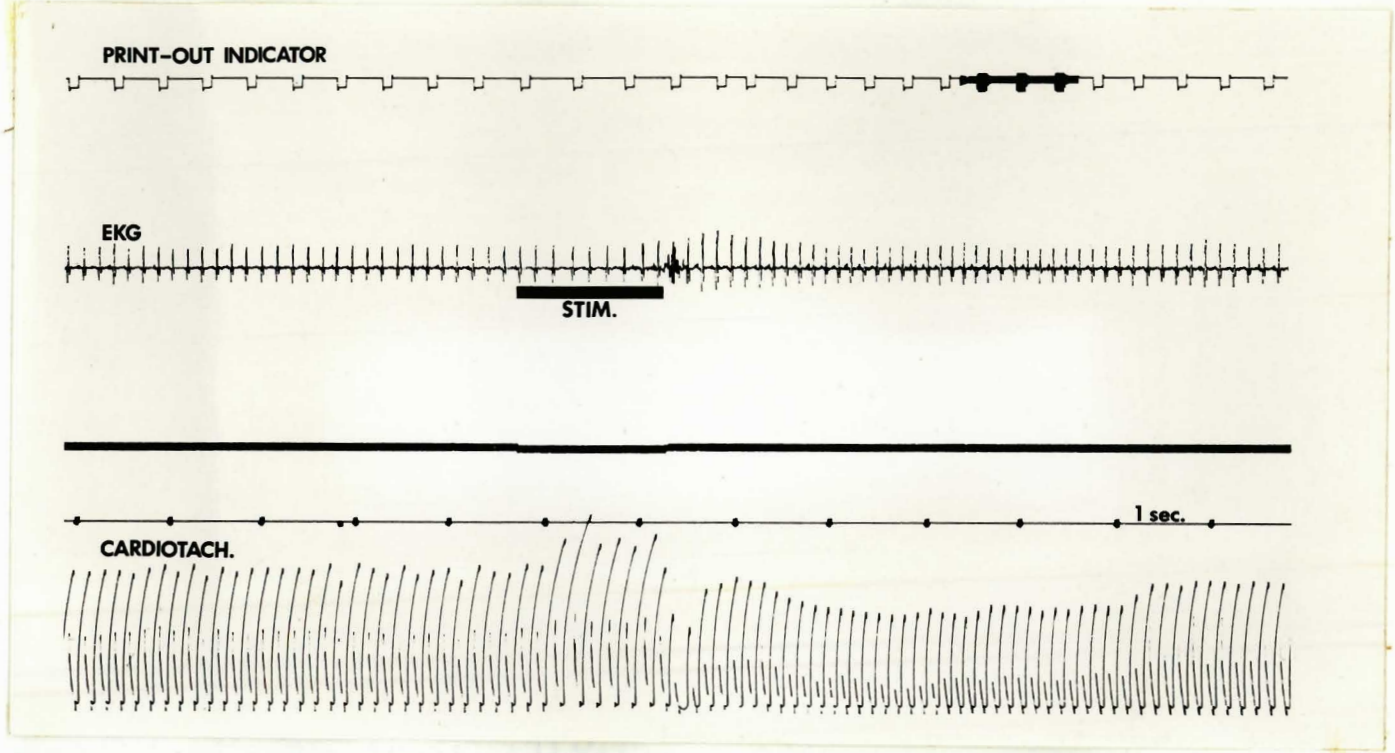

Fig. 10. Representative trial for animal ST VI showing clear cardiac slowing during, and speeding following, stimulation in the dorsal tegmental area.

Table 1a

"Septal" + "Dorsal Tegmental" Electrode Group: Current Levels and Conditions Under Which Each Animal was Tested are Shown

Rat #	Verified location of brain electrode tip		Septal screening current levels		Currents used for exper. with low level sept. stim.		EKG records taken	Current used during HR recording (in μA)
	Sept.	Tegm.	"Pos" (in μA)	"Neg" (in μA)	Sept. (in μA)	Tegm. (in μA)		
ST II	+	+	75		25	65	-	NR
ST IV	+	+	70		25	60	+	60
ST V	+	+	45		15	150	-	NR
ST VI	+	+	50		15	50	+	50
ST VII	+	+	75		25	35	-	NR
ST III	+	+		95	30	65	-	NR
ST VIII	+	+		45	15	300	-	NR
ST IX	+	+		60	20	250	-	NR
ST X	+	+		75	25	70	-	NR
ST XI	+	+		80	25	50	-	NR
A_4	-	+	NR	NR	NR	NR	+	70
D_7	-	+	NR	NR	NR	NR	+	140
D_{10}	-	+	NR	NR	NR	NR	+	50
N	+	+		95	NR	NR	-	NR
D	+	NR*	70		NR	NR	-	NR

*NR = item not relevent.

Table 1b

"Septal" + "Peripheral" Electrode Group: Current Levels and Conditions Under Which Each Animal was Tested are Shown

Rat #	Verified septal electrode	Septal screening current levels		Currents used for exper. with low level sept. stim.		EKG records taken	Current used during HR recording (in mA)
		"Pos" (in μA)	"Neg" (in μA)	Sept. (in μA)	Periph. (in mA)		
SP II	+	90		30	2.00	+	2.00
SP VII	+	20		6	1.25	-	NR
SP IX	+	60		20	1.00	-	NR
SP X	+	50		15	1.25	-	NR
SP XI	+	70		22	1.00	-	NR
SP VI	+		30	10	0.75	+	0.75
SP VIII	+		35	12	1.25	-	NR
Q	+		65	NR	NR	-	NR
R	+		45	NR	NNR	-	NR
Z	NR*	NR	NR	NR	NR	+	0.75

*NR = item not relevent.

Table 2a

Results of the Screening Test for "Positive" Reactors

Rat #	Current level used (in μA)	Mean time spent on:* Stim. side	No stim. side	Mean no. crossings to:* Stim. side	No stim. side
ST II	75	9'25"	5'36"	24	12
ST IV	70	10'12"	4'48"	37	14
ST V	45	9'32"	5'08"	26	15
ST VI	50	10'09"	4'51"	15	5
ST VII	75	9'42"	5'19"	13	6
SP II	90	10'19"	4'41"	11	1
SP VII	20	9'02"	5'59"	40	25
SP IX	60	9'39"	5'22"	27	4
SP X	50	9'14"	5'47"	37	19
SP XI	70	10'04"	4'57"	34	14
D	70	9'08"	5'53"	28	10
Gr. $\bar{X}$	61	9'41"	5'18"	27	11

*Entries are mean time (in min. & sec.), or mean number of crossings, per 15 min. session taken over two sessions.

Table 2b

Results of the Screening Test for "Negative" Reactors

Rat #	Current level used (in μA)	Mean time spent on:* Stim. side	No. stim. side	Mean no. crossings to:* Stim. side	No stim. side
ST III	95	4'55"	10'05"	3	30
ST VII	45	4'28"	10'33"	12	38
ST IX	60	3'33"	11'27"	4	30
ST X	75	4'43"	10'18"	2	30
ST XI	80	3'09"	11'51"	9	39
SP VI	30	4'53"	10'08"	10	32
SP VII	35	3'02"	11'58"	2	30
N	95	3'46"	11'14"	0	29
Q	65	4'44"	10'16"	2	23
R	45	3'21"	11'39"	5	31
Gr. $\bar{X}$	63	4'03"	10'57"	5	31

*Entries are mean time (in min. & sec.), or mean number of crossings, per 15 min. session taken over two sessions.

Table 3a

Results of Test for Effect of Low Level Septal Stimulation on Escape from Stimulation in the Dorsal Tegmentum for "Positive" Reactors

Condition / Rat #	Tegm. stim. only	Tegm.+ septal stim.
ST II	.75*	1.70
ST IV	1.61	2.53
ST V	1.79	2.62
ST VI	1.05	1.68
ST VII	1.33	2.24
Σ	6.53	10.77
$\bar{X}$	1.31	2.15

$t_{cor.} = 14.62 \quad p < .001$

*Entries are mean trial latencies of escape (in sec.) taken over six 20-trial sessions.

Table 3b

Results of Test for Effect of Low Level Septal Stimulation on Escape from Stimulation in the Dorsal Tegmentum for "Negative" Reactors

Condition / Rat #	Tegm. stim. only	Tegm.+ septal stim.
ST III	1.14*	.49
ST VIII	2.80	2.49
ST IX	2.26	- 1.79
ST X	2.21	1.42
ST XI	1.43	1.03
Σ	9.84	7.22
$\bar{X}$	1.97	1.44

$t_{cor.} = 6.21 \quad p < .01$

*Entries are mean trial latencies of escape (in sec.) taken over six 20-trial sessions.

Table 4a

Results of Test for Effect of Low Level Septal Stimulation on Escape from Aversive Peripheral Stimulation for "Positive" Reactors

Condition / Rat #	Periph. stim. only	Periph.+ septal stim.
SP II	1.98*	1.54
SP VII	2.52	1.67
SP IX	1.69	.98
SP X	1.83	1.44
SP XI	2.21	1.58
Σ	10.23	7.21
$\bar{X}$	2.05	1.44
$t_{cor.} = 7.20$	$p < .01$	

*Entries are mean trial latencies of escape (in sec.) taken over six 20-trial sessions.

Table 4b

Results of Test for Effect of Low Level Septal Stimulation on Escape from Aversive Peripheral Stimulation for "Negative" Reactors

Rat #	SP VI		SP VIII	
Session \ Cond.	Periph. stim. only	Periph.+ septal stim.	Periph. stim. only	Periph.+ septal stim.
1	2.02*	1.01	1.76	1.09
2	1.71	.86	1.83	1.37
3	1.84	1.11	1.62	1.36
4	1.71	1.15	1.61	1.27
5	1.52	1.03	1.83	1.06
6	1.61	1.00	1.65	1.09
Σ	10.41	6.16	10.30	7.24
$\bar{X}$	1.74	1.03	1.72	1.21
	$t_{indep.} = 8.52$		$t_{indep.} = 12.38$	
	$p < .001$		$p < .001$	

*Entries are mean trial latencies of escape. (20 trials per session.)

Table 5a

Escape Latency Data, in Mean Time per Trial, for Animal ST XI Immediately Before and After Reimplantation of Shorter Tegmental Electrode

Condition / Session	Before (in sec.)	After (in.sec.)
1	8.35	1.07
2	9.45	1.26
3	10.01	1.31
4	10.60	1.49
5	10.75	1.35
Σ	49.16	6.48
$\overline{X}$	9.83	1.30

Table 5b

Escape Latency Data, in Mean Time per Trial, for Animal N Immediately Before and After Reimplantation of Shorter Tegmental Electrode

Condition / Session	Before (in sec.)	After (in sec.)
1	10.07	1.69
2	10.05	2.00
3	14.43	1.98
4	11.86	1.46
5	18.47	1.53
Σ	64.88	8.66
$\bar{X}$	12.98	1.73

Table 6a

Mean Heart Rate Before and After Stimulation in the

Dorsal Tegmentum and at the Periphery

Group	Tegmentals					Peripherals		
Rat # / Period	A_4	D_7	D_{10}	ST IV	ST VI	SP II	SP III	SP VI
Pre	384*	347	347	367	393	316**	419	352
Post	450	417	476	415	440	464	462	414

* Entries are means of 60 trials. (in beats per min.)

** Entries are means of 20 trials. (in beats per min.)

Table 6b

Results of Lindquist Type I Analysis of Variance Performed on Pre- and Poststimulation Heart Rate Data Appearing in Table 6a

Source	SS	df	mS	F
Group (G)	10	1	10	-
Error (between)	5,998	6	1,000	
"Period" (P)	23,486	1	23,486	26.18*
(G x P)	135	1	135	-
Error (within)	5,382	6	897	
Total	35,011	15		

*$p < .005$