BRAIN LESIONS AND LOCOMOTOR ACTIVITY

THE EFFECTS OF SEPTAL, THALAMIC AND TEGMENTAL LESIONS ON LOCOMOTOR ACTIVITY IN THE HOODED RAT

by

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SCOPE AND CONTENTS:

Animals with one of septal, medial thalamic or tegmental reticular formation lesions were compared on three measures of spontaneous activity (a brief test in a novel maze and seven-day tests in running wheels or photocell cages) and on active avoidance learning. Wheel running was depressed by all the lesions (especially septal and tegmental lesions) while locomotion in the maze and photocell cages was unaffected. Avoidance learning was depressed by septal and thalamic lesions but not by tegmental lesions. These results are discussed in terms of the hypothesis that these brain structures form part of systems which facilitate or inhibit somatomotor activity.

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CHAPTER ONE

INTRODUCTION

Review of the Anatomy and Functions

Anatomy

In 1956 Nauta described an extensive fiber system originating in the hippocampus and extending through the septal nuclei and medial brain stem to the ventral reticular formation. Considering only the caudal projections of this system that originate in the septal nuclei, there are projections (a) via the medial forebrain bundle to the entire extent of the lateral hypothalamus, (b) via the stria medullaris to the medial habenula, (c) via the rostral columns of the fornix to the ventral medial thalamus (including n. reuniens, n. paraventricularis anterior and n. centralis medius), and (d) via the fornix and mammillary peduncle to the ventral tegmentum. It is known that there is reciprocating innervation from the ventromedial thalamus and ventral tegmentum to the septal nuclei (Nauta and Whitlock, 1954; Nauta and Kuypers, 1958).

Electrophysiological studies have provided evidence for a neural system connecting these structures that is similar to Nauta's system but differs in some details (see Adey, 1959). This pathway courses anteriorly from the rostral reticular formation through the thalamic reticular and

septal nuclei, to the hippocampus; there it synapses and proceeds to the entorhinal cortex. From there, there are two direct, descending pathways: (1) one coursing, as pathway (b) above, dorsally through the stria medullaris to the dorsomedial thalamus and nucleus parafascicularis, where it joins (2) the other pathway (similar to (c) above), which courses through nucleus reuniens and the dorsal hypothalamus. According to this account, both of these pathways end in the periaqueductal grey and dorsal portions of the tegmentum.

The present study is an attempt to explore the interrelations between some behavioral functions of three of the structures involved in Nauta's system: the septal nuclei, the ventral medial thalamus, and the ventral tegmentum.

Behavioral Functions

The Septal Nuclei

Response Inhibition. Electrophysiological studies of the septal region and subcallosal area (the latter is often regarded as an extension of the former; see Kappers, Hubers and Crosby, 1936) have shown that they are involved in the inhibition of somatic responses. Stimulation of the septal and subcallosal areas inhibits respiration (Hess, 1957; Kaada, 1960) and causes a decrease in the frequency of spontaneous movements during light anesthesia (see Kaada, 1960). It also inhibits the production of cortically induced leg flexions and reflexive knee jerks (Hodes, Peacock and Heath, 1951).

Both the septal and subcallosal areas also act as inhibitors of

autonomic activity. Stimulation of both areas produces a reduction in blood pressure (see Hess, 1957 and Kaada, 1960). Stimulation of the septal nuclei, either by the experimenter or by the subject (self-stimulation) produces an immediate fall in heart rate that does not habituate (Malmo, 1961). Furthermore, subcallosal stimulation inhibits pyloric peristalsis and causes pupillary dilatation (see Kaada, 1960).

Early work on the behavioral functions of the septal nuclei was primarily concerned with the contribution of these nuclei to emotion and learning. The marked increase in reactivity to stimulation which followed lesions in that area (Brady and Nauta, 1953; King, 1958; Thomas, Moore, Harvey and Hunt, 1959; Kenyon, 1962; Kriekhaus, Simmons, Thomas and Kenyon, 1964; Schwarzbaum and Gay, 1966), therefore, was used to infer a state of hyperemotionality (Brady and Nauta, 1953) or to explain an increase in errors made during maze-learning (Thomas et al., 1959). These investigators were not concerned with the electrophysiological evidence on this area that involved its contribution to the production of highly specific responses.

Experiments by McCleary (1961) and Kaada et al. (1962) were among the earliest attempts to evaluate the physiological evidence, very briefly outlined above, at the behavioral level. McCleary reasoned that areas of the brain, which inhibit cortically and reflexively induced movements (see Hodes et al., 1951), should also play a role in inhibiting more molar behavior and obversely, that those areas facilitating specific movements should also facilitate molar behavior. He chose to observe the effects of lesions in two opposing areas: the subcallosal region of the cortex (which has a predominantly inhibiting influence) and the anterior cingulate gyrus of the cortex (which

has a predominantly excitatory influence). Since these areas were limbic structures which are widely believed to be involved in emotion, he decided to observe responses in fear situations. Mowrer's (1960) distinction between passive and active conditioned avoidance responses (CAR's) provided an apt framework for the experiment: lesions in the subcallosal region should impair passive but not active avoidance and lesions in the anterior cingulate gyrus should impair active and not passive avoidance. This situation, therefore, was one of "double dissociation". The specific situations used to test the hypothesis were as follows: (a) in the passive avoidance problem, thirsty rats were trained to drink and then later punished for drinking (this is passive avoidance because the animal avoids shock by being passive and not approaching the water bottle), and (b) in the active avoidance problem a standard shuttle box was used. The results confirmed McCleary's reasoning precisely.

The work of Kaada et al. (1962) extended the findings on passive avoidance to include other structures where stimulation has an inhibitory effect on spinal reflexes and cortically induced movements: the septal nuclei, the preoptic area, the anterior hypothalamus and the insular cortex. Furthermore, they attempted to eliminate several alternative explanations for the results. First, the experimental animals might have been less sensitive to shock; second, they might have been more thirsty; third, they might have had less ability to learn; and finally, they might have been less emotional than controls. According to Kaada et al., the first and third alternatives may be eliminated, since septal lesions are like subcallosal lesions and facilitate active avoidance in a two-way shuttle box (Fox, Kimble and Lickey, 1964, Kenyon, 1962, and King, 1958). The second alternative may be eliminated by the

fact that septal animals did not drink more than controls (also, septal rats have a passive avoidance deficit in a non-thirst, non-hunger test, McNew and Thompson, 1966). The last alternative was eliminated, according to Kaada et al., by the fact that septal animals are "hyperemotional" (see Brady and Nauta, 1953). The findings on passive avoidance have been confirmed by Fox et al. (1954) and by McNew and Thompson (1966). Furthermore, cholinergic blocking[1] of the septal nuclei improves performance on the shuttle CAR and cholinergic stimulation depresses it (Grossman, 1964).

The electrophysiological findings mentioned above were independent of emotional states. If McCleary's reasoning was limited to emotional situations, therefore, the relevance of the electrophysiological work to behavior would be questionable. Several studies, however, have shown that the septal area is involved in the inhibition of behavior in neutral and positive situations as well as in aversive situations. Animals with lesions in that area are known to bar-press more than controls when there is no reinforcement (Schwarzbaum, Kellicutt, Spieth and Thompson, 1964) as well as when food is used as a reinforcer (Kenyon, 1962; Ellen and Powell, 1962; Ehrlich, 1963; Ellen, Wilson and Powell, 1964; Schwarzbaum and Gay, 1966). Finally, Zucker and McCleary (1964) have demonstrated that septal-limbic region lesions cause animals to have difficulty in the reversal (but not in the initial learning) of a learned position habit.

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[1]Chemical injections into the brain of drugs that inhibit cholinergic action and thus, block transmission in cholinergic neurons; this technique can be considered equivalent to a biochemically selective lesion.

In summary, experiments using both stimulation and ablation have shown that the septal nuclei are involved in the inhibition of a full hierarchy of responses from minute autonomic or somatic reflexes to complex, integrated behavior in positive, neutral and aversive situations. On the autonomic side, they are involved in the inhibition of cardiovascular, pyloric and pupillary responses. On the somatic side, they are involved in the inhibition of respiration and spontaneous movements as well as cortically and reflexively induced movements. Work by McCleary and Kaada has established that the septal area is also involved in the inhibition of learned avoidance behavior and their conclusions have been confirmed by investigators using a variety of situations from bar-pressing with or without reinforcement to the reversal of a learned position habit. It seems reasonable, therefore, to include the septal nuclei in McCleary's conclusion that "physiological and behavioral considerations suggest that the subcallosal effect results from the disruption of a pathway mediating response inhibition" (1961, p. 613).

Response facilitation. Experimental evidence that conflicts with the generalization that the primary function of the septal nuclei is to inhibit behavior, involves responses of both simple and complex types. Peacock and Hodes (1951) actually found a greater number of points in the septal area where stimulation facilitates cortically induced movements than of those where stimulation inhibits such movements. Furthermore, Hess (1957) has shown that sneezing, sniffing, and tongue and mouth movements can be elicited by septal stimulation.

Lesion studies indicate that spontaneous, short-term activity[2] is not inhibited by the septum. If spontaneous activity were inhibited by the septal nuclei, lesions placed there should result in a release from this inhibition and thus, an increase in activity. That the frontal pole cortex functions in this manner, as far as long-term activity is concerned, is suggested by the findings of Ruch and Shenkin (1943) and Zubek and DeLorenzo (1952). Ablations of a large portion of this part of the cortex result in a marked increase in running-wheel activity. If the septal nuclei were somatomotor inhibitors, therefore, lesions placed there should result in a similar increase in spontaneous activity. However, septal lesions depress the amount of running during short periods of access to running wheels (Kenyon, 1962). They also have either no effect (Zucker, 1965) or depress (Schwarzbaum and Gay, 1966) exploratory activity in an open field. No long-term studies of spontaneous activity in animals with septal lesions have been carried out as yet.

The double dissociation of effects on passive and active avoidance (found by McCleary, 1961) seemed to provide strong evidence for assigning an inhibitory function to the subcallosal cortex. The work of Kaada et al. (1962) on passive avoidance and septal lesions indicated that the septal nuclei may perform a similar function. The explanation that loss of response

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[2] Here, "short-term" activity refers to the situation where animals are placed in an apparatus and their activity recorded only for a small fraction of each test day (a few minutes to a few hours). This is in contrast to "long-term" activity, which will refer only to continuous measurement of activity for several days.

inhibition was responsible for the effect and not a decreased ability to learn was eliminated because the septal animals learned an active avoidance response better than controls. However, Mowrer (1960) has pointed out that the shuttle-box procedure, which requires an animals to return to a place where it was previously shocked, is likely to produce the same kind of inhibition that passive avoidance training evokes. The effect of septal and subcallosal lesions on shuttle-box avoidance can be explained solely on the basis of an inability to learn a passive avoidance. Thus, using a shuttle box for the test of active avoidance does not provide a test for the double dissociation so crucial to McCleary's argument. Double dissociation could only be established in this situation, if septal animals were shown to learn a one-way, active avoidance response as fast or faster than controls. Kenyon (1962), Kenyon & Krieckhaus (1965), McNew & Thompson (1966) and Vanderwolf (1964), however, have shown that septal animals learn a simple, active avoidance response slower than controls and do not require more trials than controls to extinguish an active avoidance response. Zucker and McCleary (1964), on the other hand, have found an improvement following septal lesions in cats in a "one-way" active avoidance situation that required no inter-trial handling. The technique used was to switch the position of each of the two compartments after every trial, so that the animal would always be running in the same direction relative to its location in the test room. Krieckhaus (1965), however, has suggested that the cat probably took its bearing from inside each compartment rather than from the spatial location in the room and that the cats, therefore, perceived the training procedure as two-way. Since two-way avoidance learning generally requires many more trials to

learn than the one-way procedure and since Zucker and McCleary's animals needed a considerable number of trials, the latter explanation appears more likely. Thus, the evidence rules out a loss of response inhibition as a sufficient explanation for the results.

In summary, the septal nuclei are involved in the facilitation of cortically induced movements and reflexive knee jerks. The behavioral findings, however, are more complicated. It has been shown that a loss of response inhibition does not sufficiently account for the effect of septal lesions on exploratory and avoidance behavior. It is, therefore, still an open question whether the septal area generally functions to inhibit behavior.

The Medial Thalamus

In general, experiments on the septal nuclei were attempts to show that inhibition was the dominant function of this area of the brain. In contrast to this work, experiments on the medial thalamus have emphasized the specific circumstances under which it functions in a facilitatory manner and those under which it functions in an inhibitory manner.

Response facilitation. Both electrophysiological and behavioral studies have provided evidence that the medial thalamus is involved in the production of responses. Peacock and Hodes (1951) have shown that there is a heavy concentration of points in the medial thalamus where stimulation facilitates both cortically induced movements and reflexive knee jerks. Furthermore, Hess (see 1957) has produced elevating movements of the head from medial thalamic stimulation. These results are consistent with the finding that the unspecific thalamic system, which lies in the

medial thalamic region, mediates a rapid, short-lasting desynchronization of the electroencephalogram (see Jasper, 1960). Of more direct significance to spontaneous behavior is the fact that a train of regular waves with a frequency of six to nine cycles per second (theta waves) often appears in the medial thalamus just prior to a CAR and even to such spontaneous, voluntary movements as turning around or rearing (Vanderwolf and Heron, 1964).

There is also a good deal of lesion evidence that implicates the medial thalamus in the production of movement. Animals with medial thalamic lesions are less aggressive than controls (Warren and Akert, 1960). They also freeze or crouch more readily in response to stimulation and therefore, show deficits in the performance of a conditioned escape response (Roberts and Carey, 1963). The retention of a CAR is impaired (Pechtel, Masserman, Schreiner and Levitt, 1955) and there is a marked deficit in the acquisition of a one-way, short-latency CAR (Cardo, 1961; Replogle, 1960; Thompson, 1963; and Vanderwolf, 1962, 1964). The deficits resulting from lesions are not due simply to intellectual impairment, since they do not prevent a classically conditioned vocal response and when the CS-US interval is increased from five to fifteen seconds, the avoidance response can be performed (Vanderwolf, 1962). Furthermore, they do not have the same effect on appetitive and aversive responses (Vanderwolf, 1962; Delacour, Albe-Fessard & Ribouban, 1966) even when the appetitive behavior is quite complex, such as running a maze.

Disturbances in response control following lesions may explain performance deficits in complex approach learning as well. Although there are deficits in the learning of six and twelve unit mazes (Brown and Ghiselli, 1938; Ghiselli and Brown, 1938), these can be attributed to impaired performance

as well as to intellectual impairment. For example, Thomas et al. (1959) found that hyperactive septal rats show more errors on a complex maze than septals showing normal activity even though both septal groups had similar lesions. They did not, however, require significantly more time or a greater number of trials to learn the maze. Thus, it appeared that the deficits in the active septal animals were not due to intellectual impairment. Since medial thalamic animals are also hyperactive in mazes, a similar explanation may apply to their maze behavior. In fact, the lesions made by Brown and Ghiselli included structures other than those in the medial thalamus. Using more precise lesions, Delacour, Albe-Fessard & Liboubán (1966) found only small deficits in the learning of eight-unit mazes and no deficits in the learning of three-unit mazes. Gross, Chorover and Cohen (1965) have shown that although a deficit in performance on an alternation task follows medial thalamic lesions, there are no deficits on the Hebb-Williams maze. These findings were used as support for a notion involving an impaired production of "chains of responses" (see Lashley, 1951).

In summary, the medial thalamus is involved in the production of activity in the EEG that is associated with arousal and in the facilitation of cortically and reflexively induced movements. It is also involved in the production of active avoidance responses and in the control of response during the learning of a complex maze and a double alternation problem.

Response inhibition. There is considerable evidence that implicates the medial thalamus in the inhibition of responses as well as in their production. Although Peacock and Hodes (1951) found many areas in the medial thalamus where stimulation facilitates cortically induced leg flexions and

reflexive knee jerks, they also found several points where stimulation weakens these responses (Hodes et al., 1951). Also, one of the areas found by Hess (1957) to inhibit respiration when stimulated is the medial thalamus. The same author was able to elicit behavioral sleep from stimulation of the medial thalamus (Hess, 1929). This finding has been extended to include ECG patterns that correspond to sleep as well (Akert, Koella and Hess, 1952; Hess, Koella and Akert, 1953; Monnier, Hösli and Krupp, 1963). Hess (1957) has also shown that by stimulating the same locus that produced sleep with a higher voltage and pulse frequency, an arousal or "alerting" response results. The alerting response, like the sleep response, is correlated with a specific EEG pattern (in the case of alerting or arousal this pattern consists of low voltage, high frequency waves; in the case of sleep, the pattern consists of high voltage, low frequency waves). It is not possible, therefore, to attribute either a general arousal or a general inhibitory function to this area of the brain. Both functions exist there simultaneously. In this respect, the functional organization of the medial thalamus appears similar to that of the eating and feeding centers of the hypothalamus. Chemical stimulation of a single locus in the hypothalamus produced either feeding or drinking depending on whether the stimulation was adrenergic or cholinergic (Grossman, 1960). Thus, in both areas there appear to be two neuron populations with different functions existing side by side, that are selectively activated by different forms of stimulation.

The behavioral evidence shows that the animals with lesions in the medial thalamus seldom show a depression of behavior but rather, they are more restless and fearful at least for the first twelve days after the operation (Monnier et al., 1963). This finding, however, is inconsistent with

that of Warren and Akert (1960), who found a reduction in aggressiveness following lesions of nucleus medialis dorsalis or with that of Vanderwolf (1962, 1964), whose medial thalamic animals were quiet. Nevertheless, lesions restricted to the anterior medial thalamus of the cat (Roberts and Carey, 1963) and somewhat larger lesions in the rat (Vanderwolf, 1962) result in hyperactivity in the open field. Animals with the latter lesions also run an alley faster for food (Vanderwolf, 1962). Furthermore, evidence from chemical stimulation studies indicated that there is a cholinergic inhibiting system in the medial thalamus. Cholinergic stimulation of the medial thalamus interferes with the retention and learning of both appetitive and aversive behavior (Grossman, Peters, Freedman and Willier, 1965), while cholinergic blocking agents facilitate both the acquisition and performance of an escape response, a shuttle CAR and a black-white discrimination habit (Grossman and Peters, 1966).

In summary, evidence has been presented that implicates the medial thalamus in response inhibition as well as in response production. Medial thalamic stimulation can both facilitate and inhibit cortically and reflexively induced responses. Depending on the stimulus parameters it can produce either behavioral sleep with the EEG patterns associated with normal sleep or behavioral arousal with EEG patterns associated with normal arousal. In some cases, animals with medial thalamic lesions are more restless and fearful than controls, but in others they are quiet and less aggressive than controls. Nevertheless, they show more exploratory behavior. Furthermore, medial thalamic lesions result in marked deficit in active avoidance learning but there is also strong evidence from chemical stimulation studies for the presence of a medial thalamic system involved in the inhibition of active avoidance responses. Thus,

depending on the situation and the required responses, the medial thalamus can perform either an excitatory or an inhibitory function.

The Tegmentum

Early work of both electrophysiological and behavioral nature implicated the mesencephalic reticular formation in the general arousal state of the organism (see reviews of this work by French, 1960 and Magoun, 1963). Briefly, stimulation of the tegmentum results in wide-spread cortical activation (i.e. low amplitude, high frequency waves in the ECG; Moruzzi and Magoun, 1949) as well as behavioral arousal (Hess, 1957; Segundo, Arana-Inequez and French, 1955), while destruction of it produces both behavioral coma and ECG patterns characteristic of coma (French, 1952). It is also known that stimulation of the reticular formation can result in various kinds of gross bodily movement (Hess, 1957; Hopkins, 1966).

Considering inhibitory functions, it is known that tegmental stimulation can produce sleep or quieting (Favale, Loeb, Rossi and Sacco, 1961; Monnier et al., 1963). As with the medial thalamus, a change in stimulus parameters can result in arousal from the same point of stimulation (Monnier et al., 1963).

Lesion evidence also indicates that the tegmentum is not absolutely necessary for cortical activation. Approximately one month after sustaining complete mesencephalic transection, the cortical EEG begins to show recurring patterns of activation (Batsel, 1960). Cats that have survived for a period of time after large tegmental lesions show hyperexploratory behavior (Sprague, Chambers and Stellar, 1961). With small tegmental lesions animals are not comatose and if the lesions are in the ventral tegmentum, they show more activity than controls when given short periods of access to running wheels

or to an open field (Glickman, Sroges and Hunt, 1964). Furthermore, although these animals bar-press less than normal for food or water when on a fixed-ratio or continuous reinforcement schedule, they run a straight alley faster than normal for food (Ehrlich, 1963).

In summary, early work on the tegmentum showed that stimulation produced an alerting response and lesions resulted in coma. More recently, it has been shown that stimulation of the same point in the tegmentum can produce either quieting or alerting depending on the stimulus parameters. Animals with tegmental lesions bar-press for food less than controls, but explore more and run a straight alley faster for food.

As with the septal area and the medial thalamus, therefore, the tegmentum cannot be described as a structure that usually functions either to inhibit behavior or to produce behavior. The role played by each of these areas of the brain depends both on the situation in which the animals are studied and the response observed.

Theoretical Implications

Problems in Classifying the Behavioral Functions

Classifying the functions of the septal nuclei, medial thalamus and tegmentum as being either inhibitory or excitatory has proved to be a productive source of experiments on the behavior of animals with lesions in these areas. In the foregoing review, however, it has been shown that both functions appear to exist together in all three areas. Thus, there is no basis for predicting whether a lesion will affect inhibitory or facilitatory functions in a given situation. If these concepts are to retain their usefulness, therefore, some reclassification according to the circumstances under

which an area of the brain acts as an inhibitory or as an excitatory area must be made. The reclassification would obviously have to be more complex than the earlier one and would require considerable more knowledge of the effects of lesions in these areas than is available at the present. Since there are no theories about the behavioral functions of these areas that are consistent with most of the results, there is a problem in determining what type of effects would aid in such a reclassification.

The Contribution of Studies on the Components of General Activity to the Understanding of Behavior.

A method of reclassification that might be of more use in predicting behavior would be to think in terms of neural structures controlling individual responses rather than the entire motor system. In physiological studies, Hodes et al. (1951) and Kaada (1960) have shown that there are considerable discrepancies in locations of points that facilitate (or inhibit) different responses. For example, there were a number of points which facilitated cortically induced movements without influencing the knee jerk (Peacock and Hodes, 1951) and both facilitation and inhibition of these responses are independent of accompanying respiratory or arterial pressure alterations (Kaada, 1960). In lesions studies there are similar discrepancies. For example, active avoidance behavior is markedly impaired by medial thalamic lesions but conditioned vocal responses and defecation are unaffected. Lesions of the interpeduncular nucleus in the midbrain produce a similar effect (Thompson, 1961) and while tegmental lesions depress bar pressing but enhance running speeds in a straight-alley maze (Ehrlich, 1963).

At a purely behavioral level, Bindra (1961) has shown how a knowledge of the components of general activity (i.e., the details of what animals

actually do) may aid in the understanding of the responses of animals to a variety of situations. Basically, Bindra's notion is that the occurrence of a response of a certain class in a given situation is the outcome of its "competition" with other response classes, which have a probability of occurrence greater than zero in this situation. Thus, anything that increases the probability of occurrence of one class of responses will decrease that of a competing class.

In simple reward learning, for example, one possible response is running to the goal and another possible response is exploring the apparatus. Novelty increases exploratory tendencies and should, therefore, decrease tendencies to run to the goal. The more an apparatus is different from the home environment, the more novel it should be and the less likely that an animal should perform the running response. Free environments should be more similar to a simple maze than cages and therefore, animals raised in them should perform runway responses better than those raised in cages. In fact, such a situation was shown to be the case by Forgays and Forgays (1952) and Hymovitch (1952). Alternatively, it is possible to increase the probability of running to the goal directly. Putting animals in groups increases running and similarly improves performance on simple reward learning (see Bindra, 1961).

Locomotor Activity and the Effects of Brain Lesions

It is possible that a knowledge of the components of general activity in both familiar and novel situations may be similarly useful in interpreting the effects of brain lesions on behavior. The data available on the contribution of the areas of the brain considered here to locomotor activity, however, provide an incomplete analysis of these behaviors. The tests of exploratory behavior last for only a few minutes a day on one or two test days. There are

many factors that might contribute to a lack of reliability in such short samples of behavior in changing environments. It is known, for example, that exploration will continue to decrease, both within short, daily test-sessions and between them, for several days after the initial test (Berlyne, 1955). This decrease does not reach zero, however, since activity that is indistinguishable from the initial responses of animals to novel stimuli can be seen periodically throughout every day in the home cage. A short test of exploratory behavior, therefore, cannot be used to estimate the effects of lesions on the baseline of exploration. The tests of running-wheel activity also lasted only a short time (in this case, an hour a day or less). The effects of lesions on this sort of activity, therefore, may be contaminated with the animals reaction to the novelty of the situation.

An additional factor that decreases the reliability of the short-term tests, is the fact that biological rhythms affect both exploratory behavior (Henderson, 1963) and running-wheel activity (see Pittendrigh, 1957; Richter, 1957). Activity rhythms can vary in period from the well-known diurnal cycle to the ten to twenty day cycle that results from damage to various parts of the neural and endocrine systems (see Richter, 1957 and 1960). According to Richter (1957) the frontal cortex, hippocampus, thalamus, hypothalamus and reticular system are all involved in the production of endogenous rhythms. Furthermore, damage to the hypothalamus, hippocampus and frontal cortex cause very definite peaks in running-wheel activity to occur every ten to twenty days (see Richter, 1957). A test of activity changes resulting from brain lesions, which lasted only for a few minutes a day, therefore, might be subject to variation due to both activity cycles. Conflicting results from different studies may be due to the presence of such cycles. Thus, the short-term studies

can at best provide an indication of the effect of lesions on locomotor behavior.

The mesencephalic reticular system is one of the areas that Richter considered important in the regulation of activity. No studies of the effects of lesions in this area on long-term activity have been done. It is known, however, that animals with lesions in the ventral tegmentum show more activity than controls, when given short periods of access to running wheels or to an open field (Glickman et al., 1964).

The thalamus is another structure mentioned by Richter on which there have been no studies of long-term activity. It is known, however, that medial thalamic lesions cause animals to be more active than controls when given short periods of access to an open field (Vanderwolf, 1962).

The septal nuclei were not mentioned by Richter as being structures involved in the regulation of activity cycles. However, it is thought that the effects of frontal lesions are mediated via these nuclei (Kaada et al. 1962) and one might expect, therefore, that the effect of lesions in the two areas would be similar. Furthermore, there seems to be a reciprocal relation between the septal area and the medial thalamus involving the production of responses (Vanderwolf, 1964). This area also seems to be involved in short-term activity, since septal lesions decrease activity during short periods of access to running wheels and either have no effect (Zucker, 1965) or decrease (Kenyon, 1962) it in the open field.

Thus, the tegmentum, medial thalamus and the septal area are each involved in open field activity. The ventral tegmentum and the septal nuclei are also known to affect short-term, running-wheel behavior in the same direction in which they affect open-field activity. In contrast, in some long-term studies,

it has been shown that there is a considerable difference between the effects of other variables such as food deprivation (Finger, 1958; Treichler & Hall, 1962 and Weasner, Finger & Reid, 1960) and estrus cycles (Finger, 1961) on running-wheel behavior and on locomotion in a stationary cage.

The present study, therefore, is an attempt to assess the effects of septal, medial thalamic and tegmental lesions on long-term activity both in running-wheels and in stationary cages. In order to compare the effects of the lesions on long-term activity to those on short-term activity all the animals were tested for twenty minutes a day on two successive days in a plus maze. Finally, some of the animals in each lesion group were run on a simple one-way active avoidance problem. This permitted a comparison between the effects of lesions on general activity and those on avoidance learning, which according to the notions of Kaada et al. (1962) and McCleary (1961) should be related.

CHAPTER 2

METHOD

Subjects

The Ss were 26 hooded rats (7 controls, 7 medial thalamics, 6 septals and 6 tegmentals) from Quebec Breeding Farms weighing between 250 and 350 grams just before the operations. Before surgery they were housed in colony cages and afterwards, individually until the end of the experiment when they were sacrificed. From the time of the operation until the beginning of the long-term activity tests, they were housed in constant light. During the long-term tests, they were housed in the apparatus, which was in a partially sound-proofed room with a twelve-hour light, twelve-hour dark, automatically timed light-cycle and constant temperature and humidity control. Sounds in the room consisted of noise from the counters, rats running in wheels and a muffled, nine per second click from a photostimulator that was in constant operation.

Surgery

All lesions were made by thermocoagulation with a Grass radio-frequency lesion-maker. The electrode was a .010 in. diameter nichrome wire insulated except for a 1 - 2 mm. bare portion at the tip. In all cases a maximum or near maximum voltage was used for a period of less than 10 sec. (with this instrument the lesions are made by burning the tissue and in most cases the burned tissue insulates the electrode tip before 10 sec. have passed). The electrodes were positioned in the brain by means of a Krieg stereotaxic instrument. The coordinates for the septal lesions were 2 mm. anterior to bregma, 6 mm. below the surface of the skull, and 1 mm. lateral to the midline

with an angle of 10°, which positioned the tip of the electrode just under the midline of the skull. For the ventral medial thalamic lesions the co-ordinates were 1½ mm. posterior to bregma, 6½ mm. below the skull, and 1 mm. lateral to the midline with an angle of 8°. For the ventral tegmental lesions they were 5½ mm. posterior to bregma, 7 mm. below the skull, and 1½ mm. lateral to the midline. All sham-operated controls were operated by the same method as the lesioned animals except that the electrode was not heated.

Histological Procedure

At the completion of the experiment the animals were sacrificed, perfused with normal saline and 10% formalin and the brains extracted. After remaining in a 10% formalin solution for a minimum of four days the brains were frozen and sectioned at 40 micra. Every fifth section through the lesion area was mounted on slides and stained with cresyl violet for histological examination. The results of this examination will be presented under Anatomical Findings in the Results section.

Apparatus and Procedure

General

Since only eight animals could be run at once, a repeating sessions design was used. In each such replication, two animals from each of the four lesion groups were included. In this way any interactions of lesion and seasonal effects on activity could be controlled. In each session all eight animals were run on exploration first. Then four animals (one from each lesion group) were run in the activity boxes first and the wheels second, while the other four were run on the wheels first and the boxes second. After the activity tests were finished, some of the animals were run on avoidance and at the termination of the experiment all animals were perfused and brain sections were made for

histological purposes.

There were a number of deaths due to a variety of causes (tumors, pneumonia and paratyphoid fever were determined to be the causes for some of the deaths) during the course of the experiment. In cases where there were not at least one animal per lesion group surviving the experiment, the session was not included in the results. Also, no animals were included in the results if they did not survive to the completion of the experiment.

Plus Maze

The plus maze consisted of four arms each measuring 12 by 6 by 6 in. They were placed perpendicular to each other leaving a 6 by 6 in. center space. During testing the maze was covered by hardware cloth and lighted by a 100 W bulb placed directly over the center space. The rest of the room was dark and a one-way viewing screen was placed between the experimenter and the maze. The S had not previously been exposed to the testing room.

Animals surviving the operation for a minimum of 12 days were tested in the plus maze for 20 min. on each of two successive days. A clicker marked off 12 sec. intervals. At each click the experimenter recorded what the animal was doing (lying, grooming, chewing, sniffing, rearing, walking or any possible combination of these) as well as the number of entries into the arms that had occurred during the last 12 sec. All the animals were tested in the afternoon so that even if the animals had picked up some exterior cue to which their endogenous cycles could be entrained during their recovery period in constant light, the results would not be biased by time of day effects. Furthermore, the Ss were divided into two groups of four Ss in which each of the four lesion groups were represented. One of these groups was tested first and the other second.

Activity Boxes

The activity boxes were similar to those described by Teitelbaum and Milner (1963). They were four identical cubical wooden boxes with dimensions of 12 by 12 by 12 in. A triangular food trough about 3 in. wide was at one end of the box and a water bottle at the other end. The box was bisected by a beam of light from a 12 V bulb covered with a red glass filter and positioned 1½ in. from the floor. The beam fell on a photocell attached to a photelectric relay (Lafayette model KT133A modified to work both in the light and in the dark). The relay was adapted to give a short pulse to an electromagnetic counter and a Rustrak recorder, when the beam of light was interrupted. From the counters and Rustrak recorder both the distribution and total amount of activity could be monitored for each rat for as long a time as desired. Records of total activity were taken at each change in lighting conditions so that a record of activity in the light and in the dark as well as the daily totals could be obtained.

Continuous records were obtained from these for a minimum of seven days. From time to time a failure in a photoelectric-relay tube or in one of the light bulbs caused the loss of a half-day's record. All the animals were run for an extra day in such cases. Also, in a few of the later sessions some of the groups were run for a few extra days to determine if any gross changes in their records might occur after the seven-day period. In no case, did animals remain in an apparatus for longer than two weeks and the first seven days of complete records were used in the analysis of the results.

Activity Wheels

Four Wahman activity wheels measuring 4½ in. in width by 14 in. in diameter were used. At the bottom of the wheel there was an opening leading

to a small cage measuring 10 in. in length by 6 in. in width by 5 in. in height, in which food and water were always available. A piston which activated a mechanical counter with each revolution of the wheel was equipped to activate a microswitch as well. The microswitch in turn activated a Rustrak recorder so that the relative spacing of activity in each of the four wheels could be separately recorded along with the absolute number of revolutions. As with the boxes, readings were taken at the change of lighting conditions.

The data on the activity-wheel behavior were recorded in the same way as the box data.

Avoidance Training

Avoidance learning was tested in a situation similar to the one described by Vanderwolf (1962). The apparatus was a box with each compartment measuring 10 by 18 by 18 in. with a grid floor. One compartment was painted black and the other white and the two compartments could be separated by a sliding door. A shock of about 1.0 ma. from the grid in the black compartment could be activated manually.

The animals were trained on the avoidance problem in a manner similar to that used by Vanderwolf (1962). The rat was placed in the black compartment with the sliding door open and allowed to explore the apparatus for 5 min. For each avoidance trial, the S was placed in the black compartment with the sliding door open. If it had not moved to the white compartment after 5 sec., the shock was applied. If the animal did not escape the shock after 25 sec., it was removed to the white compartment by hand. As soon as the S moved into the white compartment after being placed in the black, the sliding door was closed and the trial ended. There was a 30 sec. intertrial interval. The

data were the latencies of the responses (less than 5 sec. was an avoidance response and more than 5 sec. was an escape response). A maximum of 30 trials was given with all trials on the same day. The criterion for avoidance learning was 10 trials in succession on which avoidance responses were made.

CHAPTER 3

RESULTS

Histological Findings

The medial thalamic lesions involved mainly the nuclei in the ventromedial thalamus including nuclei reuniens, gelatinosa and rhomboideus. In the anteroposterior dimension the lesions extended from the caudal limits of the anterior thalamus to the level of the posterior commissure. Incidental damage to other structures included the following: dorsally, the lesions extended into nucleus medialis dorsalis in six of the seven animals but the medial habenuli were damaged in only two cases; ventrally, the dorsal tip of the periventricular hypothalamic nucleus was damaged in three animals and the posterior hypothalamic nucleus as well as a small portion of the mammilothalamic tract was damaged in six of the animals; laterally, a small portion of the ventral thalamic nucleus and the medial lemniscus was damaged in one animal. In one animal the lesion was more posterior than in the rest, extending well into the periaqueductal grey of the tegmentum. The pattern of damage to thalamic structures was, however, very similar to that of the other animals in the group. Two typical medial thalamic lesions are presented in Fig. 1.

The septal lesions involved mainly the ventral portions of nuclei septalis medialis, septalis dorsalis, septalis fimbrialis and triangularis septi. In the antero-posterior dimension they extended from a level just

In Figs. 1, 2 and 3 the following abbreviations are used:-

AC, anterior commissure

CC, corpus callosum

FOR, formatio reticularis

LM, lemniscus lateralis

NHL, nucleus habenularis lateralis

NIP, nucleus interpeduncularis

NLS, nucleus lateralis septi

NMD, nucleus medialis dorsalis thalami

NMS, nucleus medialis septi

NR, nucleus reuniens

PCS, pedunculus cerebellaris medius

SG, substantia grisia periventricularis

TMT, tractus mammilothalamicus

TS, tractus spinotectalis

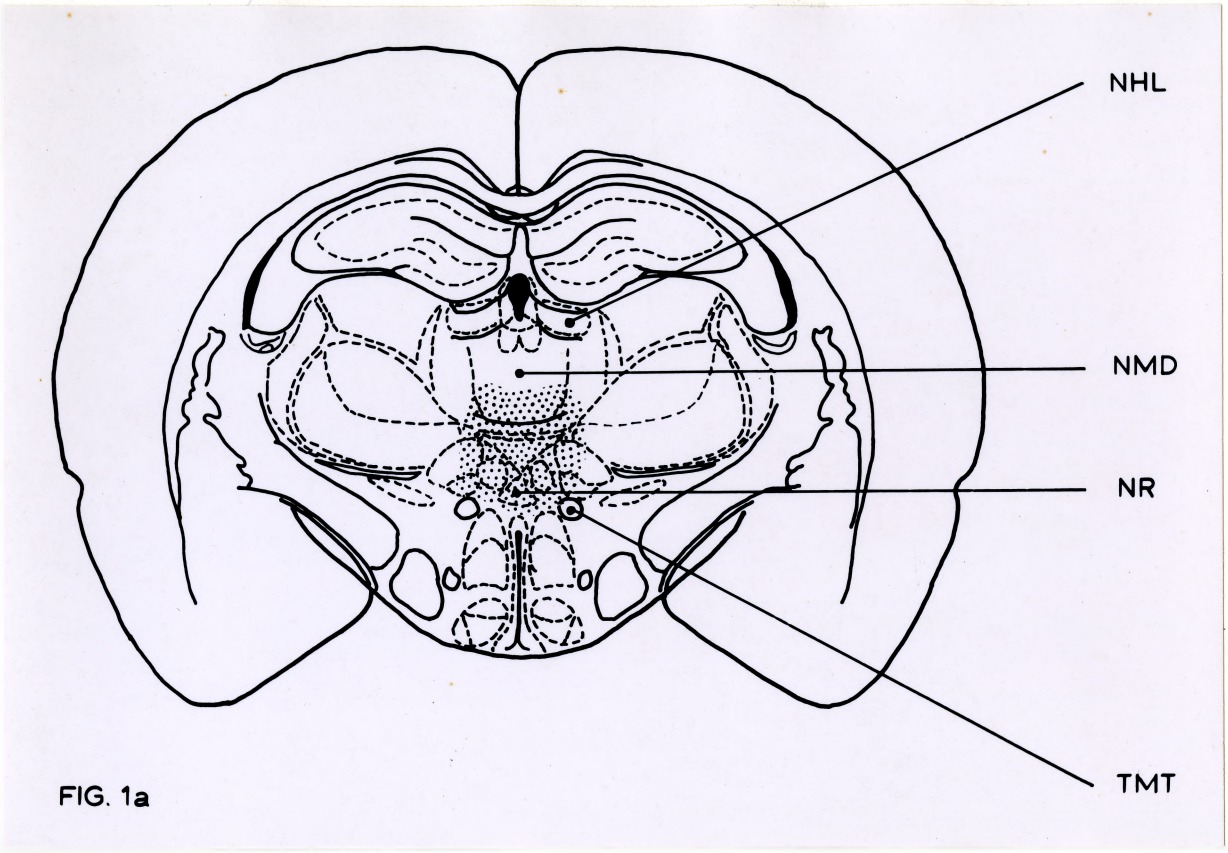


FIG. 1a

An example of a medial thalamic lesion at its greatest extent.

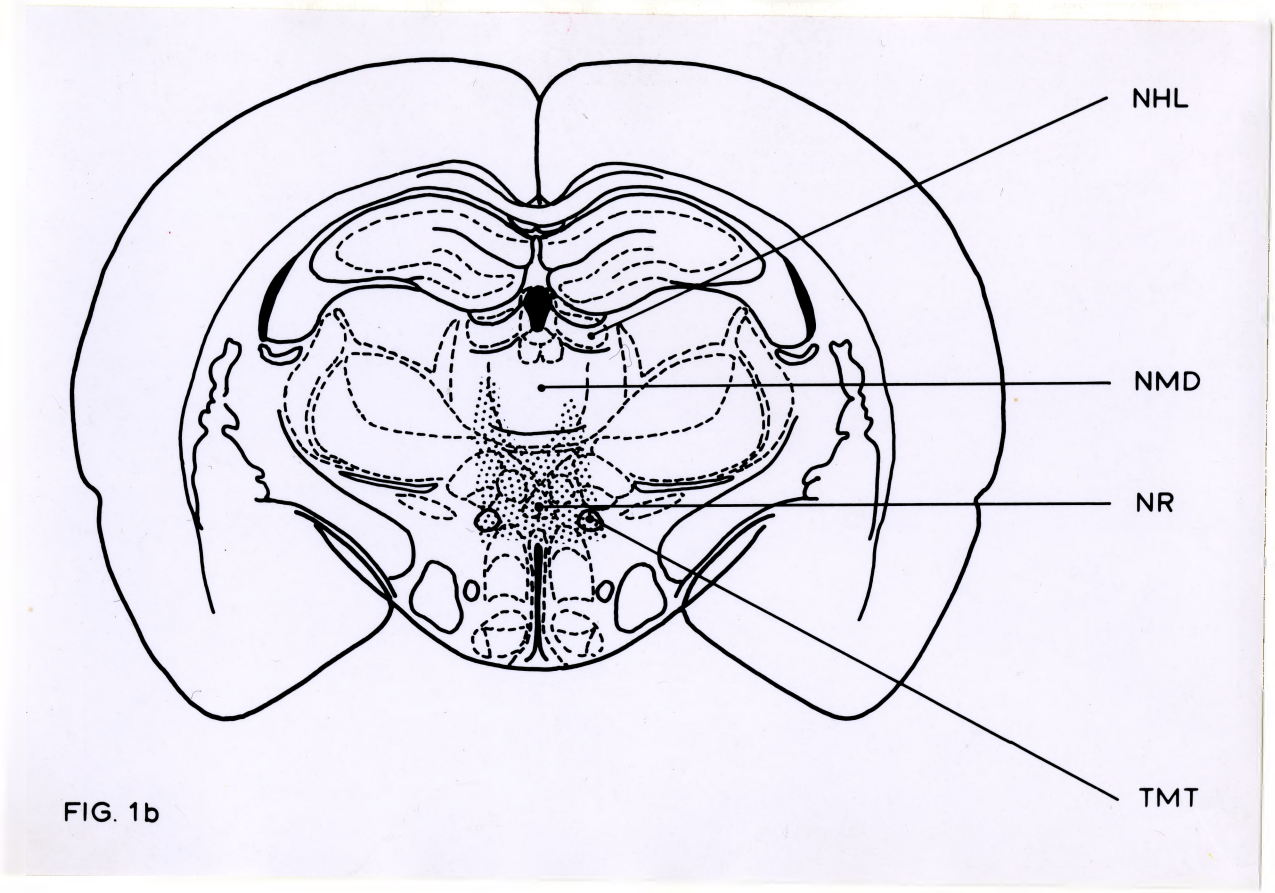


FIG. 1b

An example of a medial thalamic lesion at its greatest extent.

posterior to the genu of the corpus callosum to the anterior thalamus. Incidental damage to other structures included the following: dorsally, the corpus callosum was damaged very slightly in one case, ventrally, the anterior commissure was transected in four animals and the fornix along with a small portion of the preoptic nuclei was damaged in five cases. Two typical septal lesions are presented in Fig. 2.

The tegmental lesions involved mainly the ventrolateral portion of the mesencephalic reticular formation. In the antero-posterior dimension they extended from the level of the red nucleus to the exit of the trigeminal nerve. They were situated bilaterally, somewhat ventral to the level of the cerebral acqueduct and lateral to the red nucleus and most of the superior cerebellar peduncles. Minimal damage occurred to the lateral lemniscus, but the superior cerebellar peduncles and the rubrospinal tract were each damaged in four cases. The lesions were bilateral in every case but one. Two typical tegmental lesions are presented in Fig. 3.

Behavioral Findings

Plus Maze

The measures taken in the plus maze can be divided into two types: (1) number of entries, and (2) behavioral observations. Table 1 shows the mean and standard deviation of the entries made by each of the four groups. From this table it is clear that there was no noticeable effect of lesions on the number of entries (the largest difference between means was roughly equal to one standard deviation). Since the six different categories of behavior observed are all inter-dependent, it was not possible to compare groups on these measures with standard, statistical techniques. Consequently,

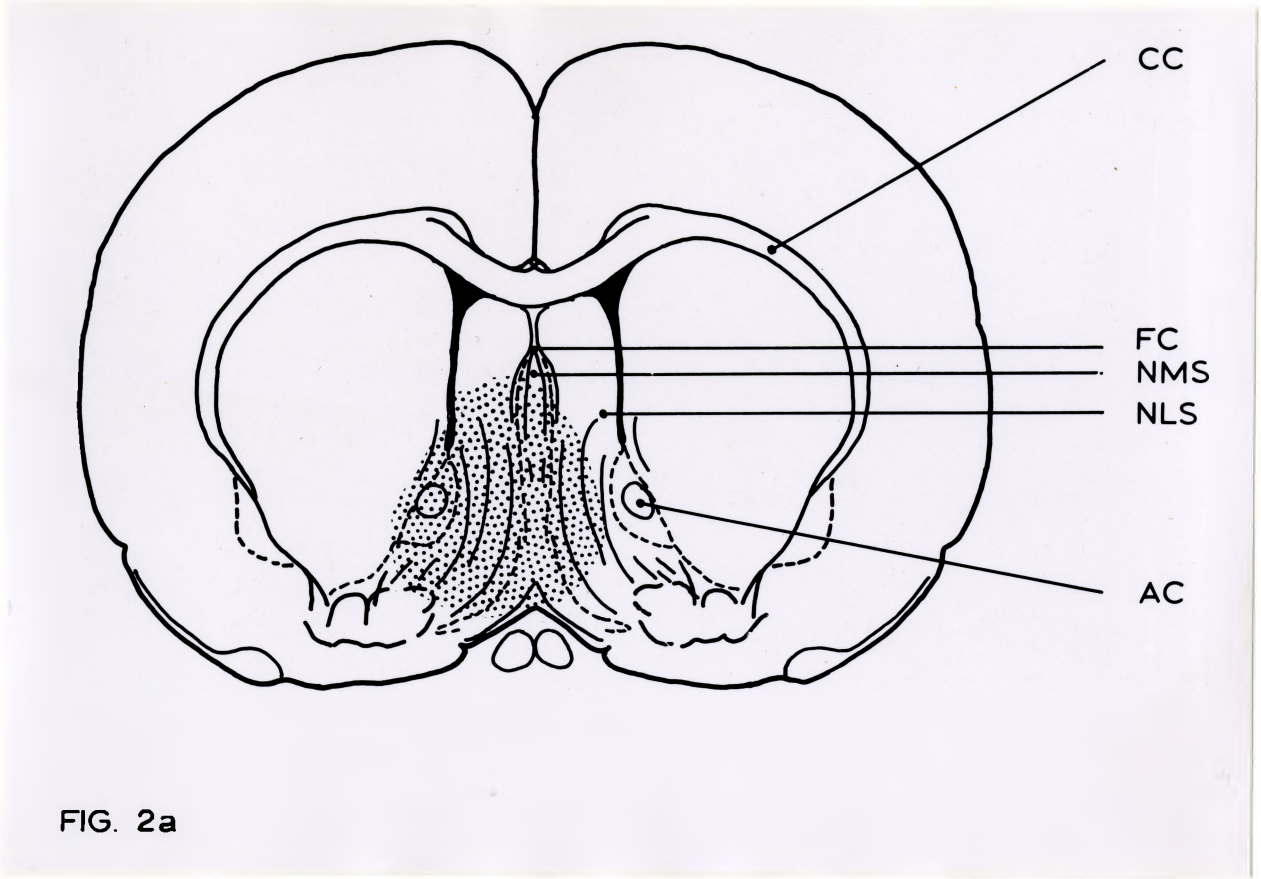


FIG. 2a

An example of a septal lesion at its greatest extent.

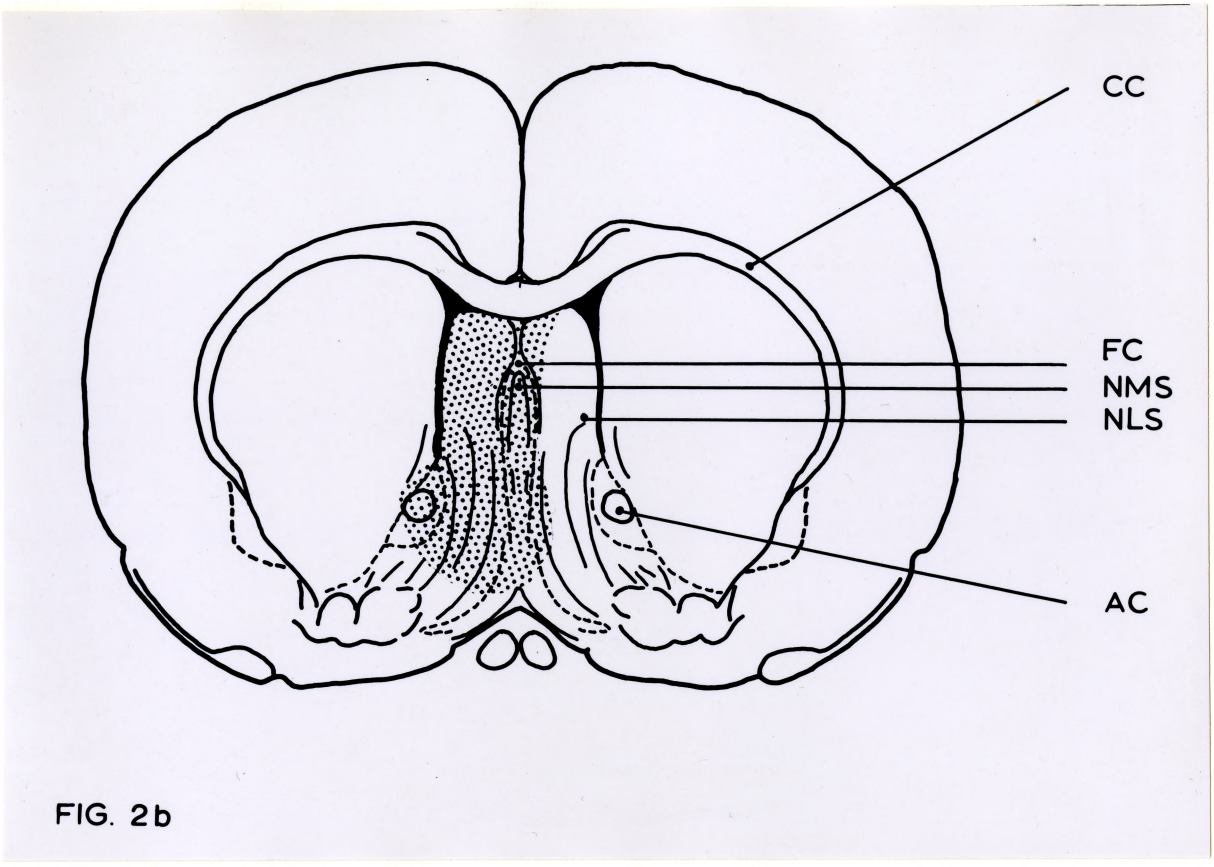


FIG. 2b

An example of a septal lesion at its greatest extent.

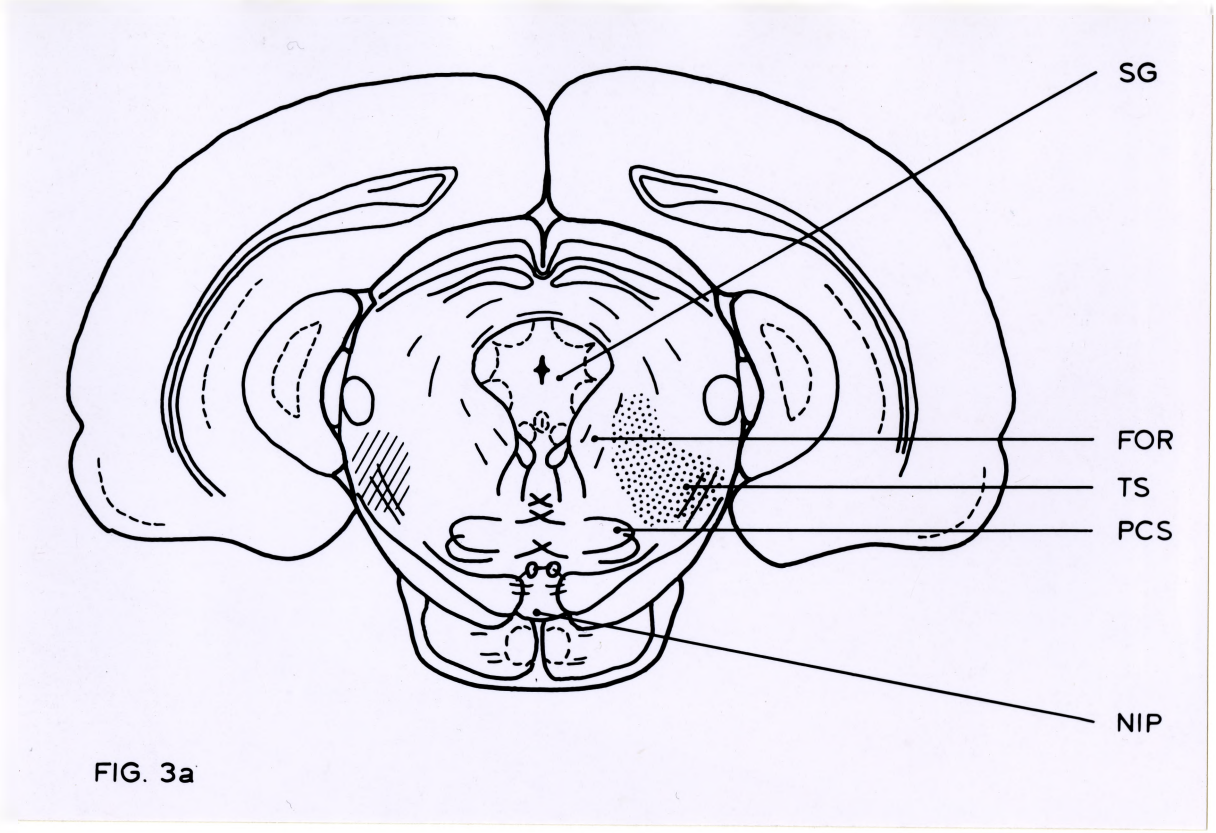


FIG. 3a

An example of a tegmental lesion at its greatest extent.

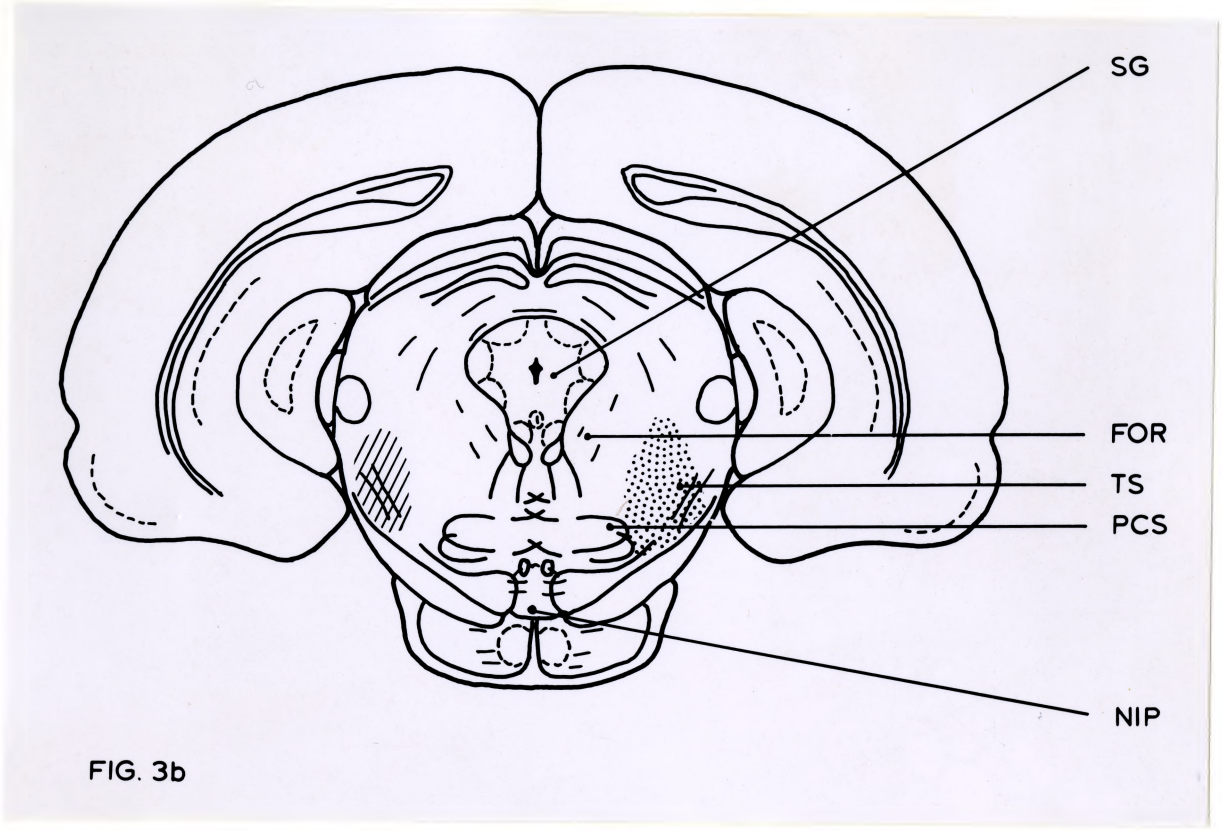


FIG. 3b

An example of a tegmental lesion at its greatest extent.

TABLE 1

Mean and SD of Arm Entries in Plus Maze for Brain-damaged and Control Rats

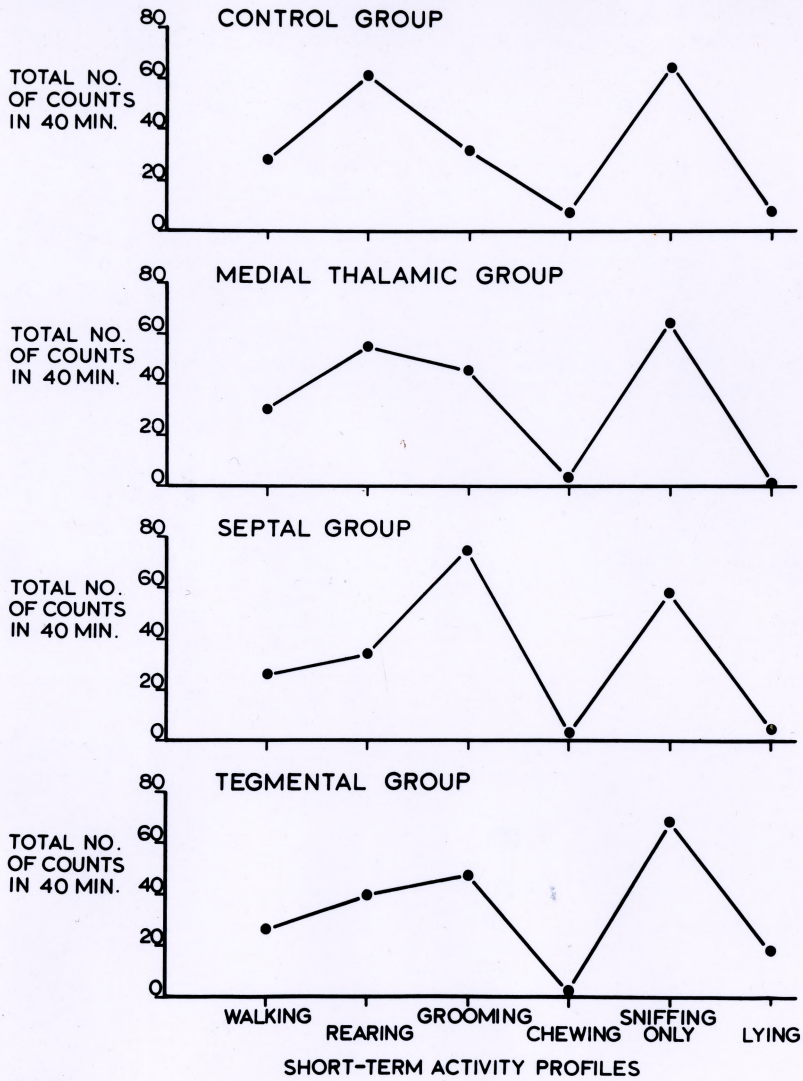
Score	Group				
	Control	Medial Thalamic	Septal	Tegmental	Total
Mean	83	92	76	76	83
SD	32	29	27	39	

the profiles of behavior are presented with no analysis other than the correlations of those measures showing some inter-group variance with each other and with the measures of long-term activity. These profiles are presented in Fig. 4. For the scores presented in this figure there is some overlap between all groups on all measures. Some trends, however, are noticeable, especially for the rearing and grooming scores, which are highly negatively correlated (see Table 2). Rearing appears less frequently in the septals and tegmentals than in the medial thalamics and controls while grooming appears most frequently in the septals and tegmentals and least in the controls. Besides the correlations between grooming and rearing, Table 2 also shows the correlations between these two measures of behavior and the number of arm entries. The overall correlations between both behaviors and the number of entries were significant. If animals reared often they made many arm entries and if they groomed often they made fewer arm entries.

Wheel and Box Activity

The results of the long-term activity measured in the wheels and boxes are summarized in Table 3. Wheel activity was diminished by all the lesions with the septals and tegmentals being most affected and the medial thalamics least. Box activity, on the other hand, was affected by none of the lesions. Diurnal cycles were also unaffected and trends over the several days of testing were apparent only in one group, the septals.

The scores were divided into activity in the light and in the dark to show the effect of diurnal cycles. The geometric means were included, since there was a strong linear relation between the arithmetic means and the standard deviations. For the same reason, the variances were non-homogenous



SHORT-TERM ACTIVITY PROFILES

FIG.4

TABLE 2

Product Moment Correlations Between Short-term Measures of Activity for Brain Damaged and Control Animals

			Measure		
:oup	df	Score	Grooming-Rearing	Grooming-Entries	Rearing-Entries
›tal	24	r	-.71	-.44	.66
		p	<.005	<.025	<.005
›ntrol	5	r	-.66	-.44	.36
		p	=.05	NS	NS
ɜdial Thalamic	5	r	-.74	-.50	.63
		p	<.05	NS	NS
ɜptal	4	r	-.61	-.23	.29
		p	NS	NS	NS
ɜgmental	4	r	-.83	-.85	.93
		p	<.025	<.025	<.005

TABLE 3

Long-term Activity of Brain Damaged and Control Animals

roup	Score	Measure: Wheels Light	Wheels Dark	Boxes Light	Boxes Dark
ntrol	AM*	100	449	403	724
	GM**	1.678	2.575	2.585	2.830
	SD***	152	336	129	252
edial Thalamic	AM	24	160	424	810
	GM	1.337	2.120	2.597	2.832
	SD	15	105	121	240
eptal	AM	10	136	511	804
	GM	0.829	1.521	2.698	2.859
	SD	8	177	120	387
egmental	AM	24	73	442	602
	GM	1.191	1.828	2.619	2.748
	SD	31	33	127	197

* AM - Arithmetic mean

** GM - Geometric mean

*** SD - Standard deviation of the raw scores

and the scores were transformed to logarithms for the major part of the analysis. These scores are presented in Fig. 5. The first bar for each group represents the two means of overall activity. The other two bars represent the means and standard deviations of the light and dark activity.

The analysis of variance on the activity scores is summarized in Table 4 and the post-hoc comparisons in Table 5. The small but significant ($p < .05$) main effect of groups was obtained by combining the total light and dark activity in both wheels and boxes. The multiple comparisons show that the controls were more active than each of the other groups and that the medial thalamics were more active than the septals and tegmentals. There was no difference between tegmental and septal animals. The main effect of lighting condition was highly significant ($p < .001$) showing the presence of strong diurnal cycles. The lighting condition versus apparatus interaction was also highly significant ($p < .001$). The post-hoc comparisons showed that this effect was due to the presence of light-dark differences that were larger in the wheels than in the boxes. Nevertheless, there was a difference ($p < .05$) between light and dark activity in the boxes. The apparatus by group interaction was also significant ($p < .01$) showing that lesions affect activity measured in wheels differently from activity measured in boxes. The multiple comparisons showed that this was a surprisingly clear-cut effect. In the wheels controls were more active than all other groups ($p < .001$). The medial thalamics were the most active lesion group and the septals were the least active.[3]

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[3] An explanation for the fact that the arithmetic mean of the wheel activity in septals is larger than that of the tegmentals is presented in the Discussion section.

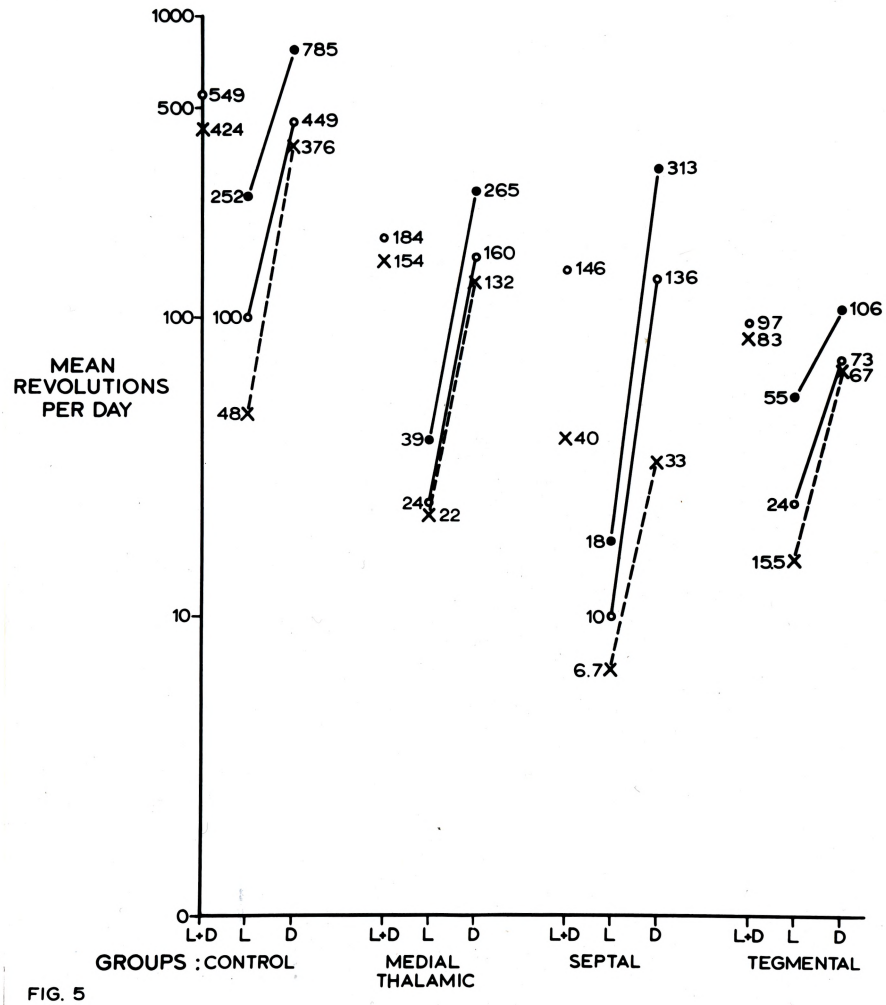

FIG. 5

Average number of wheel revolutions per day for brain damage and control animals.

(X) Antilogarithm of the geometric means
(O) Arithmetic mean
(●) One standard deviation above the arithmetic mean
L Mean revolutions in the light
D Mean revolutions in the dark
L+D Sum of the means for light and dark

TABLE 4

Analysis of Variance Summary for Long-term Activity

Source	MS	df	F	P
Bet. Ss				
Groups (G)	.924	3/22	3.67	<.05
Within Ss				
Apparatus (A)	29.376	1/22	201.62	<.001
Lighting (L)	5.938	1/22	76.62	<.001
A x L	2.051	1/22	20.74	<.001
A x G	1.165	3/22	8.00	<.01
L x G	.045	3/22	.57	NS
A x L x G	.007	3/22	.07	NS

TABLE 5

Post-Hoc Comparisons on Long-Term Activity

A. Main-Effect of Groups

Comparison*	F	P
1+5 v 2+6	19.88	<.001
1+5 v 3+7	4.25	<.06
1+5 v 4+8	10.56	<.005
2+6 v 3+7	6.15	<.025
2+6 v 4+8	1.36	NS
3+7 v 4+8	1.61	NS

B.** Lighting Condition by Group Interaction

WL v WD	15.03	<.001
BL v BD	5.08	<.05

C.* Group by Apparatus Interaction

1 v 2	80.14	<.001
1 v 3	15.14	<.001
1 v 4	33.70	<.001
2 v 3	27.12	<.001
2 v 4	9.13	<.01
3 v 4	4.27	<.06
5 v 6	.04	NS
5 v 7	.00	NS
5 v 8	.01	NS
6 v 7	.03	NS
6 v 8	.07	NS
7 v 8	.01	NS
1 v 2 + 3 + 4	60.14	<.001
5 v 6 + 7 + 8	.04	NS

* Numbers 1 through 4 refer activity in the wheels for the controls, medial thalamics, septals and tegmentals, respectively. Numbers 5 through 8 refer to box activity for groups in the same order.

**W: wheels, B: boxes, L:light, D: dark.

In the boxes, however, there were no differences between any of the groups. As might be expected from the apparatus by lesion interaction there was no overall correlation between wheel and box activity (see Table 6). Furthermore, a significant positive relation between the two types of long-term activity measures was found only for the septals. Finally, the fact that there was no lighting condition by group interaction indicates that the diurnal cycles were not appreciably affected by the lesions.

The daily activity in the wheels for two representative subjects from each group is presented in Figs. 6, 7, 8 and 9. One of the septals showed a marked increase in activity during the last part of the session and the other showed a marked decrease. One or the other of these two trends was present in all the septal animals (one septal, however, showed a smaller change than those presented; the daily maximum of this rat was 22 and the minimum was 0 revolutions). Such trends were apparent in no other groups.

Correlations Between Long- and Short-Term Measures of Activity

Correlation coefficients were computed between grooming, rearing and entries, and both wheel and box activity (see Table 7). There was no overall correlation of any short-term measure of behavior with wheel or box activity, except in the septal group. In that group the correlation between entries and boxes was quite high ($r = 0.88$, $p < .02$). The short-term and long-term measures of locomotion (entries and wheel activity) were positively correlated. As might be expected from the positive correlation between entries and rearing, the latter behavior was also positively correlated with wheel activity. Similarly, grooming was negatively correlated with wheel running.

The results of both short- and long-term activity include three

TABLE 6

Correlations Between Wheel and Box Activity of Brain Damaged and Control Animals

Group	df	r	p
Con	5	-0.26	NS
MT	5	0.54	NS
Sep	4	0.74	<.05
Teg	4	0.44	NS
Tot	24	0.16	NS

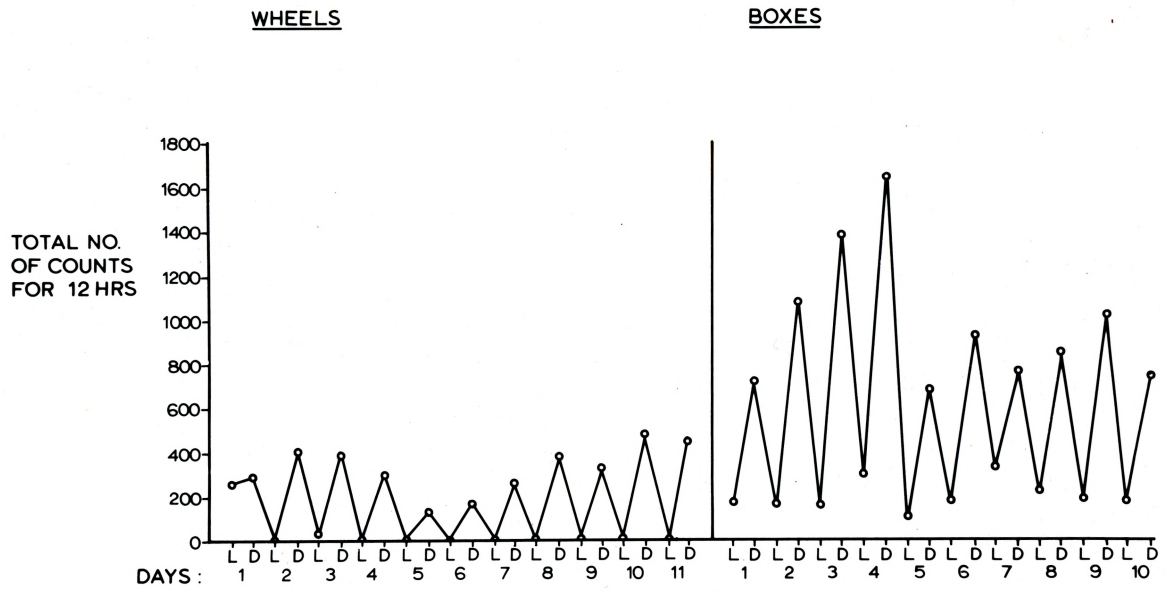

FIG. 6a LONG-TERM ACTIVITY FOR S. IV-TC (CONTROL)

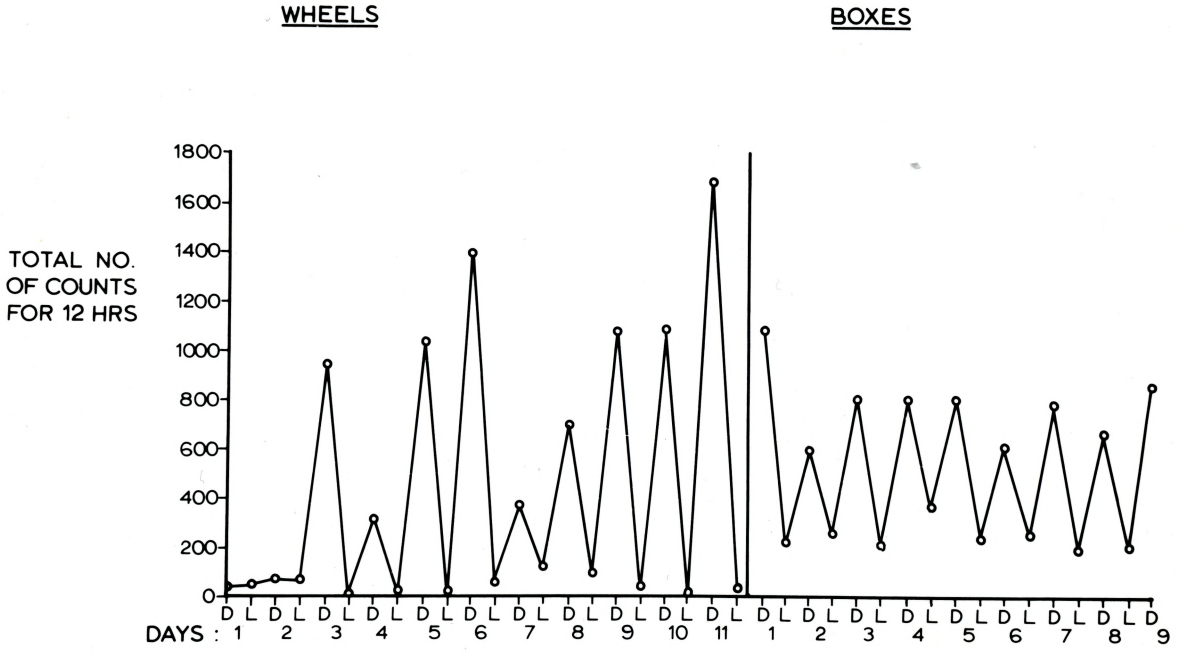

FIG. 6b LONG-TERM ACTIVITY FOR S V – TC (CONTROL)

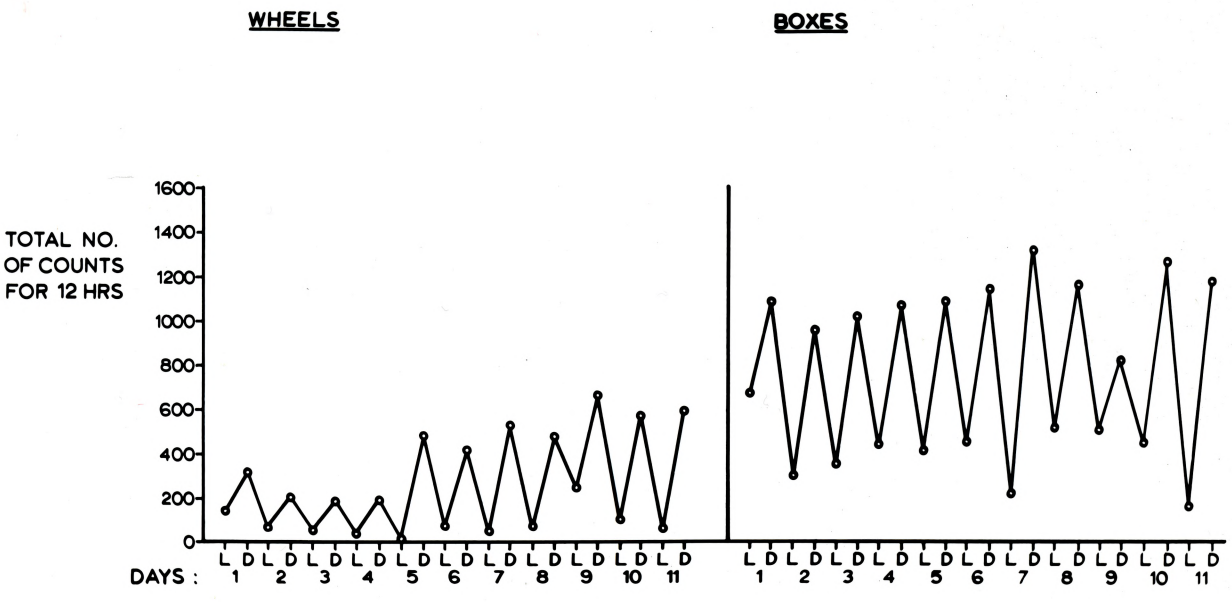

FIG. 7a LONG-TERM ACTIVITY FOR S IV – MT1 (MEDIAL THALAMIC)

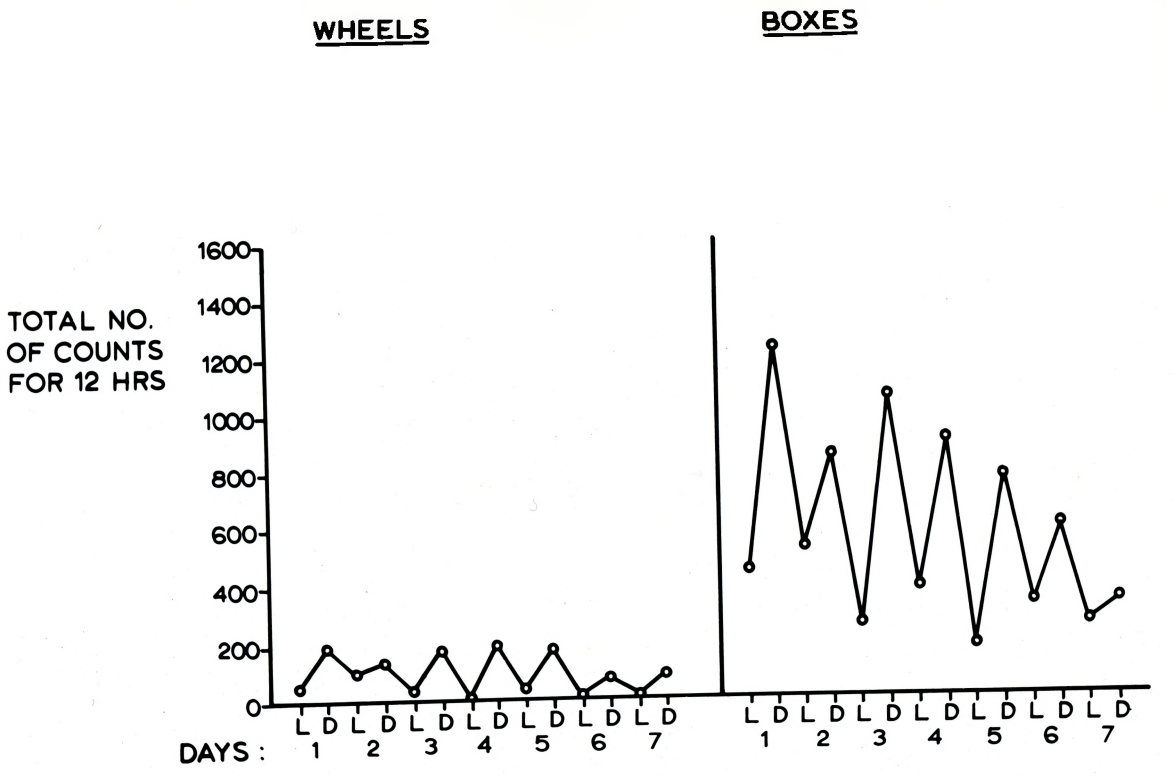

FIG. 7b LONG-TERM ACTIVITY FOR S III – MT1 (MEDIAL THALAMIC)

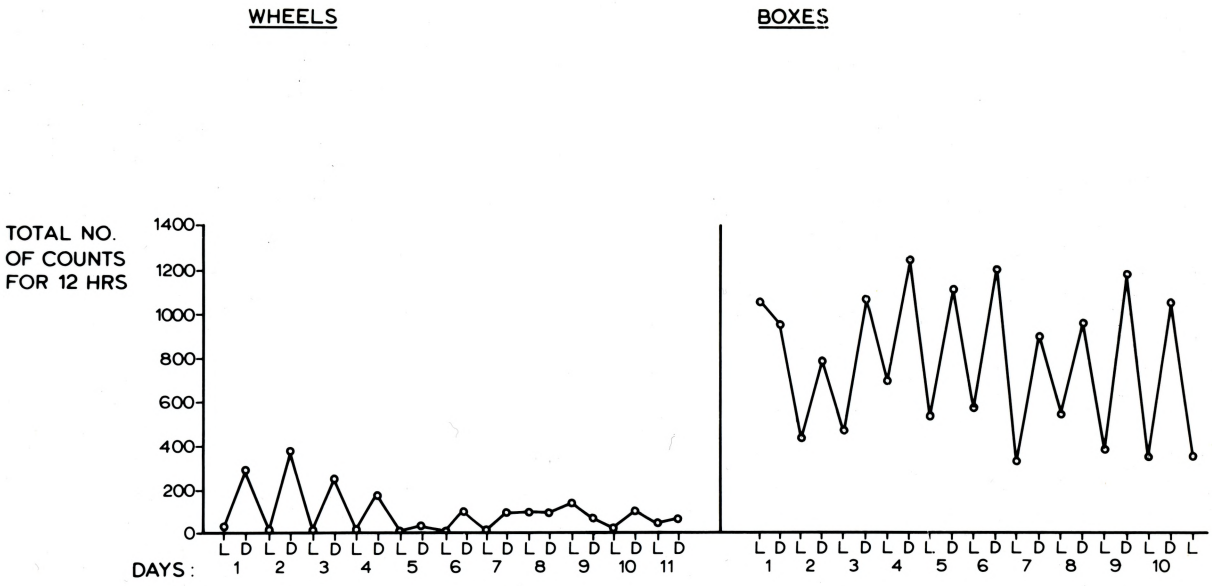

FIG. 8a LONG-TERM ACTIVITY FOR S IV S-2 (SEPTAL)

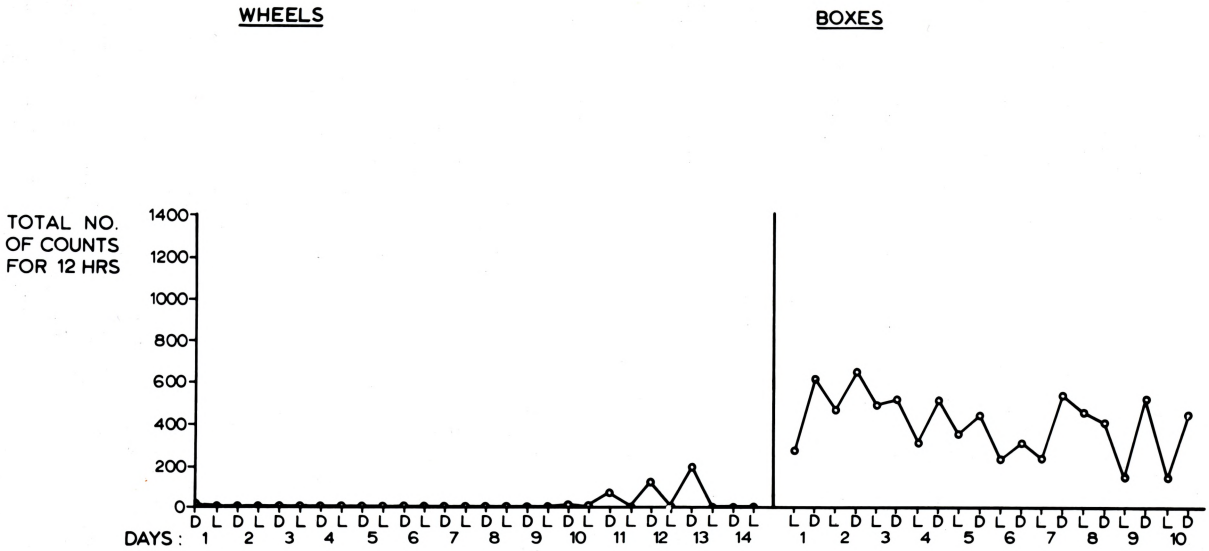

FIG. 8b LONG-TERM ACTIVITY FOR S VI S-2 (SEPTAL)

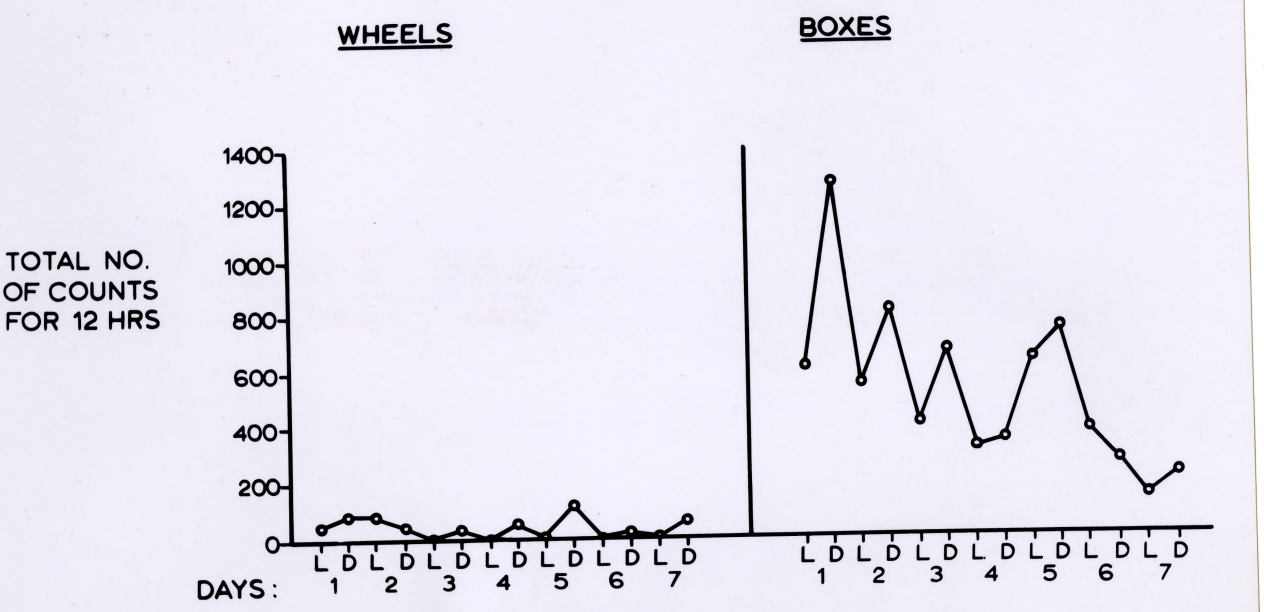

FIG. 9a

LONG-TERM ACTIVITY FOR S III T-1 (TEGMENTAL)

TABLE 7

Correlations Between Long- and Short-Term Measures of Activity

Group	df		Measure: Wheels Grooming	Wheels Rearing	Wheels Entries	Boxes Grooming	Boxes Rearing	Boxes Entries
		Long-Term Short-Term Score						
Con	5	r	-0.39	0.51	0.61	-0.10	0.41	0.39
		p	NS	NS	NS	NS	NS	NS
VT	5	r	-0.53	0.85	0.38	-0.18	0.10	-0.19
		p	NS	<.01	NS	NS	NS	NS
Sep	4	r	-0.09	-0.01	0.53	-0.06	-0.03	0.88
		p	NS	NS	NS	NS	NS	<.02
Deg	4	r	-0.79	0.39	0.40	-0.69	0.60	0.46
		p	<.05	NS	NS	NS	NS	NS
Total	24	r	-0.41	0.49	0.34	0.00	0.07	0.25
		p	<.025	<.01	<.05	NS	NS	NS

animals (one from each lesion group) whose lesions differed somewhat from the others in their groups. The first was a septal animal with damage only to the medial septal nucleus. Its behavior was indistinguishable from the rest of the group. The second was a medial thalamic, the lesion of which was more posterior than the other medial thalamic lesions. Its wheel activity was less than half that of the second least active medial thalamic, but there was enough similarity in the distribution of its daily activity and the remaining six animals in the group to justify including it in the results of that group. The last deviant animal was a tegmental with a unilateral lesion. Its activity was twice that of the rest of the tegmentals but still less than any control. It was also included with the results of its lesion group.

Avoidance Behavior

The analysis of the avoidance behavior data is presented in Table 8. In general, the results support other findings. Because of the small number of subjects per group, however, they can only be considered suggestive. The analysis of the main effect of groups produced a probability level just below significance ($p = .10$). The Mann-Whitney U's between individual groups showed no difference between the septals and medial thalamics. Two of the five medial thalamic subjects tested, however, did not learn to avoid whereas both septals did. Both the medial thalamics and the septals seemed to require more trials than the controls ($p = .12$ and $.07$, respectively), while the tegmentals required fewer trials than the controls ($p = .02$).

TABLE 8a.

Avoidance Behavior of Brain Damaged and Control Animals

	Groups				
	Control (C)	Medial Thalamic* (M)		Septal (S)	Tegmental (T)
Mean	13	13	30+	21	8
N	6	3	2	2	4

H** = 6.24
df = 3
p = 0.10

* The Medial Thalamic group is divided into those who learned the avoidance (3 Ss) and those who did not learn (2 Ss).

**Determined by the Kruskal-Wallis Analysis of Variance by Ranks.

TABLE 8b.

Individual Group Comparisons

Comparison	U	p
C v M	8	.12
C v S	1	.07
C v T	2	.02
M v S	4	.43
M v T	4	.10
S v T	0	.07

CHAPTER 4

DISCUSSION

The results show that experimental lesions of the septal nuclei, medial thalamus and tegmentum depress wheel running behavior in the rat. Previous work has shown that destruction of the neocortex has little effect on this behavior unless the lesions involve the frontal areas. In this case, an increase in activity results (Zubek and DeLorenzo, 1952). Taken together, these results suggest that subcortical structures (especially the tegmentum) play an important role in the facilitation of spontaneous motor activity while some neocortical areas are inhibitory and others exert no control at all.

It has been suggested that inhibitory fibers from the frontal cortex pass through the septal area on their course to lower centers (Kaada, 1960; Kaada, Rasmussen and Kviem, 1962; McCleary, 1961). The finding that septal damage produces a decrease in wheel-running (rather than the increase expected from section of efferent fibers from the frontal cortex) suggests that this is not so, or at least, that additional factors must be involved. Since there is a good deal of evidence suggesting that the septal areas can act to inhibit some somatomotor activities (see Introduction), the behavioral evidence appears to support physiological findings (Hodes, et al., 1951; Peacock and Hodes, 1951) that the septal nuclei contain a mixture of inhibitory and facilitatory systems.

A striking finding was that activity in photocell-equipped living cages was not depressed by the subcortical lesions studied, even though wheel-running was markedly affected. This probably reflects a real difference in the type of activity measured by the two devices. The photocell boxes are not

simply insensitive measures of activity since box activity is affected by some factors, such as diurnal rhythms. All animals in the present study showed a clear-cut daily variation in activity in the boxes as well as in the wheels. Thus, some brain lesions appear to depress one type of spontaneous motor activity (wheel-running) without having any discernible effect on other types of spontaneous activity.

Two other findings provide further support for the conclusion that the lesions studied affect different behaviors in a selective manner. First, there are the results of the test of exploratory behavior. Locomotion (entries and walking) as well as general activity in the maze (as reflected in the measures of inactivity: sitting and lying) was unaffected by the lesions. Rearing and grooming, however, were affected by them. Furthermore, rearing and grooming were the only measures which showed a high (negative) correlation between them. Considering the lack of a very strong relation between different behaviors it seems impossible to conclude that any one of these lesions affects all behavior requiring facilitation in the same way.

The final line of evidence suggesting that the lesions studied selectively affect different behaviors are the results of the test of active avoidance learning. If both wheel running and avoidance learning were facilitated by these areas of the brain, tegmental lesions should produce the greatest impairment of learning. In contrast, the tegmentals performed as well or better than controls. Furthermore, the medial thalamic lesions produced the smallest decrement in wheel running but the largest decrement in avoidance learning. Thus, there appears to be no systematic relation between the effects of these lesions on wheel running and on avoidance learning.

The lesions used here may affect the same responses in different

ways if different test situations are used. Locomotion in the open field is affected by lesions similar to all three lesions used in this study (Glickman et al., 1964; Kenyon, 1962; Schwarzbaum, Green, Beatty and Thompson, 1967; Vanderwolf, 1962). In the present study no effect was observed on exploration of a brightly lighted plus maze. This difference in results could be due to differences in the test situations, or it could be due to differences in the number of days after the operation that testing occurred. The latter possibility will be discussed below along with the explanations for the effects of these lesions. There are two possible differences in test situation which may account for these results. First, there is the possibility that differences in apparatus illumination caused the differences in effect of lesions. Schwarzbaum et al. (1967) found that septal lesions caused hyperactivity during a short-term test in the dark or in dim light and either hypoactivity or hyperactivity in bright light. Secondly, it is known that the open field produces blood adrenal-corticosteroid concentrations that are equal to or greater than those of a 0.1 ma. electric shock (see Levine and Mullins, 1966). Perhaps, the plus maze produces a less extreme emotional reaction in rats than an open field test does.

Alternatively, the discrepancy between these findings and previous studies on exploration which used similar lesions could be due to small differences in lesion placements. The tegmental lesions used in this study are quite similar to the ventral tegmental lesions of Glickman et al. (1964), who found an increase in exploration, except that some animals in the latter study showed more damage to medial structures. The medial thalamic lesions made in this study were more ventral than those used by Vanderwolf (1962), which also produced an increase in exploration. The septal lesions made here were quite

similar to those of Kenyon (1962), who found a decrease in exploration following the lesions, except that there was less damage to the anterior commissure and none to the preoptic nuclei in his study. Further work will be necessary to decide between these possibilities.

If different neural structures control different behaviors, the lesions may act by changing the relative probabilities of different responses. For example, all the lesions lowered the probability of running compared to the probability of home-cage activity. Also, septal and tegmental lesions raised the probability of grooming compared to rearing. Furthermore, for all the groups except the septals, rearing was slightly (but significantly) correlated with wheel running and grooming was negatively correlated with wheel running. Therefore, there may be some overlap between the neural processes controlling the total amount of running over a period of several days and those controlling individual activities measured for a few minutes a day. Thus, it is feasible to interpret the effects of lesions on long-term measures in terms of discrete activities, and a change in response competition seems an adequate description of these results.

Such an interpretation may help to explain some discrepancies between different findings. For example, there was an indication that septal lesions produce an activity cycle with a period of approximately two weeks. It is possible that such a cycle could affect exploratory behavior much in the same way that diurnal cycles do (see Henderson, 1963). These cycles, therefore, could cause not only a large variance in daily wheel activity both within and between subjects but also a large variance between animals in a test of exploration. Such an effect would explain both the fact that there was no correlation between wheel and plus maze behavior for the septals and also the fact that different studies

find different effects on exploration following septal lesions. No effect was found in this study; Kenyon (1962) found septal animals to be hypoactive and Schwarzbaum et al. (1967) found both hypoactivity and hyperactivity. In the last study one group of septals tested 35 days after the operation was hyperactive and another group tested six or seven days after the operation included some animals that were hyperactive and others that were hypoactive.

Although a change in the nature of response competition following brain lesions may account for the present results, other factors may also be involved. Without a great deal of further research, it is impossible to state definitively why a given brain lesion produces a reduction of wheel running activity. In some cases the explanation may be extremely simple. For example, it is well known that unilateral lesions of the tegmentum produce circling to the ipsilateral side (Skultety, 1962). If the tegmental lesions in the present experiment were somewhat asymmetrical (this often happened) the animals might have difficulty running forward in a straight line. This would interfere with wheel running to a much greater extent than box activity.

Also, it is known that changes in endocrine function can result from brain lesions and furthermore, that direct interference with endocrine function can produce changes in the level of spontaneous motor activity. For example, amygdaloid lesions produce atrophy of the adrenal glands as well as abnormal activity cycles (Woods, 1954). Thus, the activity depression observed in the present study may not be a direct effect at all but may rather, be a secondary effect dependent on changes in pituitary function, for example. It may be relevant in this connection, to note that estrus cycles, which are hormonally controlled, are very prominent in activity wheels but do not appear when activity is measured in small living cages (Finger, 1961). These

lesions also affected wheel activity and not cage activity. Also, removal of the thyroid gland results in abnormal activity cycles with a period of about two weeks. There was a suggestion in the present results that similar cycles appear in rats with septal lesions. Furthermore, Woods found that lesions of the hippocampus result in activity cycles with a period of two weeks. These similarities suggest that limbic system lesions may exert their effects on spontaneous activity by producing changes in endocrine function.

Alterations in activity levels could result from a variety of other factors. For example, it is well known that activity is increased by hunger (Finger, 1951; Hall, 1956; Moskowitz, 1959; Richter, 1922; Siegel & Steinberg, 1949; Teghtsoonian & Campbell, 1960; and Teitelbaum, 1957), especially in the presence of environmental stimulation (Amsel & Work, 1961; Sheffield & Campbell, 1954; and Teghtsoonian & Campbell, 1960). Therefore, interference with normal drive or sensory mechanisms might produce a reduction in motor activity. Activity levels can also be altered by training (Amsel & Work, 1961; Finger, Reid & Weasner, 1957, 1960; Hall, 1958; Sewart & Pereboom, 1955; and Sheffield & Campbell, 1954), so it is possible that activity changes result from interference with mechanisms involved in learning and memory.

SUMMARY

Lesions were made by thermocoagulation in the septal nuclei, the ventromedial thalamus and the ventrolateral portion of the tegmental reticular formation of hooded rats. The effects of these lesions on spontaneous locomotor activity were compared by taking three measures of activity on each subject: a brief test in a four-arm "plus" maze and seven-day tests in activity wheels or in photocell-equipped cages. A test of active avoidance learning was also included.

The main findings were as follows:

1. All lesions depressed wheel activity with the septal and tegmental groups being most affected.

2. Activity in the photocell-equipped cages was unaffected by the lesions.

3. Animals were more active in the dark than in the light in both wheels and cages, but this effect was larger in the wheels.

4. The lesions had no effect on diurnal cycles, but there was a suggestion that septal lesions produce an activity cycle with a period of approximately two weeks.

5. Avoidance learning was depressed by septal and medial thalamic lesions but not by tegmental lesions.

6. None of the lesions affected locomotion in the plus maze, but grooming was enhanced and rearing depressed by both septal and tegmental lesions.

7. There were low, but significant correlations, over all animals between wheel and plus-maze behavior.

These findings suggest the following conclusions:

1. General activity does not depend on a unitary mechanism.

2. The functions of the areas of the brain investigated are not generally facilitatory or inhibitory with respect to somatomotor activity.

3. The control of diurnal cycles does not appear to reside in any of these structures.

4. Like the frontal cortex and hippocampus, the septal nuclei may be involved in the control of activity cycles with a period of two weeks.

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