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The effect of lesions of the limbic system on species-typical and operant behaviors in female mice.

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THE EFFECT OF LESIONS OF THE LIMBIC SYSTEM ON SPECIES-TYPICAL AND OPERANT BEHAVIORS IN FEMALE MICE

A Dissertation Presented

By

Anne Elizabeth Powell

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ABSTRACT

Effect of Lesions of the Limbic System
on Species-Typical and Operant Behaviors
in Female Mice
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Large lesions of the septal region result in both disruption of species-typical behavior and facilitation of operant responding in rodents. To determine the precise anatomical basis for these effects the hippocampal, hypothalamic, and brainstem connections of the septum were selectively lesioned. Lesions to specific septal subareas were also evaluated. Behavior was measured in seven species-typical contexts (sand digging, food hoarding, predatory behavior, wheel running, nest-building, defensive burying, cage playing) and two operant paradigms (VI-60 and active avoidance).

Lesions of the entire septum, lateral septum, medial septum, and medial septum/columns fornix significantly disrupted sand digging, hoarding, nest-building, and to a lesser extent defensive burying. These same lesions facilitated performance on both operant tasks.

In terms of septo-hippocampal connections, lateral fimbria lesions significantly disrupted hoarding and nest-building. Lesions of the postcommissural fornix also disrupted sand digging, hoarding, and nest-building. Damage to dorsal fornix fibers had no significant effect on behavior, whereas medial fimbria lesions disrupted food hoarding only. Habenula lesions had no effect on behavior.

In terms of septo-hypothalamic connections, asymmetrical lesions involving either the medial or lateral preoptic areas significantly disrupted hoarding and nest-building. Lesions of the mammillary bodies disrupted hoarding, nest-building, and defensive burying. Active avoidance behavior was enhanced in all animals with lesions.

Asymmetrical lesions of the septum and ventral tegmental area significantly disrupted nest-building and enhanced responding on a VI task. Asymmetrical lesions of the septum and locus coeruleus significantly impaired hoarding and nest-building.

Wheel running, predatory behavior, and cage playing were unaffected by limbic lesions.

The nature of the species-typical deficits indicates that limbic lesions impair an animal's ability to locate itself in space. Behavior was not so much absent as it was disorganized. Enhanced operant responding may be due to the absence of other incompatible species-typical behaviors.

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CHAPTER I

INTRODUCTION

Lesions of the septal area in rodents produce a constellation of effects known as the septal syndrome. Two of the most noticeable effects include facilitation of operant responding and disruption of species-typical behavior. The goal of this study is to determine a more precise anatomical basis for these effects. As Grossman (1978, p. 234) pointed out, "the task of the investigator of septal functions is complicated by the profusion of fibre systems that originate, terminate, or course through the septal region." Large septal lesions necessarily destroy these connections. A more profitable approach to the problem would be to selectively lesion specific nuclei within the septal area, target structures, and fibers of passage. The present study will utilize this approach to determine the effect of discrete lesions of the limbic system on species-typical behavior and operant responding in the mouse.

Species-Typical Behavior

The species-typical deficits following septal lesions are well established. A review of these effects will be

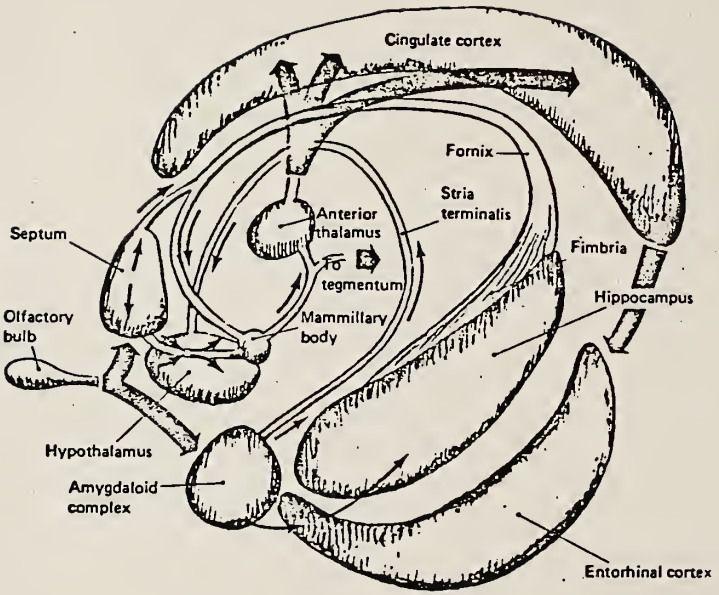
presented, focusing on the specific behaviors that the present study is concerned with. In addition, the effects of other limbic lesions on these behaviors will be discussed. Briefly, the limbic system is composed of the following structures: the hippocampus, septum, amygdala, entorhinal cortex, cingulate gyrus, and parts of the hypothalamus and midbrain (Hamilton, 1976). These can be viewed in the simplified diagram in Figure 1 (from Carlson, 1977). More detail on anatomy will be provided in later sections.

Maternal behavior

Rodents with lesions of the septal area exhibit deficits on several tests of maternal behavior. Carlson and Thomas (1968) found that mice with septal lesions were deficient in nest-building and retrieval tests when compared with control animals. Lesioned animals were inefficient responders; they exhibited the individual components of maternal behavior, but not in proper sequence and they often emitted many unnecessary responses. Slotnick and Nigrosh (1975) also observed disrupted maternal behavior in mice with septal lesions. These animals exhibited striking deficits in retrieval and nest-building tasks, characterized by aberrant behavior sequences. In addition, fewer dams with lesions nursed and only 59% of pups born to septal

Figure 1

A schematic representation of the limbic system (from Carlson, 1977).


Cingulate cortex
Fornix
Stria terminalis
Anterior thalamus
Septum
Fimbria
fo
tegmentum
Hippocampus
Olfactory bulb
Mammillary body
Hypothalamus
Amygdaloid complex
Entorhinal cortex

lesioned mothers survived as compared to 100% born to control animals. Disturbances in delivery, pup's health, nursing, nest-building, and pup-retrieval have also been observed in rats with septal lesions (Fleischer & Slotnick, 1978). These authors attributed the deficits to an inability to organize behaviors with respect to the environment (disruption in spatial organization). Disrupted nest-building has also been observed following septal lesions in the golden hamster (Shipley & Kolb, 1977), ground squirrel (Knight, 1970), and rabbit (Cruz & Beyer, 1972).

Lesions of other limbic structures have also been associated with disrupted maternal behavior. Kimble, Rogers, and Hendrickson (1967) found that bilateral aspiration of the hippocampus produced increased maternal cannibalism, decreased nursing activity, and inferior nest-building and pup retrieval in rats. Kim (1960) also noted decreased nest-building activity in rats with bilateral dorsal hippocampal ablation. Lesioned animals either ignored the material provided for nesting or scattered it over the cage floor. Similarly, Shipley and Kolb (1977) found that hamsters with hippocampal lesions would build nests, but very inefficiently. These animals picked up nesting material and dropped it at random. Terlecki and Sainsbury (1978) observed deficits in the quality of nest-building and retrieval in rats with fimbrial lesions (which

disrupted septo-hippocampal connections). Whereas control rats typically constructed one compact nest, lesioned animals frequently constructed two or more nests. In addition, lesioned animals tended to split pups up between the nests, and were less likely to cover them with bedding. The authors attributed these disturbances to an inability to isolate the critical environmental stimuli that organize behavior (again, disruption of spatial organization). This explanation is remarkably similar to that provided for deficits following septal lesions.

The medial preoptic area-anterior hypothalamus (MPO-AH) has also been implicated in maternal behavior. Marques, Malsbury, and Daood (1979) observed that anterior knife cuts (lateral to MPO-AH) produced significant increases in cannibalism of pups and significant deficits in nest quality and pup retrieval. Animals with posterior cuts (lateral to the ventromedial hypothalamus) exhibited fewer deficits on these tasks. In another study, large lesions of the medial preoptic area, which included part of the anterior hypothalamus, resulted in decreased nursing activity, nest-building, and retrieval (Numan, Rosenblatt, & Komisaruk, 1977). Lesioned animals approached and sniffed pups but did not pick them up and instead engaged in non-pup activities. Numan (1974, p. 749) reported that medial preoptic lesions

resulted in an "almost complete lack of maternal responsivity." Lesioned animals did not build nests or retrieve pups, and only one in ten animals exhibited nursing behavior. These deficits were believed to be due to lateral connections of the medial preoptic area that communicate with the medial forebrain bundle (MFB), limbic forebrain, and brainstem structures. Terkel, Bridges, and Sawyer (1979) noted that knife cuts which severed the dorsolateral connections of the medial preoptic area resulted in reduction or absence of nest-building and retrieval. The authors postulated that the critical fibers were components of the MFB and stria terminalis which link the bed nucleus of the stria terminalis with the preoptic area.

Destruction of the ventral mesencephalic tegmentum, a structure having important limbic connections, also results in disturbances of maternal behavior. This area includes the A10 cell group from which the dopaminergic mesolimbic tract originates, and is considered part of the "limbic midbrain." Gaffori and LeMoal (1979) found that lesions of this area in rats resulted in drastically altered nest-building and nursing, as well as dramatic increases in pup cannibalism. It is curious that lesions of this region also produce other components of the septal syndrome such as hyperreactivity, deficits in spontaneous alternation and passive avoidance tasks, and decreased hoarding. The

authors attributed these disturbances to an inability to organize behavior in time and space.

Numan (1983) has suggested that connections between the medial preoptic area and midbrain structures are important for maternal behavior. He proposed that both the substantia nigra and the ventral tegmental area play a role. Numan suggested that the substantia nigra most likely plays an indirect role, whereas the ventral tegmental area connections appear to be directly involved in maternal behavior that occurs in response to pup stimuli (such as pup retrieval). This descending route most likely goes from the medial preoptic area to the lateral preoptic area to the ventral tegmental area.

From the lesion data presented thus far, it would seem that virtually all components of the limbic system play an important role in maternal behavior. Destruction of the septum, hippocampus, medial preoptic-anterior hypothalamic area, or ventral tegmentum results in altered maternal behavior. In addition, transections of the fimbria and MFB also result in deficits in maternal behavior. However, certain limbic structures do not appear to play a pivotal role in this species-typical behavior. For example, lesions of the amygdala do not produce permanent deficits in maternal behavior. Amygdala-lesioned mice show no

differences from controls in retrieval tasks after the first day of testing and do not build inferior nests (Slotnick & Nigrosh, 1975). Shipley and Kolb (1977) reported that hamsters with damage to the amygdala take longer than normals to initiate nest-building activity, but eventually build good nests. In another study, mice with lesions of the cingulate cortex were slower than controls on retrieval tests, but showed no disturbance in nest-building (Slotnick & Nigrosh, 1975). Carlson and Thomas (1968) also observed that mice with cingulate lesions were only slightly different from control animals in tests of nest-building and pup retrieval. Shipley and Kolb (1977) noted that hamsters with cingulate lesions were slow to build nests, but like animals with amygdala lesions, eventually constructed high quality nests.

Social behavior

A number of investigators have reported that septal lesions alter social behavior in rodents, but the nature of this effect is a topic of much debate. Jonason and Enloe (1971) noted that septal lesions produced large and persistent increases in social cohesiveness, as measured by time spent in physical contact. Poplawsky and Johnson (1973) reported similar results following lesions of the medial but not lateral septum. Large increases in social

behavior were also reported following septal lesions in mice (Booth, Meyer, & Abrams, 1979). The authors noted increases in huddling, investigating, nosing, tail following, sniffing, grooming, and crawling under and over other animals. Sodetz and Bunnell (1970) also found an increase in social investigatory behavior in hamsters with septal lesions.

Poplawsky (1975) attempted to determine which connections of the septum were important for this effect on social behavior. He found that ventral cuts, severing connections with the hypothalamus, produced significant increases in contact time. Anterior cuts (severing olfactory connections), posterior cuts (sectioning fornix, fimbria, stria terminalis, and stria medullaris), and dorsal cuts (severing connections with the cerebral cortex) were ineffective.

With regard to other limbic structures, Kolb and Nonneman (1974) reported that rats with hippocampal lesions spent less time in contact; when physical contact did occur accidentally, lesioned animals squealed and separated. Nonneman and Kolb (1974) noted that cats with hippocampal lesions showed a marked lack of concern for other cats in a conspecific pairing situation. Lesions of the amygdala also produced decreases in social contact in rats (Jonason & Enloe, 1971; Kolb & Nonneman, 1974).

Intraspecies aggression

Septal lesions also disrupt aggressive behavior in rodents, but not in a predictable direction. To some extent the precise effect on agonistic behavior depends upon the species studied and anatomical locus of the lesion. For example, Bunnell, Bemporad, and Flesher (1966) observed an increased number of wins and increased dominance rank in hooded rats with septal lesions. Beatty, Dodge, Traylor, Donegan, and Godding (1982) also observed enhanced play fighting following septal lesions in juvenile rats. Bunnell and Smith (1966), studying the cotton rat, observed no consistent increase in rank among animals with septal lesions. In addition, lesioned animals typically terminated attack sequences early, failed to bite opponents, and if attacked exhibited disorganized flight behavior. Poplawsky and Johnson (1973) found that lesions of the lateral septum resulted in increased aggression, whereas lesions of the medial septum led to enhanced submissive behavior. To further complicate the picture, Lau and Miczek (1977) noted that septal lesions altered attack and defense tendencies in dominant but not subordinate animals.

For other rodent species, the picture is just as confusing. In one study, decreased number of attacks and wins, and increased number of escapes were observed in mice with septal lesions (Slotnick & McMuller, 1972). However,

Booth, Meyer, and Abrams (1979) noted an increase in both attack and flight behavior in mice with septal lesions. Hamsters with septal lesions exhibited significantly more aggression and less submissiveness than control animals (Sodetz & Bunnell, 1970). Shipley and Kolb (1977) reported that septal lesions in hamsters resulted in increased shock-induced aggression, but no change in territorial or inter-male aggression.

Lesions of other limbic structures produce equally perplexing results. Hippocampal lesions in cats resulted in dramatic decreases in aggression as evidenced by lack of piloerection and threat postures in the face of threatening stimuli (Nonneman & Kolb, 1974). Following surgery, all cats with septal lesions were rated as submissive, and in general reacted inappropriately to aversive stimuli (such as a model of a threatening cat). Fimbria-fornix lesions in the guinea pig also resulted in decreased inter-male aggression and decreased rank (Sainsbury & Jason, 1976). These authors attributed the deficit to a disturbance of behavior sequencing, an explanation comparable to that provided for the disruption of maternal behavior seen after limbic lesions. Lesions of the corticomedial but not central or lateral nuclei of the amygdala resulted in decreased frequency of attack behavior (Miczek, Brykczynski,

& Grossman, 1974). Lesions of the overlying piriform cortex and stria terminalis completely abolished aggressive behavior. Miczek and colleagues believed that these effects were mediated by the component of the stria terminalis that communicates with the hypothalamus, not the septum.

In summary, the effect of limbic lesions on intraspecies aggression is far from clear. A major problem in evaluating the effects of limbic lesions on aggression concerns the comparison of studies utilizing different methodologies, different species, and variable location and size of lesions. In addition, a number of these studies failed to consider the role of the lesioned animal's opponent. Conceivably different results could be obtained were the opponent lesioned, intact, dominant, subordinate, socially experienced, naive, and so forth. To their credit, Sodetz and Bunnell (1970) took the nature of the stimulus animal into account and concluded that septal lesions enhance aggression in the hamster.

Interspecies aggression

The effect of septal lesions on interspecies aggression or predatory behavior has primarily been studied by examining muricide, or mouse-killing, in rats. Wallace and Thorne (1978) observed increased incidence of muricide in rats with lesions of the septum. These lesions included the

nucleus accumbens, nucleus of the diagonal band, and the bed nucleus and tract of the stria terminalis. Albert and Brayley (1979) also found increased mouse-killing in rats with lesions ventral to the anterior septum. Animals with lateral septal lesions also increased rate and decreased latency of killing, whereas rats with lesions restricted to the bed nucleus of the stria terminalis only killed more mice than control animals on the first day of testing. Albert, Chew, Dewey, Walsh, Lee, and Ryan (1981) noted that rats with lesions of the ventral anterior septum killed twice as many rat pups as natural killer rats with sham lesions. Lesions of the medial accumbens nucleus (which is frequently classified as part of the septal region) also enhanced the intensity of mouse-killing and post-kill attacks on dead prey (Albert, Walsh, Ryan, & Siemans, 1982).

Lesions of other limbic structures have similar effects. Lesions of the medial hypothalamus resulted in extremely low attack latency and intense lunging attacks, but only in response to a second mouse (Albert et al., 1982). In addition, lesioned animals bit the mice more frequently after the kill and even remained fastened to the prey as it was lifted out of the cage by the experimenter. Rats with medial hypothalamic lesions also responded more vigorously to a dead mouse and a cotton wad saturated with mouse odor, as compared to control animals. In all cases

the comparison control animal was a spontaneous killer rat. In another study, Albert and Brayley (1979) noted that rats with medial hypothalamic damage killed with a 10 to 20 second latency, whereas only one of thirteen control rats killed mice. Furthermore, rats with hypothalamic lesions killed in both home cage and novel environments.

Opposite effects have been found with lesions of the amygdala. Karli, Vergnes, Eclancher, Shimitt, and Chaurand (1972) noted that bilateral lesions of the amygdala abolished mouse-killing in rats. These authors suggested that the ventromedial amygdala normally plays an excitatory role in muricide which is mediated by the diffuse ventral amygdalofugal pathway communicating with the ventral tegmentum. However, other investigators found no effects of amygdala lesions on muricide (Miczek et al., 1974). Animals that killed before surgery also killed after surgery, and nonkillers remained nonkillers. Kolb and Nonneman (1974) also observed no significant effects of amygdala lesions on muricide.

Predatory behavior in mice has also been studied. Mice attack crickets and other insects, and as Butler (1973) pointed out, predatory behavior is probably more common than inter-male aggression. Thomas (1969) noted that efficient predators are also more aggressive in intraspecies

situations. The effect of limbic lesions on predatory behavior in mice has received little attention.

Exploratory behavior

Exploratory behavior is also altered by lesions of the septal region. Hermann and Lubar (1976) noted an enhancement of certain exploratory responses in rats with septal lesions. However, these authors noted that whereas 80% of the field was used prior to surgery, activity was restricted to 30% of the arena following surgery. Booth, Meyer, and Abrams (1979) observed a significant decrease in exploratory behaviors following septal lesions. Corman, Meyer, and Meyer (1967) noted that rats with septal lesions were less active in an open field, and took longer than controls to enter the field immediately after surgery. Jonason and Enloe (1971) reported that septal lesioned rats engaged in stereotypical social responses to the "almost total exclusion of exploratory activities."

Looking at more specific exploratory responses, Kemble and Nagel (1975b) observed decreased rearing under deprived and ad libitum conditions following lesions of the septal region in rats. This depression of rearing persisted 76 days after surgery. Wallace and Thorne (1978) also noted that lesions of the septum and its ventral connections produced significant decreases in rearing behavior. In

addition, Kemble and Nagel (1975a) found deficits in sniffing following septal lesions. Gray (1971) observed that medial septal lesions in particular produced a reduction or disruption of sniffing, as well as disturbances in hippocampal theta rhythm which normally accompanies the bilateral synchronous vibrissal movements that constitute sniffing.

In terms of other limbic structures, Gotsick (1969) noted that rats with hippocampal lesions showed increased responsivity to a novel environment. Myhrer (1975) also reported increased locomotor activity in an open field in rats with lesions of hippocampal field CA_1 or the fimbria. Rats with amygdala lesions also showed enhanced exploratory behavior in the open field, and destruction of the amygdala reversed the exploratory deficit produced by septal lesions (Schwartzbaum & Gray, 1966).

Hoarding behavior

Hoarding behavior is another species-typical behavior that is affected by septal lesions. Wishart, Brohman, and Mogenson (1969) reported that animals with septal lesions hoarded half the number of pellets that control animals hoarded. This difference occurred only under food deprivation conditions; very few animals (lesioned or not) hoarded food under ad libitum conditions. Knight (1970)

also observed a dramatic decrease in food hoarding following septal lesions in hooded rats. This deficit was attributed to a disturbance in ordering various components of a behavior sequence. Hamsters with lesions of the septal area also showed striking deficits in food hoarding (Shipley & Kolb, 1977). Lesioned animals picked up pellets but dropped them before reaching the end of the hoarding alley, left poorly stacked pellets in the home cage, and in general emitted behavior lacking in efficiency and coordination. Animals with lesions also took significantly longer than control animals (38.8 vs. 5.4 seconds) to initiate hoarding. the authors also attributed this deficit to an inability to properly sequence chains of behavior.

Shipley and Kolb (1977) also noted hoarding impairments in hamsters with hippocampal lesions. Animals with lesions were slower to initiate hoarding and hoarded fewer pellets than control animals. Wallace and Tigner (1972) noted that rats with hippocampal lesions hoarded fewer pellets than sham lesioned animals, but this difference was not significant. They stated that this deficit occurred only when rats were not given pretrial feedings, resulting in increased eating (to the exclusion of hoarding) during the trial. The sequence of behavior was altered by hippocampal lesions, however. Lesioned animals frequently ran to the pellet bin and back to the home cage without picking up a

pellet. Contrary to these findings, Wishart and colleagues (1969) noted that rats with bilateral hippocampal lesions hoarded twice the number of pellets that controls hoarded.

Lesions of the ventral mesencephalic tegmentum in rats also resulted in a loss of food hoarding activity (Simon & LeMoal, 1978). These animals took significantly longer to exit the home cage and exhibited increased frequency of nonproductive activity (returning to the home cage without food). Control animals typically hoarded for 15 minutes, ate, hoarded all remaining pellets, and then ate or slept. Lesioned rats were completely disorganized in attempts at hoarding. They wandered around the apparatus, moved food biscuits from place to place repeatedly, and ate numerous meals of short duration. As Stinus et al. (1978, p. 294) observed, "rats were unable to link each behavioral unit to produce an adaptive response."

Lesions of the amygdala or cingulate cortex failed to impair hoarding to a noticeable degree (Shipley & Kolb, 1977).

Digging and defensive burying

Digging or burrowing is another species-typical behavior that is disrupted by septal lesions, but it has remained relatively unstudied to date. Wilsoncroft (1970) noted that a normal mouse can dig up to 12,000 grams of sand

in 45 minutes. Sand digging, like hoarding, is more likely to occur under food-deprived conditions (Fantino & Cole, 1960). Wilsoncroft (1975) has also observed that the odor of the sand is important. Mice will dig more scented sand (own or other scent) than clean sand.

A related activity observed in rats is defensive burying. This is a stereotyped response to shock that consists of kicking and pushing cage bedding over a shock source (usually a prod mounted in the cage wall). In one study, shocked control animals displayed a considerable amount of burying compared to unshocked subjects (Gray, Terlecki, Treit, & Pinel, 1981). Septal lesioned animals exhibited no defensive behavior; this behavior was eliminated in both shocked and unshocked animals with septal lesions. Gray and colleagues found that posterior septal lesions were more effective in suppressing the burying response than anterior lesions. The authors postulated that perhaps posterior lesions destroyed septo-hippocampal connections that are critical for this behavior. In a possibly related study, Knight (1970) noted that ground squirrels with septal lesions were less likely to dig burrows than control animals.

Wheel running

A final behavior to examine is wheel running, which is

also disrupted in animals with septal lesions. Its classification as a species-typical behavior is based on previous work in this laboratory and studies demonstrating that it is not simply a measure of activity (Bolles, 1975; Eayres, 1954). In fact, Gray and McNaughton (1983) point out that while septal lesions disrupt wheel running, motor activity in general is enhanced. Douglas and Raphelson (1966) also observed decreased wheel running activity in rats with septal lesions. Lesioned animals tended to run in bursts whereas control animals ran more continuously. Depressed wheel running was also observed in rats with septal lesions by Nielson, McIver, and Boswell (1965). Clody and Carlton (1969) observed significant decreases in wheel running in rats with lesions of the medial septum.

Capobianco and Hamilton (1976) attempted to discern which connections of the septum mediated this effect. These authors found that both fornix lesions (destroying dorsal connections of the septum) and medial forebrain bundle lesions (severing ventral connections) increased wheel running. In addition, destruction of a nearby structure, the nucleus accumbens (septi) also resulted in facilitation of wheel running (Lorens, Sorenson, & Harvey, 1970). Furthermore, lesions of the diagonal band and bed nucleus of the stria terminalis also resulted in increased wheel

running (Capobianco & Hamilton, 1976). These findings are difficult to reconcile with the data on large septal lesions and depressed wheel running.

Summary

In summary, lesions of the septal area in rodents produce clear deficits in the following species-typical behaviors: maternal behavior, exploratory behavior, food hoarding, digging or burying, and wheel running. The only behaviors that are enhanced by septal lesions are social contact and perhaps predatory behavior. The effect on intraspecies aggression is unclear; certainly behavior is altered by lesions, but the direction of this change remains in dispute.

Conditioned Behavior

Operant responding

Lesions of the septal region produce consistent increases in operant responding on a number of instrumental tasks. In fact, in a review of a large number of studies, Gray and McNaughton (1983) report that 87 studies found enhanced responding following septal lesions, 35 found no effect, and only 3 found impaired responding. Facilitation of responding on continuous reinforcement schedules following septal lesions has frequently been observed

(Grossman, 1978; Harvey & Hunt, 1966; Hothersall, Johnson, & Collen, 1970; Lorens & Kondo, 1969). Septal lesions also enhance responding on fixed ratio schedules (Grossman, 1978; Hothersall et al., 1970). Elevated rate of responding has also been noted following septal lesions on interval schedules (Beatty & Schwartzbaum, 1968; Ellen & Powell, 1962; Harvey & Hunt, 1965; Lorens & Kondo, 1969; Pubols, 1966; Ross & Grossman, 1975; Sodetz & Koppell, 1972) and DRL (differential reinforcement for low rates of responding) schedules (Braggio, 1976; Carlson, El-Wakil, Standish, & Ormond, 1976; Ross & Grossman, 1975). Over-responding on interval and DRL schedules actually represents impaired or inefficient performance, which Grossman (1978) described as an inability to withhold non-rewarded responses.

A number of authors have attempted to determine which connections of the septum were critical for the elevated responding. Carey (1969) reported that anterior but not posterior septal lesions resulted in elevated responding on a fixed ratio schedule. In fact, animals with posterior lesions actually responded less for water reinforcement than control animals. Braggio (1976) observed overresponding on a DRL schedule following lesions of the septum, hippocampus, dorsomedial thalamic nucleus, and dorsoventral thalamic nucleus. Lesions of the rostral basal cortex, olfactory tubercle, central tegmental nucleus, and cingulate gyrus

resulted in response rates that were not significantly different from rates for control animals. Grossman (1978) observed disinhibition of responding on DRL and FI schedules following lesions of the anterior septum, dorsal fornix, and fimbria. Grossman also reported elevated responding during extinction, FI, and DRL schedules following lesions of the hippocampus. He concluded that the critical connections for this effect were those connecting the medial septum and hippocampus.

Active avoidance responding

Lesions of the septal area also facilitate acquisition and performance of a two-way shuttlebox task (active avoidance conditioning) according to a number of investigators (Capobianco, McDougall, & Foster, 1977; Carlson, 1970; Dalby & Shuttlesworth, 1978; King, 1958; Lubar, Hermann, Moore, & Shouse, 1973; Ross & Grossman, 1975). This is a very reliable finding: Gray and McNaughton (1983) noted that 50 studies reported facilitated active avoidance responding following septal lesions, whereas none reported no effect or impaired responding. Animals with septal lesions also tend to make more intertrial responses or spontaneous crosses (Carlson, 1970; Dalby & Shuttlesworth, 1978; Ross & Grossman, 1975). Ross and Grossman (1975) noted that animals with septal lesions

may learn to avoid shock faster than intact subjects, but actually respond inefficiently on the task. For example, normal animals will typically avoid or shuttle only in the presence of the conditioned stimulus (CS), whereas lesioned animals emit many responses in the intertrial interval prior to the CS. Blatt (1976) noted that the facilitation of avoidance responding is only observed if these intertrial responses are punished (shocked). Blatt argued that the punishment of intertrial responses suppresses responding in normal animals, while failing to affect lesioned subjects; hence the "facilitation" seen following septal lesions is really a "nonsuppression." A number of authors have claimed that the facilitation is due to a lesion-induced impairment of "ineffective species defense reactions" such as freezing or jumping. Intact animals freeze or jump in response to shock, which interferes with shuttling, and hence contributes to ineffective avoidance conditioning (Blatt, 1976; Poplawsky, 1978).

Attempts have been made to determine which connections of the septum are important for this effect on active avoidance behavior. However, Grossman (1978) concluded that destruction of virtually any aspect of the septum or nearby tissue results in facilitation of conditioned avoidance responding. In support of this, Ross, Grossman, and

Grossman (1975) observed enhanced responding following large septal lesions, dorsal knife cuts (severing the fornix, stria medullaris, and stria terminalis), and ventral knife cuts (damaging the MFB, primarily). These authors explained the effects as being due to interruption of a cholinergic reticulo-septal-hippocampal circuit.

Lesions in other limbic structures have similar effects. Facilitation of conditioned avoidance responding has been observed following hippocampal lesions (Capobianco et al., 1977; Douglas, 1967), fornix transections (Capobianco et al., 1977), and lateral fimbria lesions (Myhrer, 1975b). In fact, Chozick (1983) noted that animals with hippocampal lesions in general show decreased freezing in situations where defensive postures are normally elicited (as in a novel environment or in response to a predator or pain). This may explain why they learn to shuttle in the two way avoidance situation more readily than control animals.

Facilitated avoidance conditioning has also been reported following lesions of the nucleus accumbens (Lorens et al., 1970), stria terminalis (Myhrer, 1975a), locus coeruleus or dorsal noradrenergic bundle (McNaughton & Mason, 1980), stria medullaris/habenula, and interpeduncular nucleus (Wilson, Mitchell, & VanMoesen, 1972). Facilitation was not observed following lesions of the amygdala (King,

1958) or postcommissural septum (Santacana, DeAzcarate, & Munoz, 1975).

Explanation for effects on conditioned behavior

One explanation for this enhanced responding on operant tasks is that animals with septal lesions simply do not have other behaviors available in their repertoire to engage in during operant conditioning tasks. A number of investigators have noted that normal animals will distribute responses more efficiently on temporally defined schedules (such as DRL or FI) by utilizing what is called "mediating" behavior (Laties, Weiss, Clark, & Reynolds, 1965). Mediating behavior is usually some form of species-typical behavior that is emitted between operant responses. Laties and colleagues observed that tail nibbling appeared to have discriminative properties for spacing lever presses on a DRL schedule. Laties, Weiss, and Weiss (1969) also observed collateral behaviors (nibbling, licking, gnawing) in rats placed on a DRL schedule; when this mediating behavior was thwarted, emission of the operant increased and number of reinforcers earned decreased. It is possible that animals with septal lesions overrespond on operant tasks because they are unable to engage in other "mediating" or "time-filling" behaviors.

Evidence for this explanation comes from studies that

have shown that septal lesioned animals are able to suppress their responding if encouraged to engage in other tasks. Slonaker and Hothersall (1972) provided lesioned rats with soft pine blocks and cardboard strips following regular DRL training. Animals that interacted with these materials significantly improved their DRL performance by suppressing responding. A .93 correlation was observed between amount chewed and DRL efficiency, suggesting that the mediating behaviors were responsible for the improvement. Of course, intact animals provided with the "mediation" exposure also improved their DRL performance. In fact, intact animals were always better than lesioned animals, even when provided with the mediating tasks.

Similarly, it has been suggested that septal lesioned animals show facilitated avoidance conditioning because they fail to demonstrate the normal species-typical response to shock, which is freezing (Blatt, 1976). Freezing is incompatible with the target response of shuttling or avoiding, which is why intact animals perform poorly. Hence, the lack of species-typical behaviors following septal lesions can explain both the operant overresponding and the enhanced active avoidance performance.

Table 1 summarizes the effects of limbic lesions on species-typical behavior and operant responding.

Table 1

EFFECTS OF LIMBIC LESIONS ON A VARIETY OF BEHAVIORS

	Lesion Location					
Behavior	SEPT	HPPC	HYPO	VTA	LC	AMYG
Species-Typical						
Maternal	-	-	0	-	-	?
Social	+	-	-	+	?	?
Aggression Intraspecies	+/-	-	-	?	?	?
Aggression Interspecies	+	?	-	+	?	?
Exploratory	-	+	+	?	?	-*
Hoarding	-	-	?	?	-	?
Digging	-	?	?	?	?	?
Wheel Running	-	+	+	+	?	?
Conditioned						
Operant	+	+	?	?	?	0*
Active Avoidance	+	+	0	+	?	+*

\+ refers to response increase
\- refers to response decrease
0 refers to no change
? refers to insufficient data
* from McNaughton & Mason, 1980

SEPT=Septal Area
HPPC=Hippocampus
HYPO=Hypothalamus Preoptic Area
VTA=Ventral Tegmental Area
LC=Locus Coeruleus

Anatomy of the Limbic System

The composition of the limbic system depends upon who is doing the defining, as noted by Hamilton (1976). Isaacson (1974) described two components of the limbic system: the inner ring (hypothalamus, amygdala, septum, and hippocampus) and the outer ring of transitional cortex (entorhinal cortex, retrosplenial cortex, cingulate cortex, and periamygdaloid cortex). Hamilton (1976) also included certain midbrain structures and even neocortex. The various structures of the limbic system are connected by a large number of fiber bundles, many of which pass through the septal region. Isaacson (1974, p. 45) stated that "all parts (of the septum) receive massive input from a variety of limbic regions."

The septal area

Before attempting to describe these various connections, it is important to have a clear sense of where the septal area is located and how it has been subdivided. Swanson and Cowan (1976) place the septum ventral to the corpus callosum, dorsal to the decussation of the anterior commissure, medial to the lateral ventricles, rostral to the fimbria and ventral hippocampal commissure, and caudal to the frontal and infralimbic cortex. The septal area has been subdivided in a number of ways; the approach utilized

by Swanson and Cowan (1976, 1979) will be utilized here. The lateral division of the septum is composed of a dorsal zone, a ventral zone, and an intermediate zone based on cytoarchitecture. The medial division is composed of the medial nucleus and the nucleus of the diagonal band. The septofimbrial and triangular septal nuclei make up the posterior division. The ventral division consists of the bed nucleus of the stria terminalis, and is crossed by the anterior commissure and stria medullaris. This division is bounded ventrally by the medial preoptic area/anterior hypothalamus and rostrally by the nucleus accumbens. The divisions of the septal area can be viewed in Figures 2a and 2b.

Fibers leave the septum for a number of structures as summarized below. The major efferents terminate in the hippocampus, hypothalamus, amygdala, thalamus, and habenula. The septum also has important connections with brainstem structures, most notably the ventral tegmental area. Fibers enter the septum from virtually every structure that receives septal efferents. The major source of these afferent connections are the hippocampus, hypothalamus, amygdala, and habenula. In fact, Hamilton (1976) has estimated that at least half of the fibers terminating in the septum originate from the hippocampus and hypothalamus. The septum also receives noradrenergic input from the locus

Figure 2a

Cross section through the anterior septum.
Numbers refer to mm from bregma.

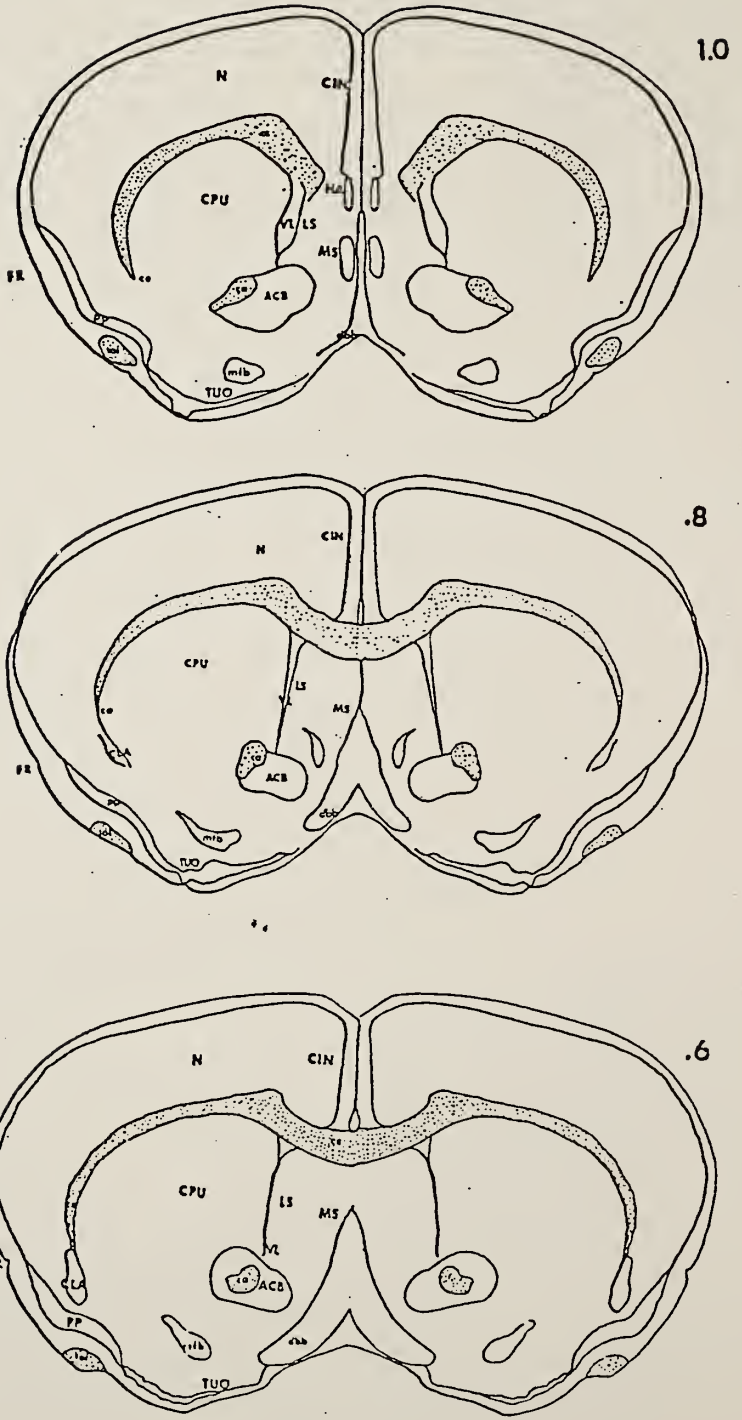

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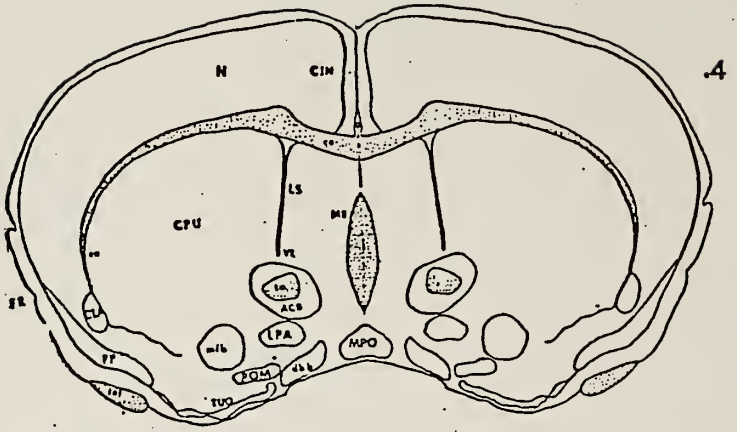
Figure 2b

Cross section through the posterior septum.
Numbers refer to mm from bregma.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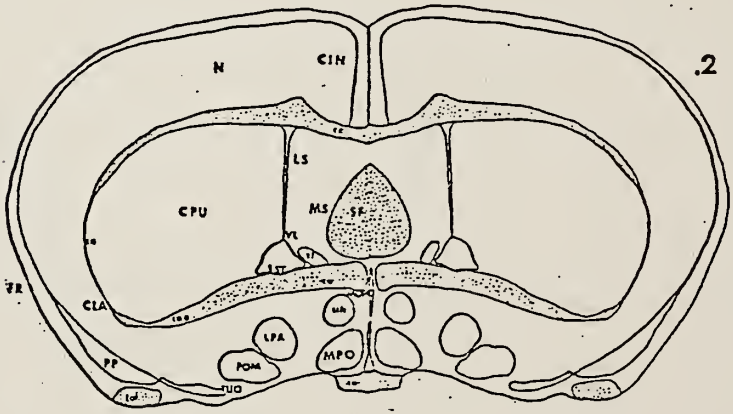
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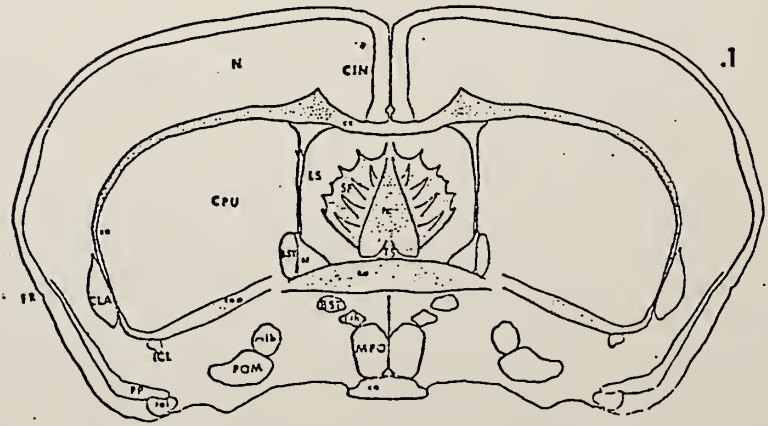
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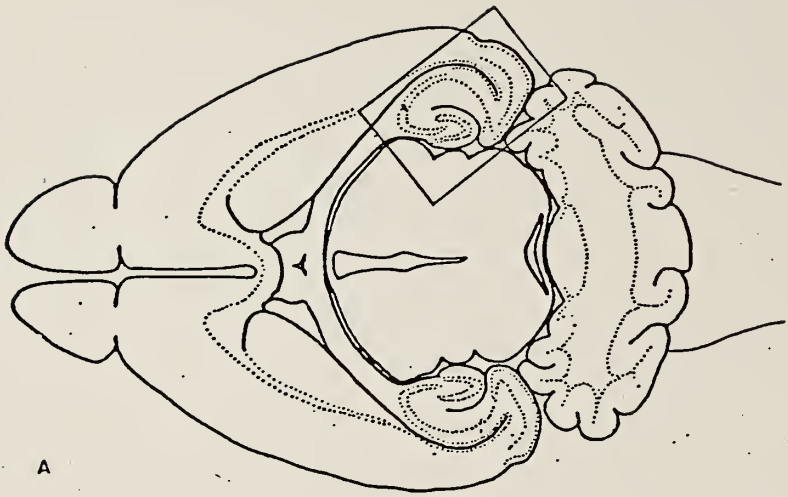
coeruleus, dopaminergic fibers from the ventral tegmental area, and serotonergic input from the raphe. This grossly simplified summary of septal connections will be expanded upon in the following paragraphs.

Hippocampus

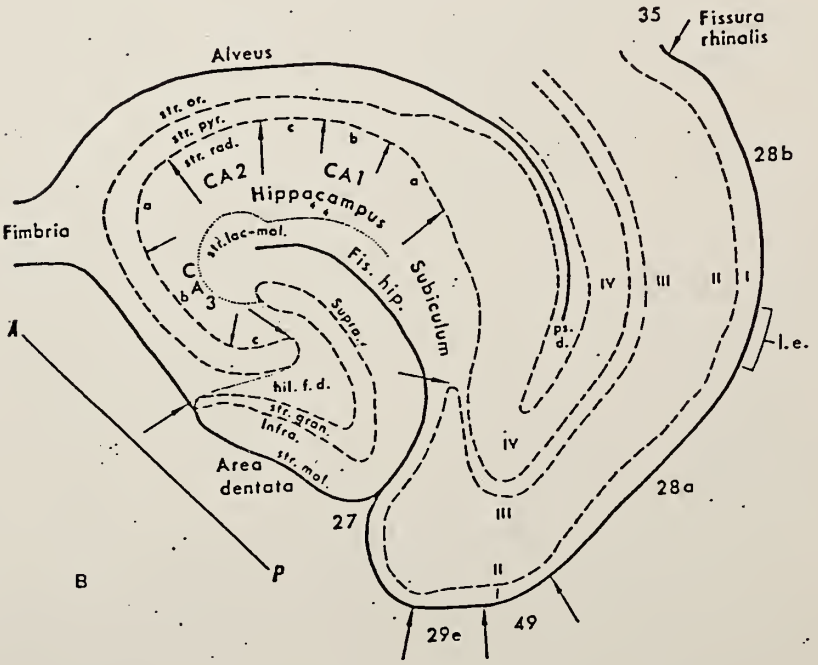
The hippocampus is an important limbic structure which projects to the septum and receives fibers in return from the septal area. The precise nature of these connections has been extensively studied in rodents. Before presenting the details of these connections, it is important to describe the various components of the hippocampal complex. The complex is composed of the hippocampus proper, the dentate gyrus, and the subiculum, as can be seen in Figure 3 (from Angevine, 1975). Most references made here will be to the hippocampus proper, which has been described by Hamilton (1976, p. 55) as a "complex layered structure that appears to have been rolled into a tube like a jelly roll." Based on cytoarchitecture, the hippocampus has been divided into four CA fields (CA representing cornu Ammonis or Ammon's horn). CA_1 is composed of pyramidal cells that are densely packed; this field is often referred to as the superior region. CA_3, or the inferior region, is characterized by a less compact arrangement of pyramidal cells. CA_2 is a small region between CA_1 and CA_3, and CA_4 is found before the

Figure 3

A: Location of hippocampus, and B: Actual horizontal section of mouse hippocampus (from Angevine, 1975).



A


35
Fissura rhinalis
Alveus
str. or.
str. pyr.
str. rad.
CA2
CA1
c
b
a
Hippocampus
Fimbria
str.lac-mol.
Fis. hip.
Subiculum
28b
IV
III
II
I
l.e.
Ps. d.
hil. f. d.
str. gran. Infra.
str. mol.
Area dentata
27
28a
29e
49
B
p

hippocampal-dentate gyrus transition. Pyramidal cells are important because they are the source of axons which leave the hippocampus via the fornix for diencephalic and other telencephalic structures (Isaacson, 1974). According to Hamilton (1976), CA_1 and CA_2 are largely represented in the dorsal hippocampus, whereas CA_3 and CA_4 are found in the descending horns of the ventral hippocampus.

Hamilton (1976, p. 53) describes the fornix system as a "bundle of fibers which forms partially reciprocating connections between hippocampus, septum, hypothalamus, thalamus, and midbrain." The fornix is composed of two major components: the fimbria and the dorsal fornix. Dorsal fornix fibers arise mainly from pyramidal cells in CA_1. Dorsal fornix fibers originating in anterior hippocampal regions descend in the postcommissural columns of the fornix and terminate in the anterior thalamus and medial and lateral mammillary nuclei. According to Hamilton (1976), there is no septal termination. Dorsal fornix fibers arising from posterior levels of the hippocampus descend in the precommissural fornix to innervate the entire extent of the septal complex. However, Meibach and Siegel (1977a) observed dorsal fornix fibers originating from both anterior and posterior hippocampal levels, with termination primarily in the lateral septum. These authors also noted that the subicular complex sends fibers by way of the dorsal

fornix to the dorso-lateral septum. The dorsal fornix also carries fibers from the medial septum-diagonal band area to the hippocampus. Swanson and Cowan (1979) followed these fibers via autoradiography into CA_3 and the subicular complex, whereas Meibach and Siegel (1977a) noted bilateral projections to all CA fields, the dentate gyrus, and subicular cortex.

The fimbrial system is composed of a number of fiber bundles. According to Hamilton (1976), fimbrial fibers originate in CA_3 and CA_4 and travel in the precommissural fornix to terminate in the dorsolateral septum and diagonal band. A number of investigators have confirmed that CA_3 sends bilateral fimbrial projections to the lateral septum (Chronister & DeFrance, 1979; Meibach & Siegel, 1977a; Swanson, 1978; Swanson & Cowan, 1979). Swanson and Cowan (1979) also observed that the dorsal hippocampus sends to the dorsolateral septum and the ventral hippocampus projects to the ventrolateral septum. The ventral fimbria carries fibers originating in the anterior and posterior dorsal hippocampus, the medial fimbria collects from posterior levels, and the extreme lateral fimbria carries fibers from the anterior ventral hippocampal formation (Meibach & Siegel, 1977a). The fimbria also carries fibers originating in the medial septum/diagonal band region which terminate in

CA_3 (Swanson & Cowan, 1979) or possibly all CA fields and the dentate gyrus (Meibach & Siegel, 1977b). This septo-hippocampal connection has been confirmed by autoradiography, HRP studies, and AChE staining (Kuhar, 1975; Lynch, Rose, & Gall, 1978). AChE stains are used because this septo-hippocampal connection is primarily cholinergic.

The above description of connections between septum and hippocampus is largely based on work with rats. In cats, it is clear that the diagonal band (vertical limb) contributes fibers to all CA fields of the dorsal and ventral hippocampus (Krayniak, Weiner, & Siegel, 1979, 1980). In addition, the dorsal hippocampus sends fibers via the dorsal fornix to the medial septum/diagonal band region, whereas the ventral hippocampus sends fibers via the lateral fimbria to the lateral septum and diagonal band. Posterior hippocampal regions contribute fimbrial fibers to both the medial and lateral septum (Siegel, Edinger, & Ohgami, 1974). These septo-hippocampal projections have also been observed in the gerbil and rabbit (Siegel et al., 1974). Krayniak, Siegel, Meibach, Fruchtman, and Scrimenti (1979) observed markedly different projections in the squirrel monkey. Using the HRP method, these investigators noted that all hippocampal fields project to the caudal septum, whereas the subicular complex contributes fibers to the rostral lateral

septum.

In summary, it appears that in rodents the hippocampus projects via the dorsal fornix (from CA_1 primarily) and fimbria (via CA_3 primarily) to the lateral septum. The lateral septum in turn projects to the medial septum/diagonal band region (Swanson & Cowan, 1979). The medial septum/ diagonal band (MS/DB) complex in turn projects by way of the dorsal fornix and fimbria to the hippocampus, completing the loop.

Hypothalamus

Given that the hypothalamus borders on the ventral septum it is not surprising that these two structures are extensively connected. The hypothalamus stretches from the preoptic area to the mammillary bodies, and is divided into a periventricular region, a medial zone (where most of the nuclei are), and a lateral division (Isaacson, 1974).

The major pathway connecting the septum and the hypothalamus is the medial forebrain bundle (MFB) which contains descending and ascending fibers. As Hamilton (1976) observed most MFB connections are reciprocal in nature. A major portion of the input to the hypothalamus originates in the hippocampus and septum. According to Hamilton, the hippocampus sends fibers in the precommissural fornix to the septal area where some terminate and others

pass through. Other fibers originate in the septum and join these passing fibers to form the septohypothalamic tract which enters the MFB for distribution to hypothalamic and downstream structures. The hypothalamus and brainstem structures in turn project via the MFB back to the septum.

The major septal source of MFB fibers is the bed nucleus of the stria terminalis (BNST), according to Swanson and Cowan (1979). Fibers originating in the BNST terminate along the entire extent of the hypothalamus, including the preoptic and mammillary complexes (Swanson, 1978; Swanson & Cowan, 1976). In addition, the lateral septum projects to the lateral preoptic area, anterolateral hypothalamus, and mammillary complex (Meibach & Siegel, 1977b; Swanson & Cowan, 1976, 1979). The lateral septum also projects heavily to the medial septum which along with the diagonal band sends fibers to the preoptic area, lateral and dorsomedial hypothalamus, and medial mammillary nucleus (Swanson & Cowan, 1976, 1979).

The hypothalamus projects back to the septum as follows. The major return loop is formed by fibers leaving the lateral preoptic area and lateral hypothalamus for termination in the medial septum/diagonal band complex (Swanson 1978; Swanson & Cowan, 1976, 1979). There is also some input from the ventromedial hypothalamus to the septal complex (Swanson & Cowan, 1976) but in general there are

fewer connections as one moves caudally in the hypothalamus (Raisman, 1966).

Amygdala

The septum also communicates extensively with the amygdala. The amygdala is a collection of nuclei located in the anterior portions of the temporal lobes. According to Isaacson (1974), the number of individual nuclei ranges from 5 to 22 (depending on classification scheme). The major concern here will be with the corticomedial division and the basolateral division. Although the amygdala's major connections are with the hypothalamus, fibers are sent to the septum via the stria terminalis.

The stria terminalis fibers connect the bed nucleus of the stria terminalis (BNST) in the ventral septum to the corticomedial division of the amygdala (Krettek & Price, 1978; Swanson, 1978; Swanson & Cowan, 1976). According to Meibach and Siegel (1977b), the horizontal and vertical limbs of the diagonal band both send fibers to the basolateral division of the amygdala. In return, the amygdala sends fibers via the stria terminalis to the BNST and lateral septum (deOlmos, 1972; Isaacson, 1974). These fibers originate mainly in the corticomedial division of the amygdala, although the basolateral area does contribute some fibers (Hamilton, 1976; Lammers 1972). Raisman (1966) also

observed connections from the amygdala and pyriform cortex to the diagonal band complex. According to Hamilton (1976), these connections are made by the ventral amygdalofugal pathway.

Thalamus and habenula

The thalamus and septum are also interconnected. According to Powell and Hines (1974), the anterior thalamus is a "focal point" in the limbic system where fibers from the hippocampus, septum, mammillary bodies, and cingulate gyrus converge. According to Powell and Hines (1975), the medial septum projects to the anteroventral, anteromedial, and anterodorsal thalamic nuclei via the stria terminalis and fornix. The dorsolateral septum has similar connections with the anterior thalamic nuclei, and the ventral septum communicates via the MFB and stria terminalis with the dorsomedial nucleus (Powell & Hines, 1975). Meibach & Siegel (1977b) also observed connections between the medial septum/diagonal band region and the dorsomedial and anteromedial thalamic nuclei. The anterior thalamus projects back to the septum indirectly via the subiculum and entorhinal areas, which are connected with the hippocampus and septum (Swanson, 1978). According to Swanson (1978), the BNST and lateral septum both send fibers to the paraventricular and parataenial nucleus of the thalamus;

Swanson and Cowan (1979) also reported medial septum-parataenial connections. These septo-thalamic connections are by way of the stria medullaris (Swanson & Cowan, 1979).

The posterior septum heavily innervates the habenular nuclei which are found in the epithalamus. The septofimbrial nucleus communicates with the ipsilateral medial habenular nucleus, whereas the triangular septal nucleus projects bilaterally to both the medial and lateral habenula (Swanson, 1978; Swanson & Cowan, 1976, 1979). The ventral septum (BNST) also projects bilaterally to the medial habenula via the stria medullaris (Swanson & Cowan, 1976, 1979). The medial septum/diagonal band region also sends some fibers to the medial and lateral habenula (Meibach & Siegel 1977b; Swanson & Cowan, 1979). In summary, as Herkenham and Nauta (1977) noted, the postcommissural septum projects mainly to the medial habenular nucleus via the stria medullaris, whereas the ventral septum projects to both nuclei. According to Swanson (1978), the medial habenula projects back to the septal complex. However, the major output of the habenula is to the interpeduncular nucleus and reticular formation (Hamilton, 1976).

Brainstem connections

There are many brainstem inputs to the septal region.

These include the dorsal noradrenergic bundle from the locus coeruleus, the ventral noradrenergic bundle, the ventral dopaminergic pathway originating near substantia nigra, and a serotonergic system from the raphe (Hamilton, 1976; Segal & Landis, 1974). According to McNaughton and Mason (1980), the medial septum/diagonal band region is the main recipient of fibers from the locus coeruleus; in fact, this fiber system may account for approximately 50% of the noradrenalin found in the septum. Striking similarities between the behavioral effects of locus coeruleus damage and septal or hippocampal damage suggest that this is an important limbic structure. Lindvall (1975) observed a rich catecholaminergic innervation of the lateral septum which he attributed to fibers originating in the A10 cell group in the mesencephalon. These ascend to form what has been termed the mesolimbic pathway. In rats, the region in the ventral mesencephalon is called the ventral tegmental area of Tsai; and it communicates with the lateral septum, nucleus accumbens, and olfactory tubercle (Deniau, Thierry, & Feger, 1980). Similar connections between the ventral tegmental area and the septum have been observed in the squirrel monkey using HRP techniques (Krayniak, Meibach, & Siegel, 1981).

Although not emphasized, the septum also projects to a number of brainstem structures. The medial septum sends

fibers to the ventral tegmental area and the raphe; the lateral septum also communicates with the ventral tegmental area (Swanson & Cowan, 1979). The BNST projects to the central tegmentum, central gray, and ventral tegmental area (Swanson & Cowan, 1976, 1979). The majority of the descending (and ascending) fibers travel in the MFB.

Cortical areas

Cortical areas have also been implicated in limbic system function. Hamilton (1976) considered the entorhinal cortex to have direct impact on limbic circuitry. The medial and lateral entorhinal areas project to the dentate gyrus and CA_3 in the hippocampus by way of the medial and lateral perforant pathways (Hamilton, 1976; Lynch, Rose, & Gall, 1978). Field CA_3 in turn sends fibers back to the entorhinal cortex. Hence, the entorhinal cortex is intimately connected to the septo-hippocampal system. Cingulate cortex has important connections with specific thalamic nuclei (Hamilton, 1976), and according to some investigators it also communicates with subicular and entorhinal areas (Chronister & White, 1975). Cingulate cortex is considered by some to be a "transitory link" between limbic structures and neocortex (Vinogradova, 1975).

Summary

In summary, the septum sends multiple efferents to and receives extensive afferents from the hippocampus, hypothalamus, and amygdala. Important connections also occur between the septum and the thalamus, habenula, and certain cortical areas. Brainstem input from the locus coeruleus and ventral tegmental area may also play a critical role in limbic functioning. According to Hamilton (1976), the limbic system is involved in the modulation of sensory, motor, and homeostatic systems. Hamilton suggested that limbic structures play pivotal roles in allowing the organism to survive in a complex environment (via emission of appropriate species-typical behaviors). When damage to limbic structures occurs, these survival behaviors should also be disrupted. In addition, the limbic system appears to be essential for the inhibition of otherwise "prepotent" responses (Hamilton, 1976). Disruption of limbic functioning should result in disinhibition of such responses as may be seen in overresponding on operant tasks. The aim of the present study is to determine which limbic connections/structures are particularly important for producing these effects on species-typical and operant behaviors.

CHAPTER II

METHOD

General Method

The following information on subjects, surgery, lesion rationale, histology, and data analysis applies to all nine experiments. More specific descriptions of apparatus and procedure will be provided for each individual experiment.

Subjects

The subjects for these experiments were 124 female B6D2F_1 mice obtained from Jackson Laboratory, Bar Harbor, Maine. Animals were between two and eight months old at the start of testing. All subjects participated in all nine experiments. Approximately half of the animals were tested in the experiments in the order presented here, with appropriate rest intervals between experiments. The remaining animals received the reverse order of experiments, with the exception that cage playing was always tested after the animals had been trained on the operant task, for reasons described later. The various groups are described under the section on lesion rationale. There were 19 lesion groups and a no lesion control group. No fewer than 4 animals were tested in each lesion group; the precise number varied from group to group and ranged from 4 to 12.

Animals were allowed free access to food and water unless otherwise indicated. A 12 hour light/12 hour dark cycle was used, with lights coming on at approximately 7:00 a.m. Ambient temperature ranged from 65 to 75 degrees Fahrenheit.

Surgery

Lesions were produced by anesthetizing mice with sodium pentobarbital (75 mg/kg body weight). Animals were then placed in a Kopf No. 900 stereotaxic apparatus, using a Slotnick headholder during surgery (Slotnick, 1972). Lesions were made by passing current from a Grass Instrument radio-frequency lesion maker through stainless steel insect pins insulated with enamel except at the tip. Animals were allowed to recover for approximately one week prior to the beginning of testing. Stereotaxic coordinates for the lesions are provided in Table 2.

Lesion rationale

The rationale of the bilateral lesions (to be described) was straightforward. Lesions were made in critical areas of the limbic system and behavior was evaluated. If behavior was altered in significant ways, one could infer that the lesioned structure plays a role in that behavior. The changes in behavior observed after lesions could be attributed to a number of factors; including loss of excitatory input to an area, release from inhibition, and

Table 2

STEREOTAXIC COORDINATES OF TARGET STRUCTURES

Lesion	Anterior-Posterior	Dorsal-Ventral	Lateral*
Septum	+.9	-3.5	.4
Lateral Septum	+.9	-3.4	.6
Medial Septum	+.9	-3.7	0
Habenula	-1.2	-2.5	.2
Fornix Columns	+.4	-3.7	0
Dorsal Fornix	-.3	-2.2	.2
Medial Fimbria	-.5	-2.3	.4
Lateral Fimbria	-.5	-2.7	1.6
Medial Preoptic	+.7	-5.1	.5
Lateral Preoptic	+1.0	-4.8	1.2
Mammillary Bodies	-2.4	-5.6	.3
Ventral Tegmental Area	-2.7	-5.0	.6
Locus Coeruleus	-5.3	-4.3	.5

*Note: In the case of bilateral lesions, the coordinates should read + and - .4; in the case of unilateral lesions, the coordinates would be either +.4 or -.4, depending on whether the lesion was made on the right or left.

so forth. A major problem with lesion studies is that damage is seldom restricted to the target tissue; fibers of passage are often damaged. In addition, it is difficult to determine which connections are important because destruction of a single structure affects many fiber systems (both inputs and outputs of the structure). Hence, the present study utilized the technique of asymmetrical lesions to disconnect the septum from the structures that it communicates with. For example, it is known that the septum communicates with the medial preoptic area. To determine the importance of this connection in the behaviors of interest, the septum was lesioned on one side and the medial preoptic area was lesioned on the opposite side. Because the connections are almost entirely ipsilateral, this procedure effectively disconnects the septum and the medial preoptic area. This procedure is preferred over bilateral lesions of the medial preoptic area because such lesions would destroy not only its connections with the septum, but other fiber bundles leaving, entering, or passing through the medial preoptic area. An additional advantage of asymmetrical lesions is the likelihood that such lesions will not drastically alter other functions of the target structures. In many cases, an intact structure on one side of the brain (for example, the left medial preoptic area) is able to support the activities previously

supported by the left and right components of the structure (for example, both medial preoptic areas). This assumption should, of course, be assessed by performing unilateral lesions (for example, of the septum and medial preoptic area on the same side). The experimenter predicted that while unilateral lesions might alter behavior, this effect will be significantly smaller than that produced by asymmetric lesions. The specific lesions that were performed are described in the following paragraphs.

Septal lesions

To assess the effects of lesions of the septum on behavior, the following lesions were produced. Large bilateral lesions of the septal area were made; these lesions typically destroyed the medial and lateral septum, the diagonal band, and most of the posterior septum (SEPT, N=5). Unilateral septal lesions were also produced, to assess the ability of the remaining septal tissue to support behavior (UNIS, N=7). In addition, selective lesions were made of the medial septum (MEDS, N=6) and lateral septum (LATS, N=7). Finally, some lesions intended for the medial septal area also caused damage to the columns of the fornix; these lesions were grouped together for analysis (MSCF, N=5).

Hippocampal connections

To assess the impact of lesions of the connections between the septum and hippocampus, the following lesions were produced. According to the literature, the dorsal fornix and fimbria are the major fiber bundles connecting these two structures. Hence, bilateral lesions of the dorsal fornix (DSFX, N=6), medial fimbria (MEFI, N=5), and lateral fimbria (LAFI, N=4) were made. Asymmetric lesions were not produced because contralateral connections exist between the septum and the hippocampus. In addition, to assess the importance of postcommissural fornix fibers, lesions to the columns of the fornix were also produced (COFX, N=8). Finally, although the habenula is not a part of the septo-hippocampal system, bilateral lesions of this structure were produced (HABN, N=6). The habenula is included with the hippocampal lesions because of its proximity to the hippocampal formation and its extensive connections with the posterior septum.

Hypothalamic connections

To assess the importance of the connections between the septum and hypothalamus, the following lesions were made: asymmetrical medial preoptic area and septum (AMPO, N=7), asymmetrical lateral preoptic area and septum (ALPO, N=7), unilateral medial preoptic area and septum (UMPO, N=6), and

unilateral lateral preoptic area and septum (ULPO, N=4). The latter two groups were included as unilateral control groups. Finally, lesions of the mammillary bodies (including the supramammillary region) were produced (SMMB, N=8). The mammillary bodies comprise a major target of the postcommissural fornix.

Brainstem connections

Brainstem connections were assessed by making the following lesions: asymmetrical ventral tegmental area and lateral septum (AVTA, N=6) and asymmetrical locus coeruleus and septum (ALCR, N=5). Appropriate unilateral control groups were also included: unilateral ventral tegmental area and lateral septum (UVTA, N=5) and unilateral locus coeruleus and septum (ULCR, N=5).

Comments

The "intact" control group included animals that had not received surgery (NORM, N=12). Unequal numbers of animals were used across groups for the following reason. A minimum of four animals were tested in each group, and additional animals were tested only to clarify ambiguous results. It was not deemed necessary or ethical to use additional animals if the results were clear and consistent across animals within a group.

Histology

Mice with lesions were sacrificed and perfused through the heart with 10 ml of a .9% saline solution, followed by 10 ml of 10% formalin in .9% saline. The brain was removed from the skull and placed in formalin for at least 24 hours, followed by another 24 hours in a 30% sucrose solution. Tissue was sliced on a rotary microtome at a thickness of 40 micrometers. A minimum of 24 slices was retained in order to cover the entire extent of the lesion. The slices were mounted on slides, dried overnight, and stained with cresylecht violet. Lesions were evaluated by determining the degree of destruction to target structures/fibers. Also considered was the extent to which non-target adjacent structures were damaged.

Data analysis

Each dependent measure was analyzed with a one-way analysis of variance for independent groups, the main factor being lesion location. In addition, all possible post-hoc comparisons between groups were made using a modified Neumann-Keuls procedure for groups of unequal size. Finally, performance on the various dependent measures was correlated (across all animals) to determine whether deficits on one task (such as nest-building) tended to occur in combination with deficits on another task (such as food

hoarding).

All behavioral measures were recorded by the principal investigator and four assistants. While recording data the observers were blind to the lesion status of the animals.

Experiment 1: Sand Digging

This experiment examined the effect of limbic lesions on the species-typical behavior of sand digging. Although pilot studies suggested that septal lesions suppress sand digging, the anatomical correlates of this behavior have not been examined in the literature.

Method

Apparatus. The apparatus for sand digging consisted of a Plexiglas and sheet metal chamber (23 cm x 23 cm x 26 cm high). A vertically-oriented hollow plastic tube was mounted in the corner of each chamber. This tube was 43 cm high and 3.8 cm in diameter, and was cut diagonally at the lower end. The bottom edge of the tube rested on a 10 cm x 10 cm square of sheet metal, which was mounted on a floor of hardware cloth. An inverted half gallon plastic milk container with the bottom removed was attached to the top of the plastic tube. The tube was filled with sand, which was allowed to flow out over the metal plate. The milk container was filled halfway with sand and served as a

reservoir. The sand that was dug by the animal fell through the grid floor and was funneled into a collecting basin. A rough sketch of the apparatus appears in Appendix A.

Procedure. Prior to testing, the tube and bottle in each chamber were filled with about 3500 grams of sand. The sand was a mixture of clean and scented sand (all sand that was dug was strained to remove feces and recycled). Each animal was placed in the chamber for 30 minutes. Sand that the animal pushed into the collecting basin was removed and weighed to the nearest gram. If the animal dug the entire amount of sand available, it received a maximum score of 3500 grams. Animals were tested on four consecutive days, for one 30 minute trial per day. Average amount dug per day was used in the data analysis.

Experiment 2: Food Hoarding

The effect of limbic lesions on food hoarding was evaluated in this experiment. Pilot studies in this laboratory have recorded deficits in food hoarding from animals with lesions of the septum, fimbria, nucleus accumbens, stria terminalis, mammillary bodies, habenula, ventral tegmental area, and locus coeruleus. The literature on limbic lesions shows that destruction of the septum, hippocampus, and ventral tegmental area produce hoarding deficits.

Method

Apparatus. The hoarding apparatus consisted of a clear yellow plastic tubular alleyway and adjacent box. The alleyway (33 cm long x 5 cm diameter) and attached box were connected to the animal's home cage via a hole cut into one end of the home cage. The home cage (28 cm x 18 cm x 13 cm high) was a clear Plexiglas container filled with a layer of wood shavings as bedding. A cage top of metal bars and water bottle were also present. The hoarding box was filled with 100 grams of Big Red dog food pellets (obtained from Agway, Inc.) of relatively uniform size and shape (100 grams is approximately equal to 165 pellets). A diagram of this apparatus can be found in Appendix B.

Procedure. Animals tested in this experiment were maintained on a restricted diet (5 grams/day) of Purina rat chow and Big Red dog food for five days prior to testing. Previous work has shown that animals exhibit more hoarding when partially food deprived (Wishart et al., 1969).

Thirty minutes before each trial animals were fed two pieces of dog food (about one gram) to prevent them from spending the entire trial eating rather than hoarding. Any uneaten portion was removed at the beginning of the trial (animals usually ate the entire portion of food provided).

At the start of a trial, hoarding boxes were filled with pellets and were connected to the home cage. The

animal's behavior was then observed for four, five minute periods. The number of crossings from home cage to hoarding box or hoarding box to home cage was tabulated. In addition, after each five minute period, the number of pellets carried into the home cage was noted. Throughout the observation, information was recorded on how the animal hoarded the pellets (mouth carrying, kicking with hind paws, nose pushing, and so forth). Finally, at the end of 20 minutes, the following measures were taken: number of pellets deposited in the home cage, number of pellets remaining in the tube, number of pellets left in the hoarding box, and number eaten.

Hoarding alleyways and boxes were removed and washed after each trial. In addition, pellets deposited in the home cage were removed. Animals were then given their daily allotment of food. Hoarding was tested for four days, one 20 minute trial per day. The following measures were subjected to statistical analysis: number of pellets in home cage, number in tube, total hoarded (number in home cage plus half the number in the tube to reflect partial hoarding), and number of crosses in the alleyway. A hoarding efficiency index was also calculated as the total number of pellets hoarded divided by the number of crossings.

Experiment 3: Predatory Behavior

The effect of limbic lesions on interspecies aggression was evaluated in this experiment. Previous work in this laboratory has shown that mice with septal lesions are very effective as cockroach killers (Carlson, unpublished observations). The present experiment examined predatory behavior directed toward crickets, and is included in the battery of tests because it is the only species-typical response that seems to be enhanced following septal lesions.

Method

Apparatus. Predatory behavior was studied in the animal's home cage, a Plexiglas chamber (28 cm x 18 cm x 13 cm high) equipped with wood chip bedding, Purina rat chow, and a water bottle. The prey utilized in this experiment were house crickets obtained from Exotic Fish and Pet World, Inc.

Procedure. A cricket was dropped into the animal's home cage, within the animal's field of vision. An empty Plexiglas cage was turned upside down on top of the animal's home cage to prevent the cricket from escaping. The mouse's behavior was observed and recorded for 10 minutes, or until it killed the cricket. Latencies to first contact, bite, attack, and kill were recorded. If an animal failed to kill in 10 minutes, the cricket was left in the home cage

overnight and another test was undertaken on the following day. Only one trial was deemed necessary as previous work in this laboratory revealed considerable day-to-day reliability in this measure. In this experiment, the average latency was taken as the score for data analysis.

Experiment 4: Wheel Running

The influence of limbic lesions on wheel running was examined in this experiment. Pilot studies indicated that wheel running decreased following lesions of the septum and medial preoptic area, with slight increases following habenula lesions. Because wheel running fluctuates across the estrous cycle (Morin, Fitzgerald, & Zucker, 1977; Wade, 1976), it was desirable to maintain animals under constant hormonal influence (progesterone). Hence, wheel running was measured on the same days that nest-building was measured in order that the animals be exposed to the progesterone released from the implanted pellet.

Method

Apparatus. The apparatus consisted of a 28 cm x 18 cm x 13 cm high Plexiglas basin with a similar basin (inverted) serving as a cover. Inside this chamber was a 17 cm diameter steel wire running wheel which was connected to a magnetic switch to record wheel revolutions. Paper toweling

was placed under the wheel to absorb urine and feces and was replaced after each trial.

Procedure. The animal was placed in the chamber and allowed to run in the wheel for 30 minutes. Wheel running was measured for five consecutive days, and average number of revolutions per day was used for data analysis.

Experiment 5: Nest-building

This experiment examined the effect of limbic lesions on nest-building in non-ovariectomized females maintained under constant hormonal conditions (progesterone). Progesterone is known to stimulate nest-building in nonpregnant female mice (Lisk, Pretlau, & Friedman, 1969). Furthermore, this behavior normally occurs during gestation when progesterone levels are high (Carlson, 1980). Preliminary studies have shown that nest-building is disrupted by lesions of the septum, fimbria, and hippocampus. In addition, the literature suggests an important role for both the preoptic area and the ventral tegmental area in nest-building.

Method

Apparatus. Animals were tested for nest-building in the home cage, a Plexiglas container measuring 28 cm x 18 cm x 13 cm high. A thin layer of wood shavings was spread on

the floor of the cage, and a lid held a water bottle and Purina rat chow. Each animal was provided with one strand (1.5 cm diameter) of a 13 cm length of Manila rope.

Also required for this experiment were pellets of progesterone which were prepared by heating the substance (obtained from Sigma Chemical Company) on wire loops. The pellets weighed approximately 25 mg.

Procedure. Prior to the start of testing, progesterone pellets were implanted subcutaneously between the scapulae under ether anesthesia. Animals were allowed to recover for two days. A piece of rope was placed in the home cage on the first day and remained there for the observation period of five consecutive days. Each day the quality of the nest was rated on a 5 point scale: 0 = no rope shredded, 1 = some rope shredded but no nest formed, 2 = most rope shredded and rudimentary nest formed, 3 = all rope shredded to form an adequate but not fully formed nest, and 4 = all shredded into a well shaped rounded nest (after Carlson & Thomas, 1968). Also taken into consideration was whether the animal built more than one nest or utilized home cage bedding (in addition to rope) to construct a nest.

Vaginal smears were taken on all animals to ensure that the progesterone pellet had the intended hormonal effect. If the progesterone was not successful in maintaining the

animal in diestrus, based on the results of the smear, the pellet was removed and a new pellet was implanted.

The rating achieved on the fifth day of nest-building was the score used in the statistical analysis.

Experiment 6: Defensive Burying

The effect of limbic lesions on defensive burying was evaluated in this experiment. Pilot studies and experiments by Gray et al. (1981) indicated that lesions of the septum abolish burying that is directed toward an aversive stimulus.

Method

Apparatus. The apparatus for defensive burying was a 28 cm x 18 cm x 13 cm deep Plexiglas cage filled with sand to a height of 5 cm. A similarly sized cage was used as a cover to prevent escape during the trial. Two wooden dowels (4.5 cm x 2.2 cm diameter) were mounted on the long chamber wall, 3.2 cm from the corners and 5.5 cm above the chamber floor. Holes were drilled into one of the dowels and plastic tubing was inserted into the center of the dowel. This tubing was attached to a reservoir of compressed air (50 lb/in^2). A hand switch operated an electric valve in the tubing to release the air from the storage tank into the line. The resulting air blast occurred in the vicinity of

the dowel and proved to be an adequate aversive stimulus (determined by pilot studies). The other dowel in the chamber was a control dowel and did not serve as the source of any aversive stimulation. This arrangement was employed to measure whether the animal was digging in response to an aversive stimulus or simply to bury an object (Pinel & Treit, 1978). A timer and thumb switch to operate the timer were also used. The apparatus is schematically represented in Appendix C.

Procedure. The apparatus was filled with 5 cm of sand that was levelled out beneath the dowels. The reservoir was filled with air to the appropriate pressure and the animal was placed into the chamber. When the animal approached or made contact with the target dowel (source of aversive stimulus), the hand switch was depressed. This action operated the valve, releasing a blast of air through the holes in the dowel. Following the air blast, the animal remained in the apparatus for 15 minutes. During this time the experimenter recorded duration of burying movements toward the target dowel or the control dowel. At the end of the trial, the height of the highest pile of sand and its distance from the target dowel was measured (as suggested by Pinel & Treit, 1978, 1979). The same was done for the control dowel. Finally, a burying index was created by dividing the height of the sand pile by the distance from

the dowel. This index and the duration of burying for both dowels was subjected to statistical analysis.

Experiment 7: Cage Playing

In this experiment, cage playing was evaluated in mice with limbic lesions. Previous work in this laboratory has shown that this behavior almost never occurs in animals with septal lesions. This particular measure of play has not been described in the literature, but it was considered a valuable measure of species-typical behavior in the present study.

Method

Apparatus. Each subject was observed in the home cage, a 28 cm x 18 cm x 13 cm deep Plexiglas basin with a cover of metal bars approximately 1 cm apart. A water bottle was also available.

Procedure. Recording of cage playing was accomplished by momentarily observing each animal every 15 seconds for 10 minutes to see if cage playing was absent or present. If the animal was clinging to the bars of the lid with all paws off the cage floor, a positive score was made on the data sheet for that animal. A maximum of 40 cage playing counts could be observed per session. Cage playing was observed for 10 minutes a day for 10 consecutive days. Animals were

maintained on a deprivation schedule (3.5 gm per day) for the duration of the experiment, as previous work in this laboratory has demonstrated that this is required to achieve adequate levels of cage playing. Cage playing occurs much less frequently under ad libitum conditions. Cage playing was always measured following performance of the operant task (usually 30 minutes after the animal had responded on the VI-60 second schedule). The total number of cage playing episodes across the 10 day period was the score used for statistical analysis.

Experiment 8: Responding on a Variable Interval Schedule

This experiment examined the effects of limbic lesions on responding on a variable interval-60 second (VI-60) schedule of reinforcement. Previous work in this laboratory has shown facilitation of responding on this task following lesions of virtually any subdivision of the septal region.

Method

Apparatus. Animals were tested in an operant chamber enclosed in a sound-proof box. Each chamber measured 15 cm x 15 cm x 24 cm high with Plexiglas walls and ceiling and a grid floor. Each chamber was equipped with a food dispenser that delivered 20 mg Noyes pellets into a cylindrical Plexiglas tube that was mounted on one of the walls. A

photocell was mounted in the base of the tube and a light was situated above the tube. Responses were recorded by the photocell when the beam of light was broken, usually by a poke of the animal's head into the tube. Responses and number of reinforcers earned were recorded by a computer or programming equipment.

Procedure. Animals were tested on a VI-60 schedule. During acquisition, responding was initially maintained on a VI-5 schedule, followed by VI-20, VI-40, and finally VI-60 schedules. Animals were moved from one schedule to the next when they had earned at least 10 reinforcers on the current schedule. Responding on VI-60 was recorded for 10 consecutive days, each session lasting 20 minutes. Animals were maintained on a restricted diet (3.5 grams of pigeon pellets plus approximately 10 Noyes pellets per day) for the duration of the experiment. Data subjected to statistical analysis included average number of responses, average number of reinforcers, and days to reach VI-60.

Experiment 9: Two-Way Active Avoidance Behavior

This experiment investigated the effect of limbic lesions on performance of a two-way shuttlebox task. Preliminary studies showed that enhanced shuttlebox performance reliably follows lesions of the septal region.

Method

Apparatus. The shuttlebox was composed of two compartments (each 13 cm x 15 cm x 42 cm high) which were separated by a partition of pressed hardboard. A 5.2 cm x 6.5 cm door was cut into this partition to allow movement from one compartment to the next. The back of the chamber was made of pressed hardboard, the far sides of sheet metal mounted on pressed hardboard, and the front and ceiling of clear Plexiglas. Each ceiling was fitted with a light that flashed during the trial and served as the conditioned stimulus (CS). The grid floors in the chamber were constructed of stainless steel rods, mounted 0.6 cm apart. The grid was connected to a seven-line shock scrambler, which delivered a 60-cps square pulse of 350-400 microamps. This shock served as the unconditioned stimulus (US). All responses were recorded by a computer or programming equipment.

Procedure. The animal was placed into one of the compartments (the dark, "safe" one) and a button was depressed, signaling the computer to set up the first of 50 massed avoidance trials. At the start of the trial, the light flashed (CS) in the compartment containing the animal and was followed five seconds later by the shock (US) if no avoidance response was made. The trial was terminated when the animal crossed into the adjacent compartment. Crosses

with a latency of less than five seconds were defined as successful avoidances. During the intertrial interval (which averaged 40 seconds) spontaneous crosses into the adjacent chamber were recorded. These crosses were punished because the shock (and light) remained on in the adjacent compartment between trials. The computer recorded latency to cross on each of the 50 trials, number of successful avoidances and average latency for blocks of 10 trials, a grand mean latency, and number of spontaneous crossings. The total number of avoidances, average latency across all 50 trials, and number of spontaneous crosses were the scores utilized in the data analysis.

C H A P T E R I I I

RESULTS

General Comments

The results of each experiment will be presented separately. Within each experiment, the various lesion groups will be organized into the following clusters for analysis. One cluster, the septal group, consists of the following lesion groups: NORM (intact controls), UNIS (unilateral septal lesions), SEPT (bilateral septal lesions), LATS (lateral septal lesions), MEDS (medial septal lesions), and MSCF (combined medial septal/columns fornix lesions). Another cluster, the hippocampal group, consists of the following groups: NORM, UNIS, SEPT, COFX (columns fornix lesions), MEFI (medial fimbria lesions), LAFI (lateral fimbria lesions), DOFX (dorsal fornix lesions), and HABN (habenula lesions). The third cluster, the hypothalamic group, consists of the following: NORM, UNIS, SEPT, SMMB (mammillary bodies and supramammillary region), AMPO (asymmetrical medial preoptic area and septum), UMPO (unilateral medial preoptic area and septum), ALPO (asymmetrical lateral preoptic area and septum) and ULPO (unilateral lateral preoptic area and septum). The final cluster consists of the brainstem group as follows: SEPT,

UNIS, SEPT, AVTA (asymmetrical ventral tegmental area and lateral septum), UVTA (unilateral ventral tegmental area and lateral septum), ALCR (asymmetrical locus coeruleus and septum, and ULCR (unilateral locus coeruleus and septum). In each cluster post hoc comparisons were made between the lesion groups and the intact control animals (NORMS), animals with large bilateral septal lesions (SEPT), and animals with unilateral septal lesions (UNIS).

Experiment 1: Sand Digging

Septal group

As can be seen in Figure 4, lesion status had a significant effect on the amount of sand dug by animals in a 30 minute period ($p < .001$). Post hoc tests revealed that normal animals dug significantly more sand than animals with lesions in any part of the septal region ($p < .05$). Although animals with unilateral septal lesions dug more sand than other lesioned animals, this difference was not significant.

Hippocampal group

As can be seen in Figure 5, lesion status had a significant effect on amount of sand dug ($p < .01$). Animals with lesions of the dorsal fornix dug the most sand, followed by normal animals and animals with habenula

Figure 4

Septal Group: The effect of lesion status on sand digging (abbreviations explained in text).

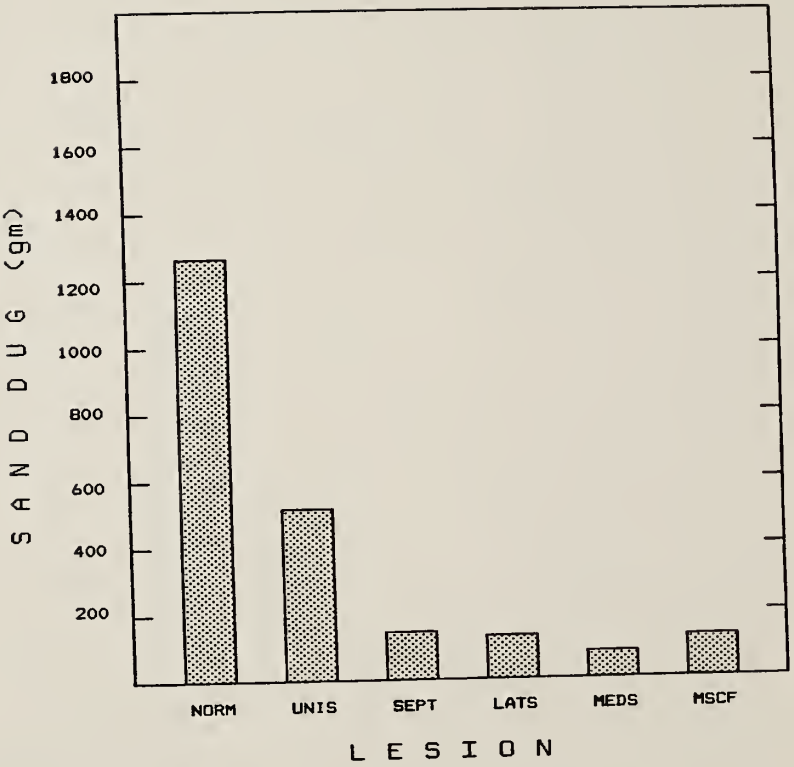
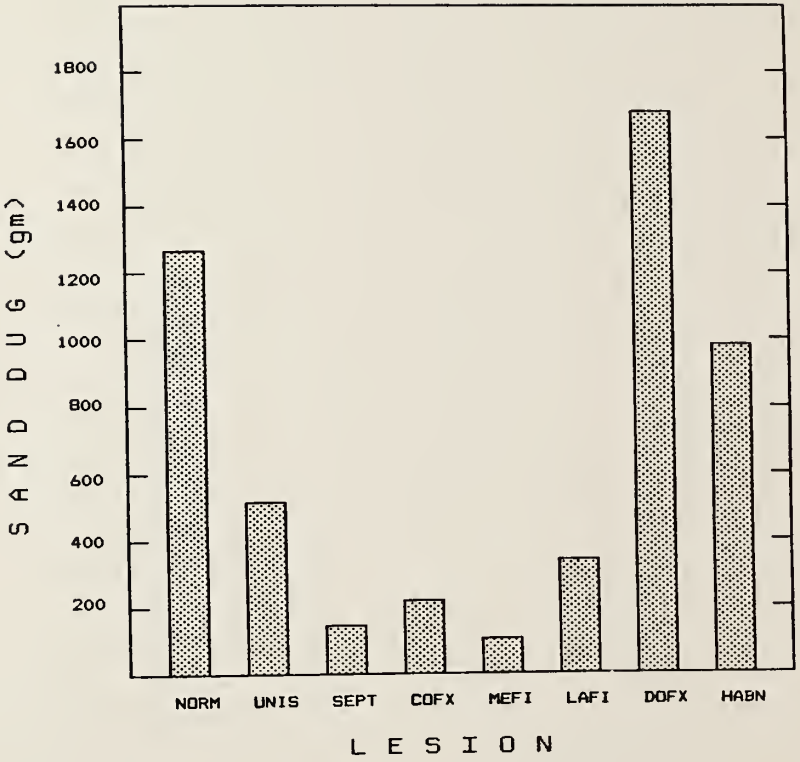

1800
1600
1400
1200
1000
800
600
400
200
SAND DUG (gm)
NORM
UNIS
SEPT
LATS
MEDS
MSCF
LESION

Figure 5

Hippocampal Group: The effect of lesion status on sand digging.


SAND DUG (gm)
1800
1600
1400
1200
1000
800
600
400
200
NORM
UNIS
SEPT
COFX
MEFI
LAFI
DOFX
HABN
LESION

lesions. Lesioning either the fimbria or the columns of the fornix suppressed sand digging, indicating the importance of certain hippocampal connections. Post hoc analyses revealed that animals with dorsal fornix lesions dug significantly more sand than animals with lesions of the columns fornix, septum, and medial fimbria ($p < .05$). In addition, normal animals dug significantly more sand than animals with columns fornix lesions ($p < .05$). Other comparisons failed to reach significance because of large within group variability.

Hypothalamic group

The effect of lesion status on amount of sand dug was not significant for the hypothalamic group. While it is apparent from Figure 6 that normal animals dug more than lesioned animals, and animals with septal lesions dug less than all other animals, these differences were not statistically significant.

Brainstem group

As seen in Figure 7, there was a significant effect of lesion status on amount of sand dug ($p < .05$). Lesions of the ventral tegmental area had no effect on sand digging, whereas both unilateral and asymmetrical lesions involving the locus coeruleus disrupted digging. Asymmetrical locus coeruleus lesions suppressed digging as much as bilateral

Figure 6

Hypothalamic Group: The effect of lesion status on sand digging.

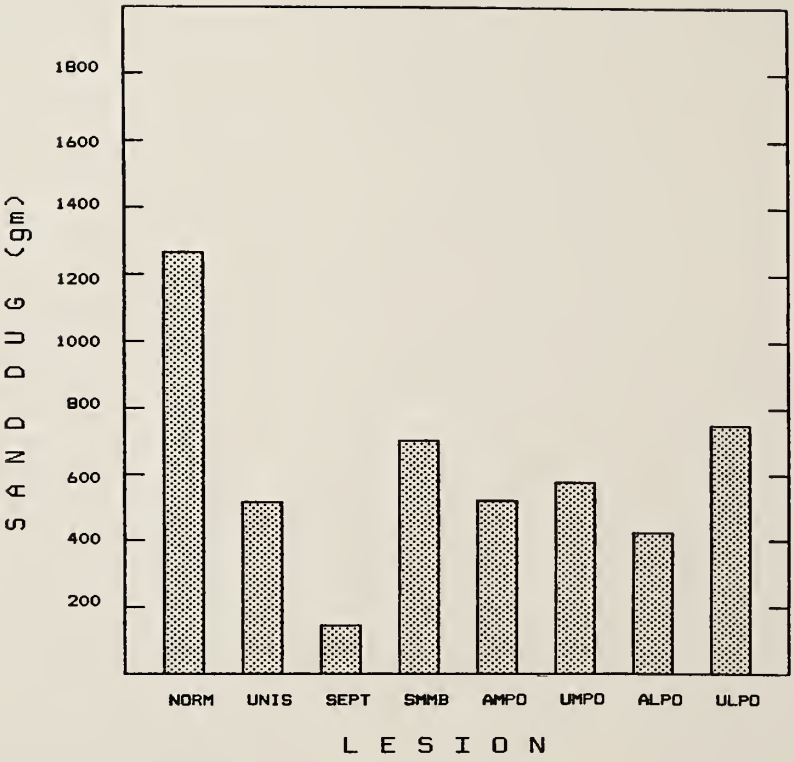
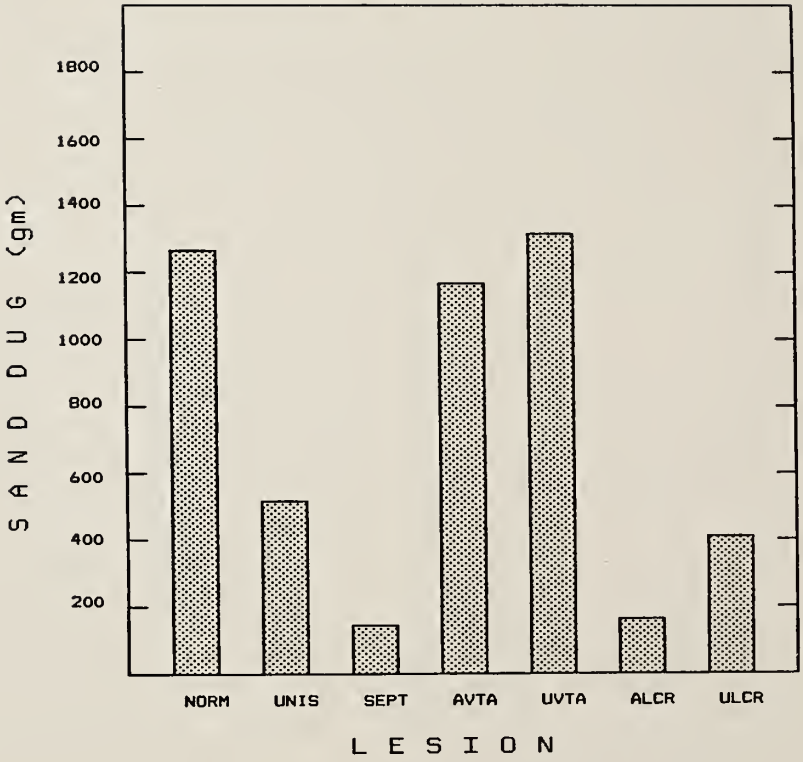

1800
1600
1400
1200
1000
800
600
400
200
S A N D D U G (gm)
NORM
UNIS
SEPT
SMMB
AMPO
UMPO
ALPO
ULPO
L E S I O N

Figure 7

Brainstem Group: The effect of lesion status on sand digging.


SAND DUG (gm)
1800
1600
1400
1200
1000
800
600
400
200
NORM
UNIS
SEPT
AVTA
UVTA
ALCR
ULCR
LESION

septal lesions did, whereas comparable deficits were seen in the unilateral locus coeruleus and unilateral septal groups. These findings point to the importance of connections between the septum and locus coeruleus for the species-typical behavior of sand digging.

Statistical analyses are summarized in Table 3.

Table 3

ANALYSIS OF VARIANCE FOR SAND DIGGING

Septal Group

Source	MS	df	F	p
Lesion	2075450.00	5	6.44	.001
Error	322187.00	36		

Hippocampal Group

Source	MS	df	F	p
Lesion	2275390.00	7	3.81	.01
Error	597659.00	45		

Hypothalamic Group

Source	MS	df	F	p
Lesion	923565.00	7	1.55	NS
Error	595933.00	48		

Brainstem Group

Source	MS	df	F	p
Lesion	1708700.00	6	2.99	.05
Error	570800.00	38		

Experiment 2: Food Hoarding

Septal group

As can be seen in Figure 8, lesion status had a significant effect on number of pellets hoarded ($p < .001$). Post hoc analyses reveal that normal animals hoarded significantly more pellets than animals with lesions in any part of the septal region ($p < .05$). While animals with unilateral septal lesions hoarded more pellets than animals in the other lesion groups, this difference was not significant.

Furthermore, as is apparent from Figure 9, lesion status had a significant effect on number of crosses made between home cage and hoarding box ($p < .001$). Post hoc analyses revealed that animals with lesions of the lateral septum or medial septum/columns fornix made significantly more crosses than normal animals ($p < .05$). Furthermore, animals with lesions of the lateral septum crossed more frequently than animals with medial septal lesions.

To evaluate how efficient animals were at hoarding food pellets, an index was calculated as the total number of pellets hoarded divided by the number of crosses. This score is essentially the average number of pellets hoarded per cross. Figure 10 shows the dramatic and significant difference in efficiency index across groups ($p < .001$).

Figure 8

Septal Group: Effect of lesion status on total number of pellets hoarded.

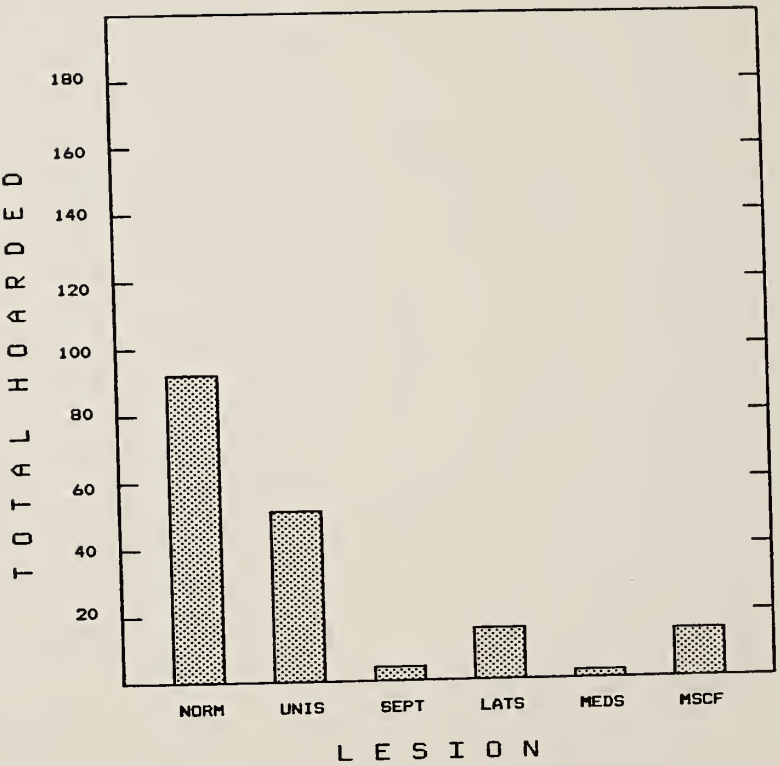

TOTAL HOARDED
180
160
140
120
100
80
60
40
20
NORM
UNIS
SEPT
LATS
MEDS
MSCF
LESION

Figure 9

Septal Group: Effect of lesion status on number of crosses between hoarding and home cage.

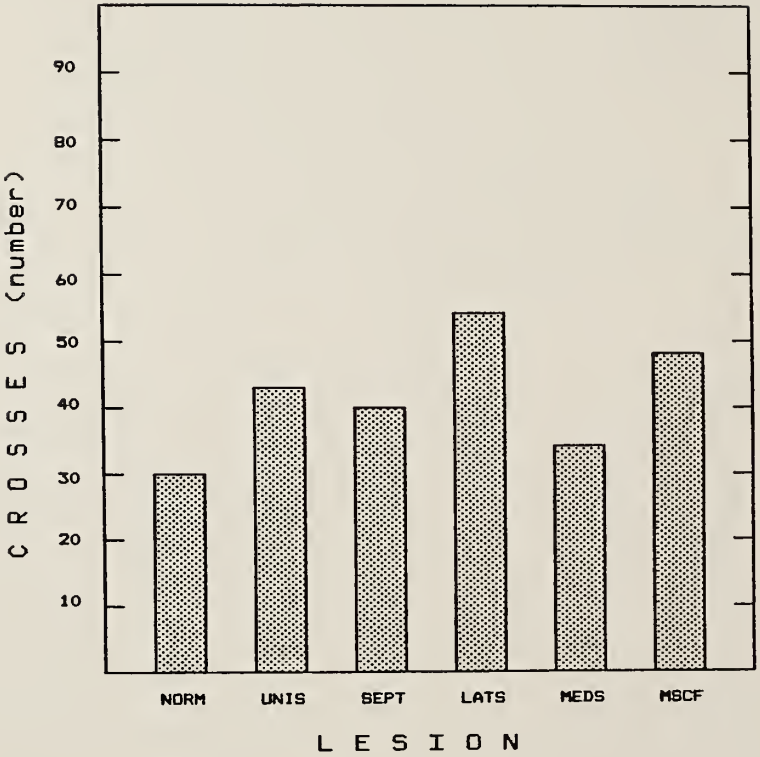
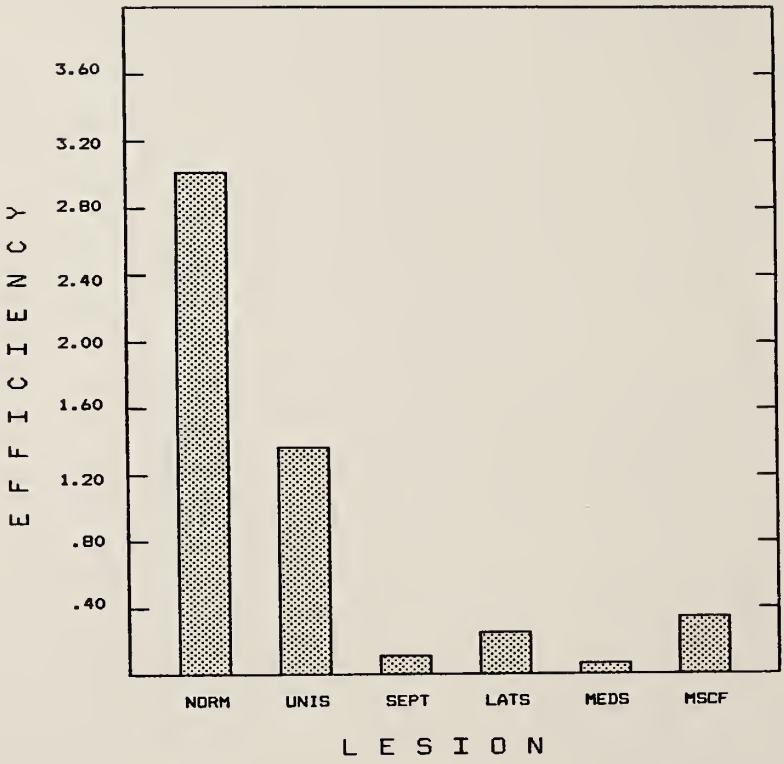

CROSSES (number)
90
80
70
60
50
40
30
20
10
NORM
UNIS
SEPT
LATS
MEDS
MSCF
LESION

Figure 10

Septal Group: Effect of lesion status on efficiency index for hoarding.


3.60
3.20
2.80
2.40
2.00
1.60
1.20
.80
.40
EFFICIENCY
NORM
UNIS
SEPT
LATS
MEDS
MSCF
LESION

Post hoc analyses revealed that normal animals were significantly more efficient than animals with lesions in any other part of the septal region ($p < .05$). Again, animals with unilateral septal lesions were more efficient than animals with other lesions, but this difference was not significant.

Hippocampal group

As Figure 11 indicates, lesion status had a significant effect on total number of pellets hoarded ($p < .001$). Normal animals and animals with lesions of the dorsal fornix and habenula hoarded the most pellets; animals with unilateral septal lesions, columns fornix lesions, and medial fimbria lesions hoarded a moderate number of pellets; and animals with lesions of the septum or lateral fimbria hoarded very few pellets. Post hoc analyses revealed that animals with dorsal fornix and habenula lesions hoarded significantly more pellets than animals in all of the other lesion groups ($p < .05$). Normal animals hoarded significantly more than animals with lesions of the septum, lateral fimbria, and columns fornix ($p < .05$).

In terms of number of crosses, there was a significant effect of lesion status ($p < .05$). As Figure 12 reveals, normal animals made fewer crosses than animals in all lesion groups. With respect to efficiency, normal animals and

Figure 11

Hippocampal Group: Effect of lesion status on total number of pellets hoarded.

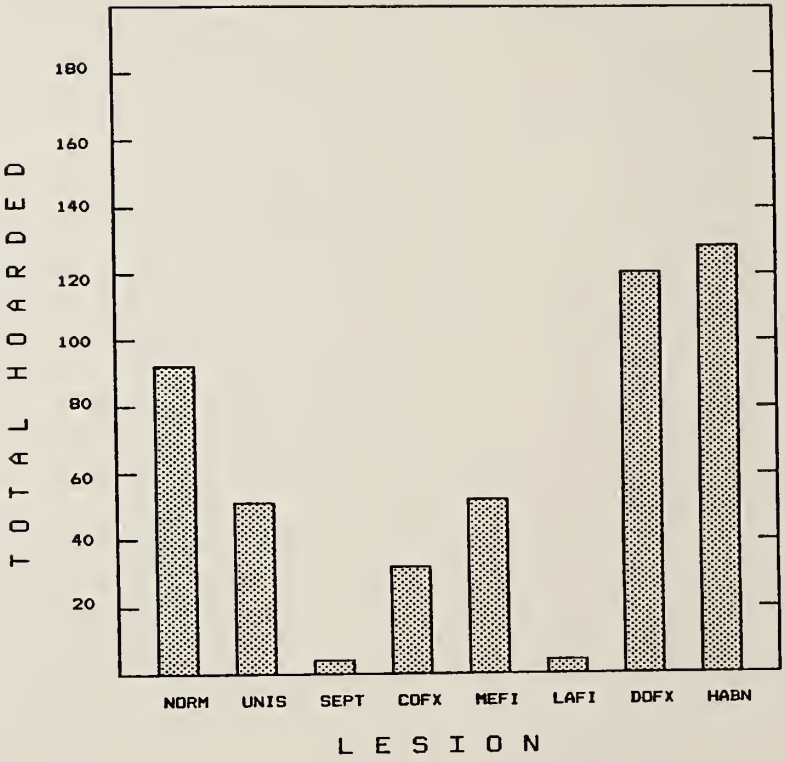
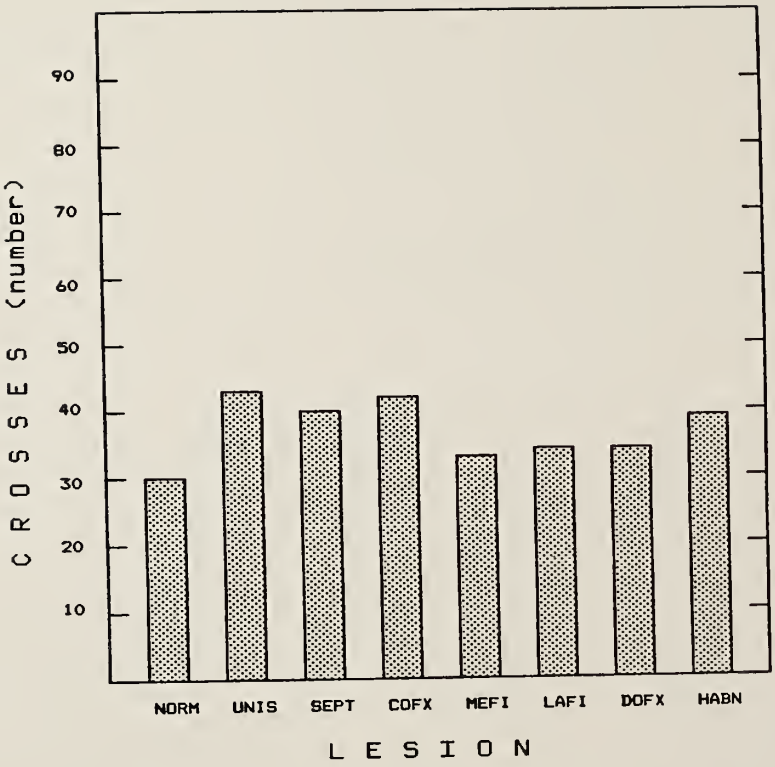

TOTAL HOARDED
180
160
140
120
100
80
60
40
20
NORM
UNIS
SEPT
COFX
MEFI
LAFI
DOFX
HABN
LESION

Figure 12

Hippocampal Group: Effect of lesion status on the number of crosses between hoarding and home cage.


CROSSES (number)
90
80
70
60
50
40
30
20
10
NORM
UNIS
SEPT
COFX
MEFI
LAFI
DOFX
HABN
LESION

those with lesions of the habenula and dorsal fornix achieved the highest efficiency ratings; animals with lesions of the unilateral septum, medial fimbria, and columns fornix had intermediate ratings; and animals with septal and lateral fimbria lesions were very inefficient hoarders. Post hoc analyses revealed that animals in the dorsal fornix, habenula, and normal groups had significantly higher ratings of efficiency than animals in all other lesion groups ($p < .05$). These data are shown in Figure 13.

Hypothalamic group

As is evident in Figure 14, lesion status significantly affected number of pellets hoarded ($p < .01$). Post hoc analyses revealed that normal animals hoarded significantly more pellets than animals with bilateral septal lesions or asymmetrical lesions involving either the medial or lateral preoptic area ($p < .05$).

Figure 15 indicates no significant differences between groups in terms of number of crosses. However, lesion status did have a significant effect on efficiency index ($p < .001$). As Figure 16 and post hoc analyses show, normal animals were significantly more efficient at hoarding than animals with lesions in any area ($p < .05$). Animals with lesions of the septum, MPO, and LPO were particularly inefficient.

Figure 13

Hippocampal Group: Effect of lesion status on efficiency index for hoarding.

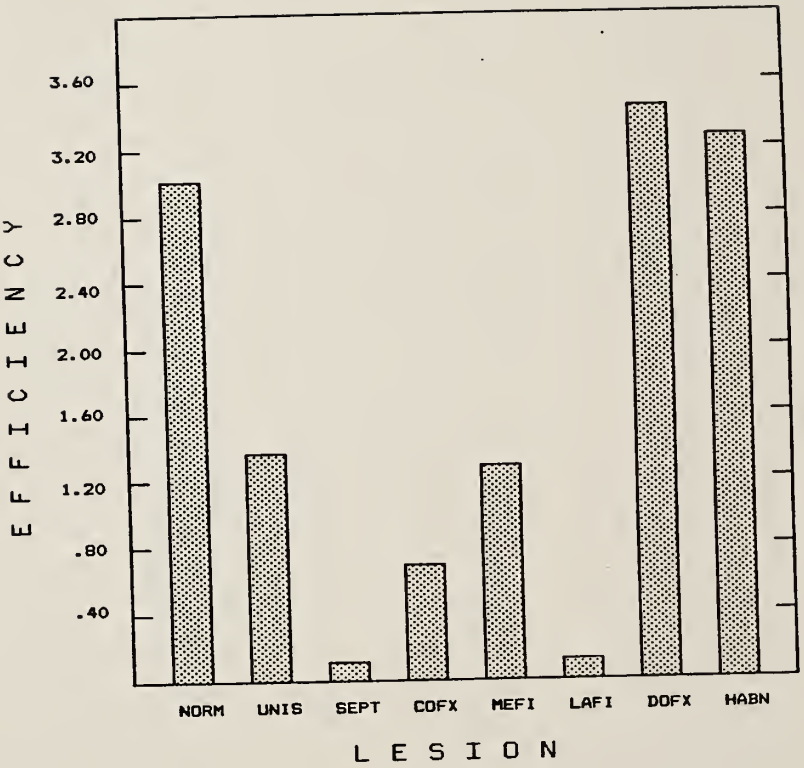

EFFICIENCY
3.60
3.20
2.80
2.40
2.00
1.60
1.20
.80
.40
NORM
UNIS
SEPT
COFX
MEFI
LAFI
DOFX
HABN
LESION

Figure 14

Hypothalamic Group: Effect of lesion status on the total number of pellets hoarded.

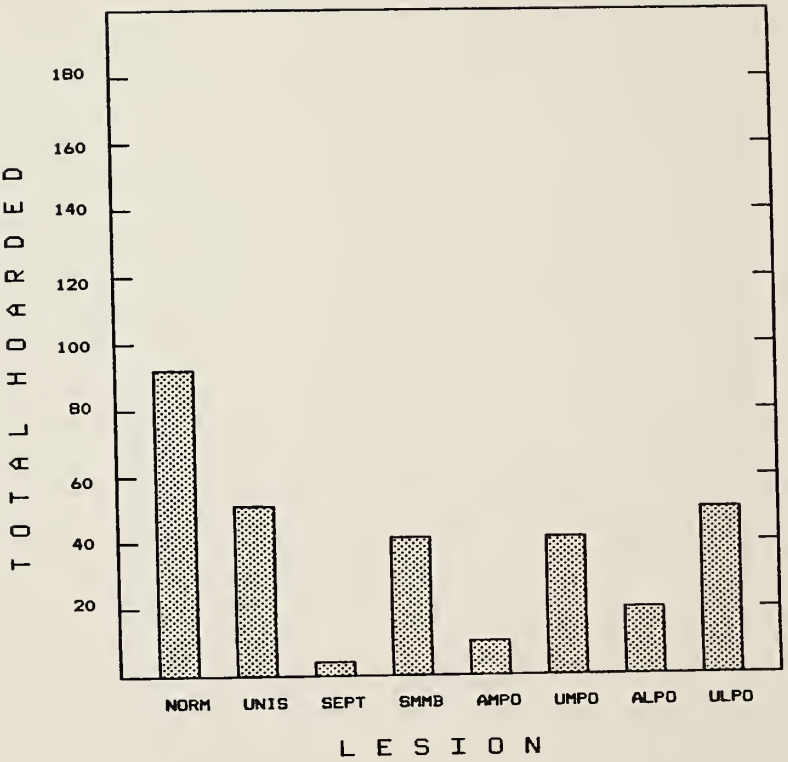

TOTAL HOARDED
180
160
140
120
100
80
60
40
20
NORM
UNIS
SEPT
SMMB
AMPO
UMPO
ALPO
ULPO
LESION

Figure 15

Hypothalamic Group: Effect of lesion status on the number of crosses between hoarding and home cage.

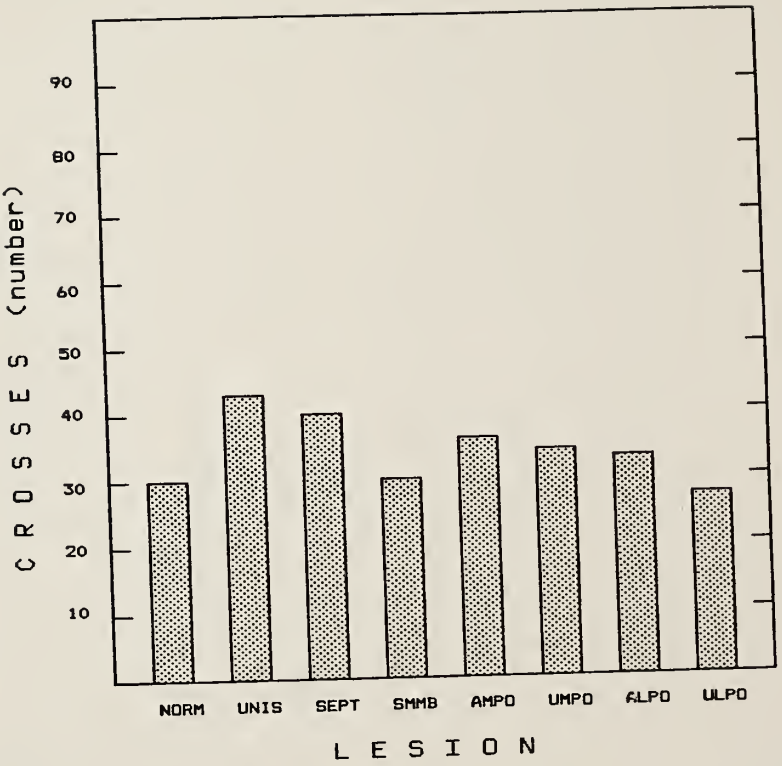
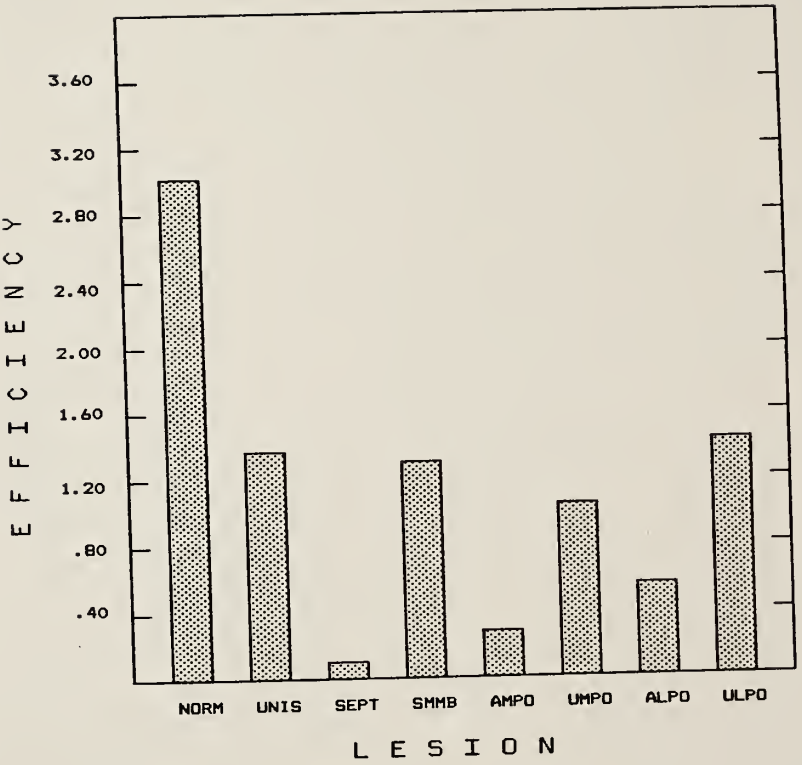

CROSSES (number)
90
80
70
60
50
40
30
20
10
NORM
UNIS
SEPT
SMMB
AMPO
UMPO
ALPO
ULPO
LESION

Figure 16

Hypothalamic Group: Effect of lesion status on efficiency index for hoarding.


EFFICIENCY
3.60
3.20
2.80
2.40
2.00
1.60
1.20
.80
.40
NORM
UNIS
SEPT
SMMB
AMPO
UMPO
ALPO
ULPO
LESION

Brainstem group

Figure 17 shows that lesion status significantly affected the total number of pellets hoarded ($p < .001$). Post hoc analyses reveal that normal animals hoarded more pellets than animals with septal lesions, asymmetrical lesions of the ventral tegmental area and the locus coeruleus, and unilateral lesions involving the locus coeruleus ($p < .05$). Animals with unilateral lesions of the VTA also hoarded a large number of pellets.

The data on number of crosses indicate that lesion status had a small but significant effect ($p < .05$) such that normal animals made fewer crosses than animals with lesions (see Figure 18). As Figure 19 and post hoc analyses show, normal animals were significantly more efficient at hoarding than animals with septal lesions, asymmetrical lesions involving the locus coeruleus, and unilateral lesions involving the locus coeruleus ($p < .05$). Again, animals with unilateral lesions involving the ventral tegmental area were almost as efficient as control animals.

Behavioral descriptions

Across all groups, certain patterns were observed in animals that were "efficient hoarders" and quite different patterns were observed in "inefficient hoarders." Mice that hoarded efficiently typically crossed less and rarely

Figure 17

Brainstem Group: Effect of lesion status on total number of pellets hoarded.

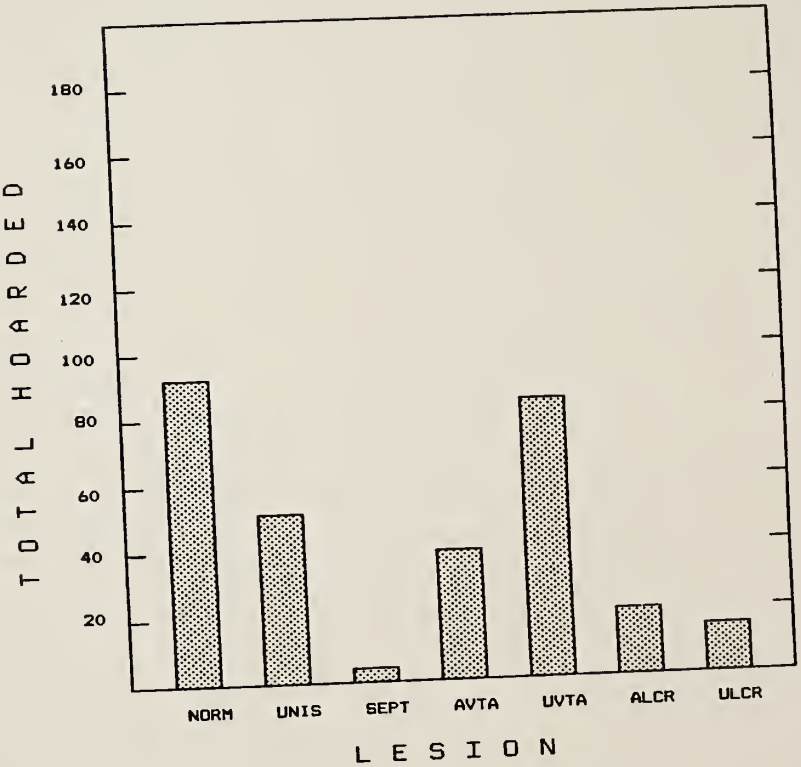

TOTAL HOARDED
180
160
140
120
100
80
60
40
20
NORM
UNIS
SEPT
AVTA
UVTA
ALCR
ULCR
LESION

Figure 18

Brainstem Group: Effect of lesion status on number of crosses between hoarding and home cage.

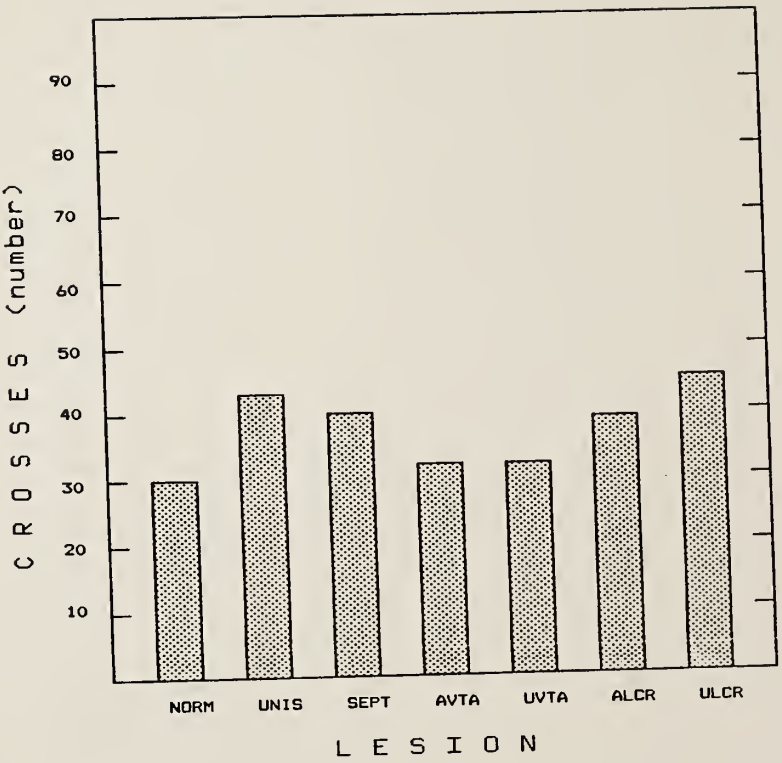
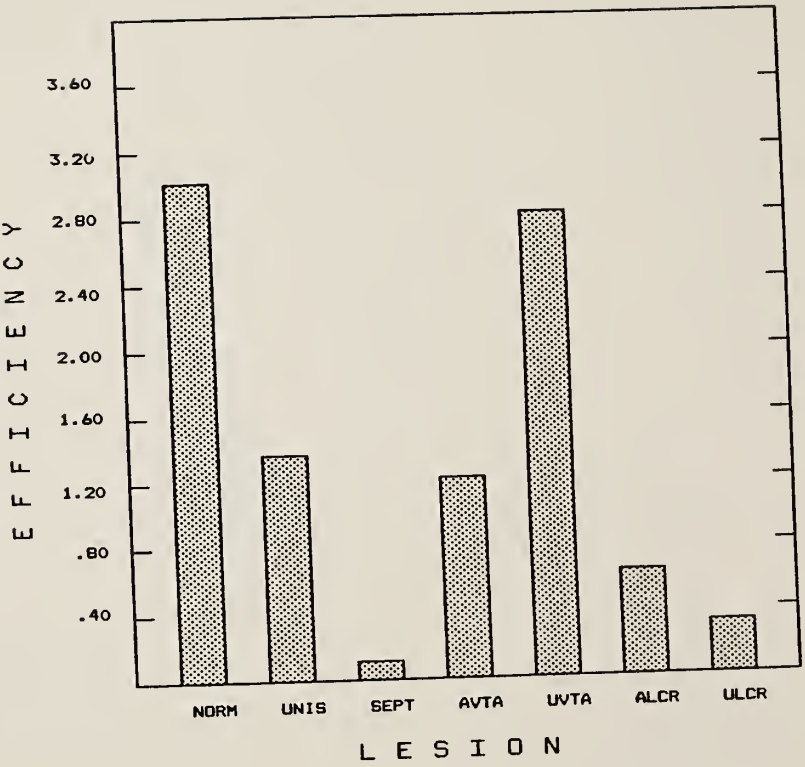

CROSSES (number)
90
80
70
60
50
40
30
20
10
NORM
UNIS
SEPT
AVTA
UVTA
ALCR
ULCR
LESION

Figure 19

Brainstem Group: Effect of lesion status on efficiency index for hoarding.


3.60
3.20
2.80
2.40
2.00
1.60
1.20
.80
.40
EFFICIENCY
NORM
UNIS
SEPT
AVTA
UVTA
ALCR
ULCR
LESION

hoarded pellets in their mouths. Rather, the efficient subjects used either a kicking motion with their rear legs or pushing movements with their nose and front paws to move large numbers of pellets down the tube in a short period of time. Some of the most efficient animals engaged in frenzied hoarding, moving almost 100% of the pellets in a few minutes. Once in the home cage, these animals moved the pellets around, buried them under the wood chip bedding, and finally settled down to eat what they had hoarded.

Inefficient hoarders exhibited quite a different pattern. If these animals hoarded at all they used their mouths to carry pellets, or they hoarded pellets in both directions. At times these animals pushed pellets that had spilled over from the hoarding box into the tube back into the hoarding box. Occasionally an animal carried bedding into the hoarding alley. If these animals did any eating at all it was in the tube or hoarding box.

The statistical data for food hoarding are summarized in Tables 4 through 6.

Table 4

ANALYSIS OF VARIANCE FOR TOTAL NUMBER OF PELLETS HOARDED

Septal Group

Source	MS	df	F	p
Lesion	11291.50	5	11.11	.001
Error	1016.67	36		

Hippocampal Group

Source	MS	df	F	p
Lesion	13561.00	7	7.27	.001
Error	1864.96	45		

Hypothalamic Group

Source	MS	df	F	p
Lesion	6940.72	7	4.35	.01
Error	1597.08	48		

Brainstem Group

Source	MS	df	F	p
Lesion	8218.25	6	5.89	.001
Error	1394.28	38		

Table 5

ANALYSIS OF VARIANCE FOR NUMBER OF CROSSES DURING HOARDING

Septal Group

Source	MS	df	F	p
Lesion	629.10	5	5.57	.001
Error	112.85	36		

Hippocampal Group

Source	MS	df	F	p
Lesion	188.10	7	2.40	.05
Error	78.54	45		

Hypothalamic Group

Source	MS	df	F	p
Lesion	189.39	7	1.57	NS
Error	121.04	48		

Brainstem Group

Source	MS	df	F	p
Lesion	251.80	6	2.43	.05
Error	103.53	38		

Table 6

ANALYSIS OF VARIANCE FOR HOARDING EFFICIENCY INDEX

Septal Group

Source	MS	df	F	p
Lesion	12.68	5	14.75	.001
Error	.86			

Hippocampal Group

Source	MS	df	F	p
Lesion	12.13	7	9.79	.001
Error	1.24	45		

Hypothalamic Group

Source	MS	df	F	p
Lesion	7.72	7	6.14	.001
Error	1.26	48		

Brainstem Group

Source	MS	df	F	p
Lesion	9.43	6	6.70	.001
Error	1.41	38		

Experiment 3: Predatory Behavior

Septal group

There were no significant differences between groups in the septal cluster in terms of latency to kill crickets. As Figure 20 indicates, animals with large septal lesions killed somewhat more quickly than normal animals. However, animals with more specific lesions in any part of the septal region took longer to kill than normal animals. This was especially true for animals with medial septal lesions. There were no apparent differences in latency to approach or bite the crickets.

Hippocampal group

Again, lesion status had no significant effect on latency to kill crickets in the hippocampal group. As Figure 21 indicates, animals with no lesions or lesions of the entire septum or dorsal fornix killed rather quickly. Mice with lesions of the habenula clearly took the longest to kill; in fact, several animals in this group did not kill in the 10 minute period of observation on both trials. They also exhibited an unusual strategy of spraying bedding over the cricket (resembling defensive burying), or burying themselves deep in the bedding. Other animals buried the cricket, but then dug the cricket out and attacked it.

Figure 20

Septal Group: Effect of lesion status on latency to kill crickets.

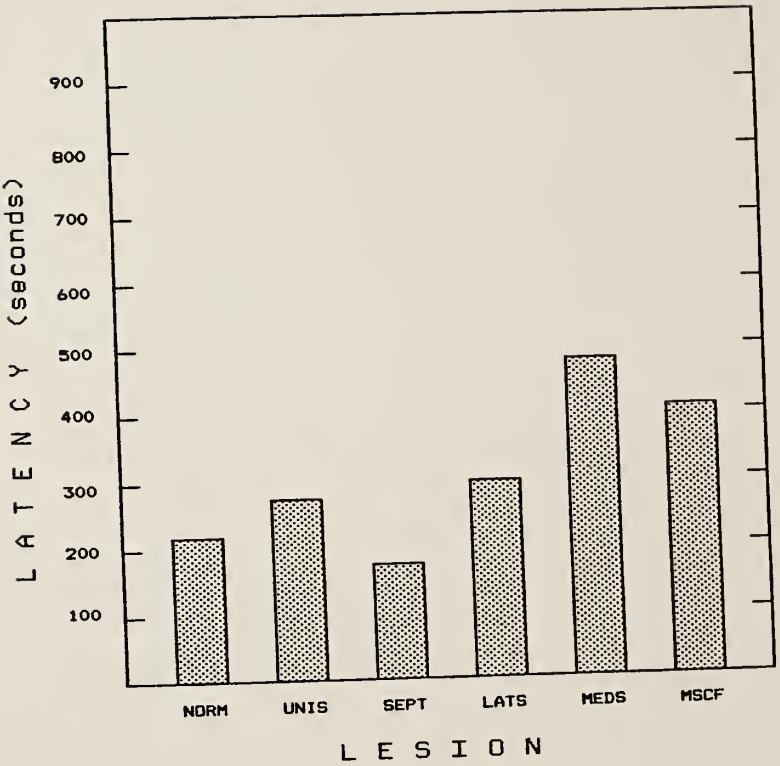
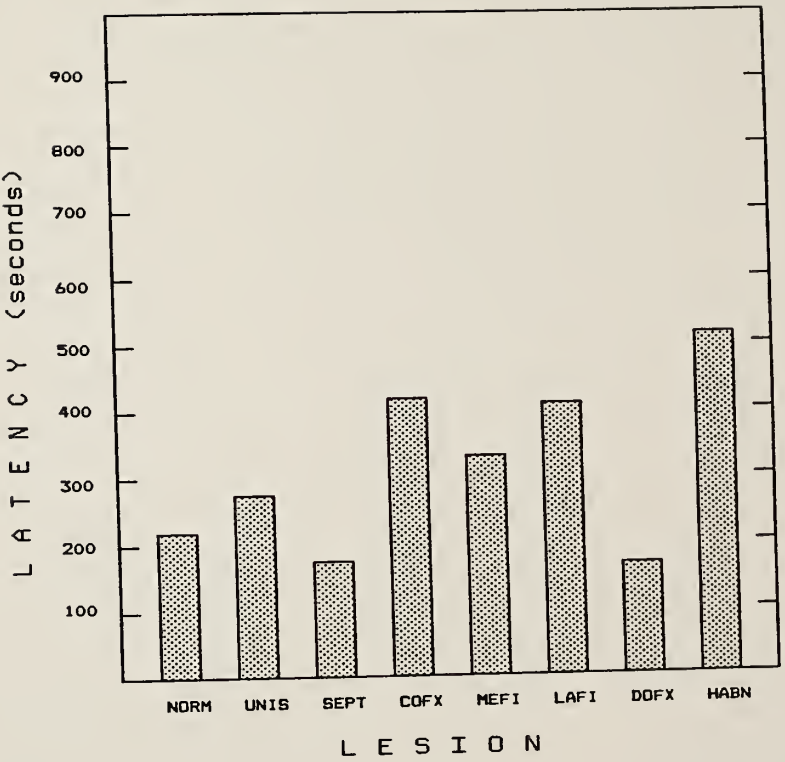

LATENCY (seconds)
900
800
700
600
500
400
300
200
100
NORM
UNIS
SEPT
LATS
MEDS
MSCF
LESION

Figure 21

Hippocampal Group: Effect of lesion status on latency to kill crickets.


LATENCY (seconds)
900
800
700
600
500
400
300
200
100
NORM
UNIS
SEPT
COFX
MEFI
LAFI
DOFX
HABN
LESION

Hypothalamic group

Lesion status had a significant effect on latency to kill in the hypothalamic group ($p < .01$). Figure 22 and post hoc analyses reveal that animals with lesions of the lateral preoptic area (LPO) took significantly longer to kill crickets than normals or mice with lesions of the entire septum, unilateral septum, or unilateral medial preoptic area/septum ($p < .05$). In fact, the subjects with LPC lesions had an average latency of about 600 seconds, indicating that they almost never killed a cricket in the allotted 10 minutes of observation time.

Brainstem group

Lesion status had no significant effect on latency to kill crickets in the brainstem group. Figure 23 does indicate, however, that animals with lesions anywhere in brainstem regions took longer to kill than animals with no lesions or damage restricted to the septal area. This was particularly true for animals with asymmetrical lesions of the ventral tegmental area and septum.

Comments

Although the group means indicate that differences exist, the failure to find statistically significant differences reveals the tremendous degree of variability within groups. As Table 7 shows, some mice are simply

Figure 22

Hypothalamic Group: Effect of lesion status on latency to kill crickets.

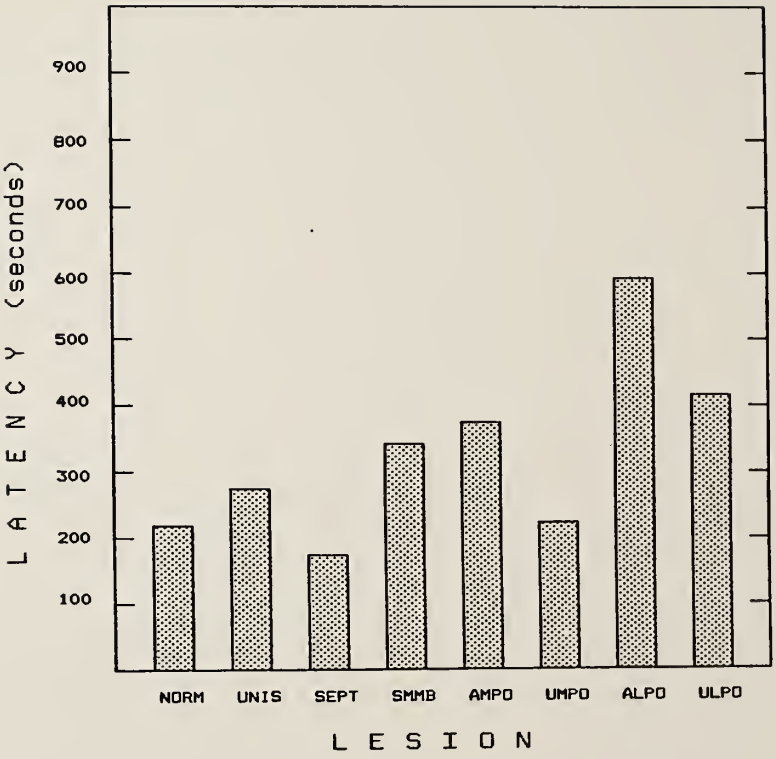

LATENCY (seconds)
900
800
700
600
500
400
300
200
100
NORM
UNIS
SEPT
SMMB
AMPO
UMPO
ALPO
ULPO
LESION

Figure 23

Brainstem Group: Effect of lesion status on latency to kill crickets.

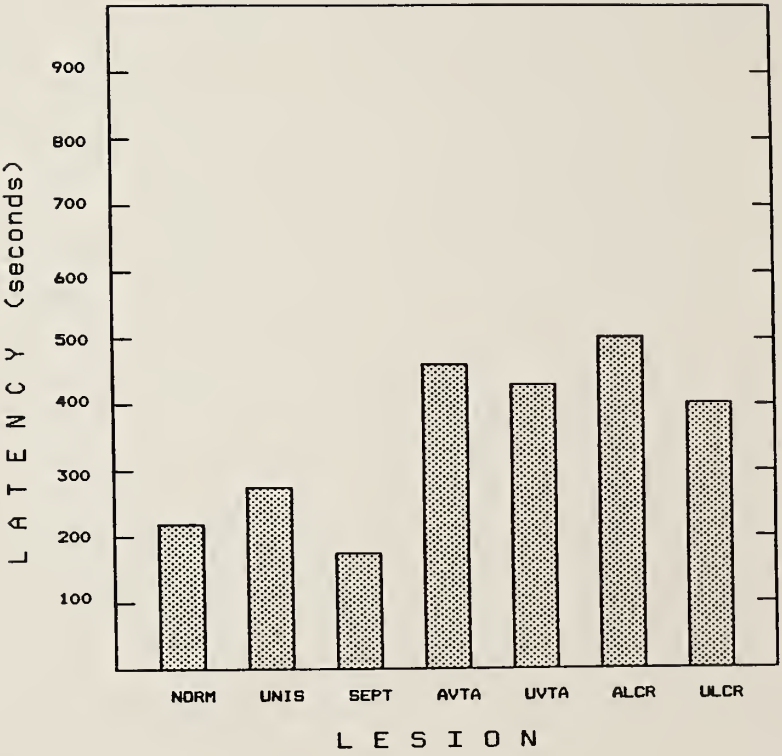

LATENCY (seconds)
900
800
700
600
500
400
300
200
100
NORM
UNIS
SEPT
AVTA
UVTA
ALCR
ULCR
LESION

Table 7

NUMBER OF KILLERS PER GROUP

Lesion	Total N	Number of Killers	%
NORM	12	10	83
UNIS	7	5	71
SEPT	5	5	100
LATS	7	5	71
* MEDS	6	2	33
MSCF	5	4	80
COFX	8	4	50
MEFI	5	3	60
LAFI	4	3	75
DOFX	6	5	83
* HABN	6	2	33
SMMB	8	7	88
AMPO	7	4	57
UMPO	6	6	100
* ALPO	7	1	14
ULPO	4	3	75
* AVTA	6	2	33
UVTA	5	3	60
ALCR	5	3	60
ULCR	5	3	60

* less than 50%

"killers" whereas others appear to be "nonkillers" regardless of lesion status. With the exception of a few groups (MEDS, HABN, ALPO, AVTA) where nonkillers exceeded killers, and two groups (SEPT, UMPO) containing 100% killers, the remaining 14 groups contained a fair number of killers and a few nonkillers.

The statistical data are summarized in Table 8.

Table 8

ANALYSIS OF VARIANCE FOR LATENCY TO KILL: PREDATORY BEHAVIOR

Septal Group

Source	MS	df	F	p
Lesion	82822.80	5	1.75	NS
Error	47392.00	36		

Hippocampal Group

Source	MS	df	F	p
Lesion	100236.00	7	2.08	NS
Error	48310.30			

Hypothalamic Group

Source	MS	df	F	p
Lesion	126256.00	7	3.23	.01
Error	39091.00	48		

Brainstem Group

Source	MS	df	F	p
Lesion	102890.00	6	2.29	NS
Error	44982.50	38		

Experiment 4: Wheel Running

Septal group

There was no significant effect of lesion status on wheel running. Figure 24 indicates a tendency for normal animals to run more than animals with lesions in any part of the septal region. In general, running was depressed across all groups (possibly related to influence of progesterone).

Hippocampal group

Again, lesion status had no significant effects on wheel running. Figure 25 indicates that animals with lesions of the dorsal fornix ran considerably more than animals in other groups. Careful analysis reveals that this inflated rate was due to a single animal.

Hypothalamic group

Figure 26 shows that wheel running was not significantly influenced by lesion status. Animals with LPO lesions appear to run more than other animals, but this high rate can again be attributed to a single subject.

Brainstem group

Wheel running in the brainstem groups appears to be affected by lesion status, according to Figure 27. However, these differences were not significant.

Statistical data appear in Table 9.

Figure 24

Septal Group: Effect of lesion status on wheel running under influence of progesterone.

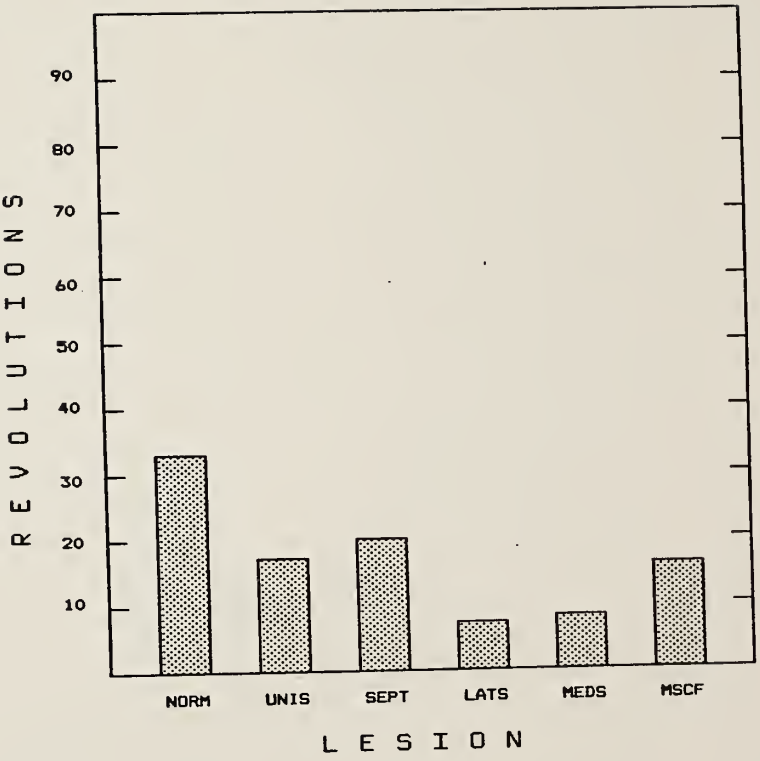

REVOLUTIONS
90
80
70
60
50
40
30
20
10
NORM
UNIS
SEPT
LATS
MEDS
MSCF
LESION

Figure 24

Hippocampal Group: Effect of lesion status on wheel running under influence of progesterone.

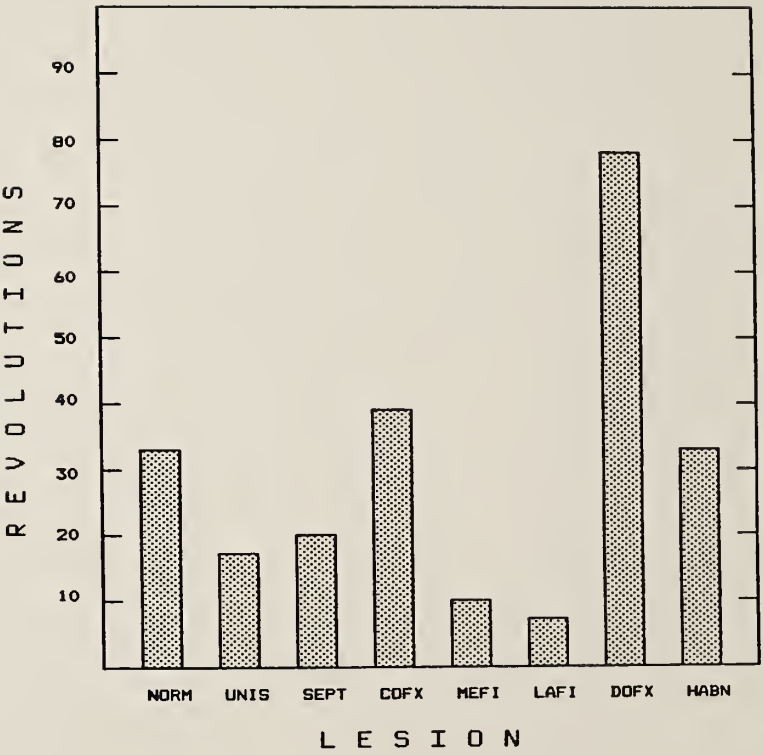

REVOLUTIONS
90
80
70
60
50
40
30
20
10
NORM
UNIS
SEPT
COFX
MEFI
LAFI
DOFX
HABN
LESION

Figure 26

Hypothalamic Group: Effect of lesion status on wheel running under influence of progesterone.

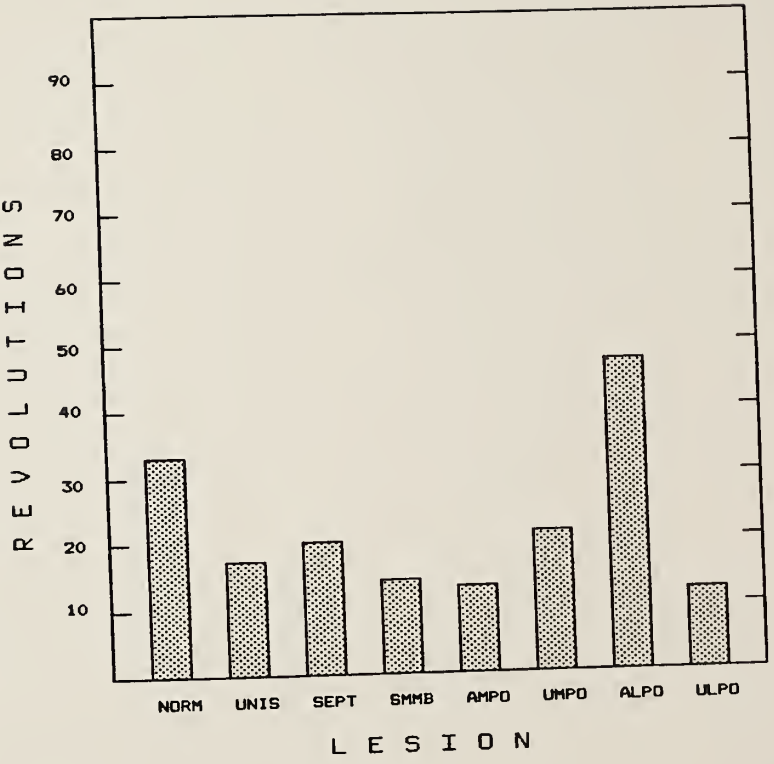

REVOLUTIONS
90
80
70
60
50
40
30
20
10
NORM
UNIS
SEPT
SMMB
AMPO
UMPO
ALPO
ULPO
LESION

Figure 27

Brainstem Group: Effect of lesion status on wheel running under influence of progesterone.

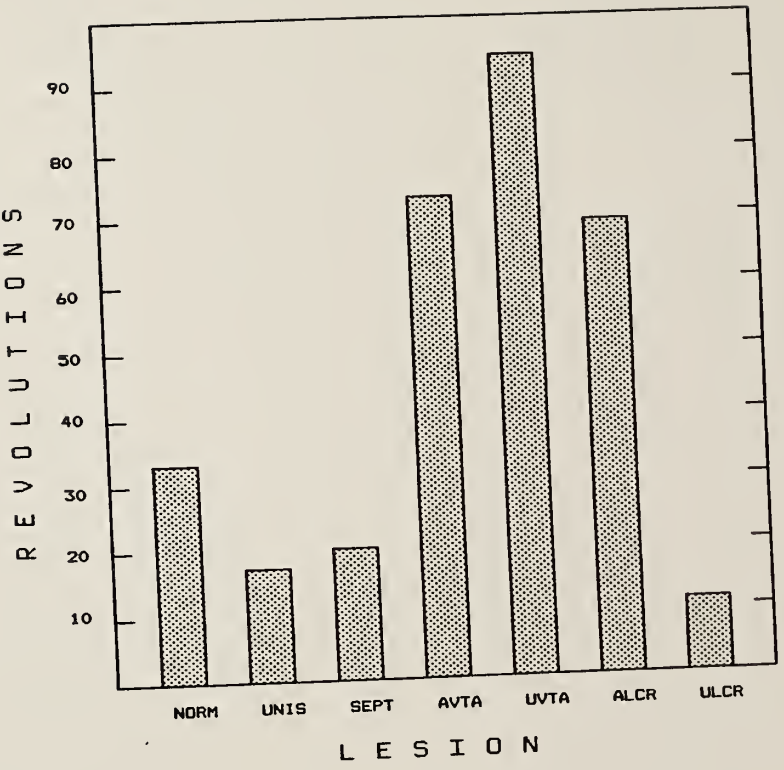

REVOLUTIONS
90
80
70
60
50
40
30
20
10
NORM
UNIS
SEPT
AVTA
UVTA
ALCR
ULCR
LESION

Table 9

ANALYSIS OF VARIANCE FOR WHEEL RUNNING

Septal Group

Source	MS	df	F	p
Lesion	876.50	5	.72	NS
Error	1217.67	36		

Hippocampal Group

Source	MS	df	F	p
Lesion	2893.83	7	.70	NS
Error	4144.33	45		

Hypothalamic Group

Source	MS	df	F	p
Lesion	1068.06	7	.65	NS
Error	1651.37	48		

Brainstem Group

Source	MS	df	F	p
Lesion	5889.54	6	.99	NS
Error	5971.39	38		

Note: In no case did between groups variability exceed within groups variability.

Experiment 5: Nest-Building

Septal group

As indicated in Figure 28, normal animals constructed nests of significantly higher quality than animals with lesions in any part of the septal region ($p < .001$). Post hoc tests confirmed that mice without lesions built superior nests, as compared to all other groups ($p < .05$). Animals with unilateral septal lesions constructed rudimentary nests, whereas mice with lesions elsewhere in the septal region constructed very inadequate nests or no nests at all.

Hippocampal group

As is evident from Figure 29, reasonably good nests were built by mice with no lesions, medial fimbria lesions, dorsal fornix lesions, and habenula lesions. On the other hand, mice with bilateral septal lesions or lateral fimbria lesions were quite deficient at building nests. Animals in these groups often failed to shred the twine preparatory to building a nest, or they shredded the twine and spread it in a haphazard fashion over the home cage floor. The effect of lesion status on nest-building was significant ($p < .001$), as were many of the post hoc comparisons ($p < .05$). The significant comparisons of concern are as follows: LAFI x all groups, SEPT x all groups, NORM x UNIS, COFX.

Figure 28

Septal Group: The effect of lesion status on nest-building.

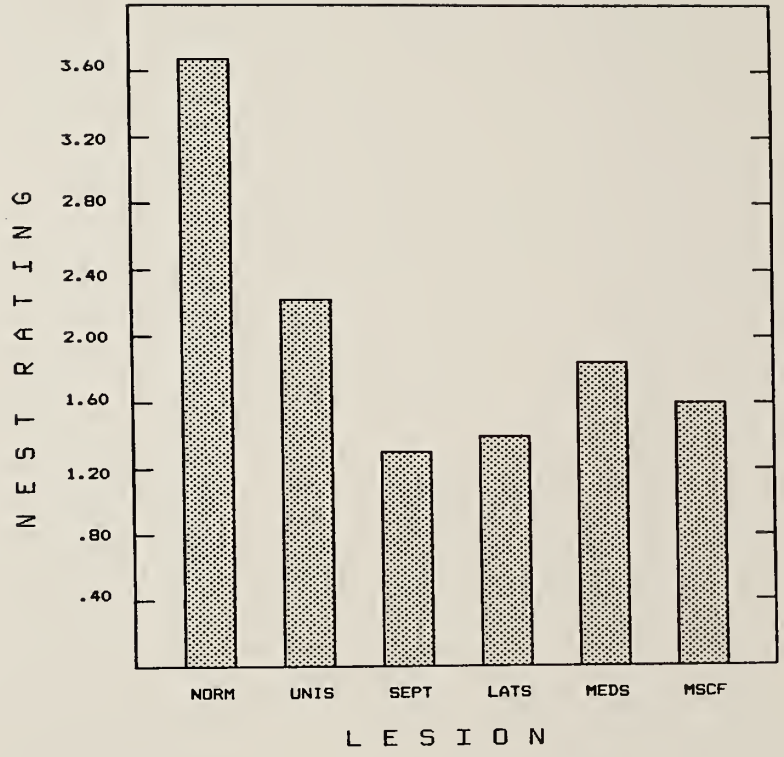
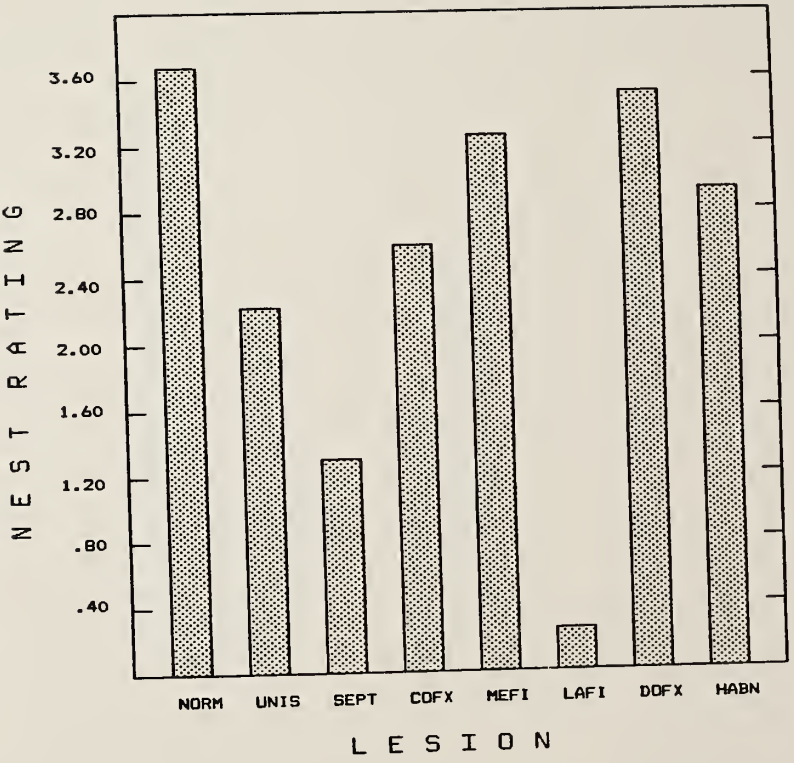

NEST RATING
3.60
3.20
2.80
2.40
2.00
1.60
1.20
.80
.40
NORM
UNIS
SEPT
LATS
MEDS
MSCF
LESION

Figure 29

Hippocampal Group: Effect of lesion status on nest-building.


NEST RATING
3.60
3.20
2.80
2.40
2.00
1.60
1.20
.80
.40
NORM
UNIS
SEPT
COFX
MEFI
LAFI
DOFX
HABN
LESION

Hypothalamic group

Lesion status had a significant effect on nest-building in the hypothalamic group ($p < .001$). As indicated in Figure 30, and confirmed by post hoc tests, normal animals constructed significantly better nests than mice with mammillary bodies lesions, bilateral septal lesions, asymmetrical lesions involving the medial preoptic area (AMPO), and asymmetrical lesions involving the lateral preoptic area (ALPO) ($p < .05$). Furthermore, mice with unilateral medial preoptic area (UMPO) lesions built significantly better nests than their asymmetrical counterparts (AMPO) ($p < .05$).

Brainstem group

Again, lesion status had a significant effect on nest-building ($p < .001$). Figure 31 and post hoc analyses reveal that normal animals built significantly better nests than animals with bilateral septal lesions, unilateral septal lesions, asymmetrical lesions involving the ventral tegmental area (AVTA), and asymmetrical lesions involving the locus coeruleus (ALCR) ($p < .05$).

Behavioral descriptions

Animals that constructed high quality nests typically shredded all of the twine in the first two days and had constructed round compact nests by the third day. Those

Figure 30

Hypothalamic Group: Effect of lesion status on nest-building.

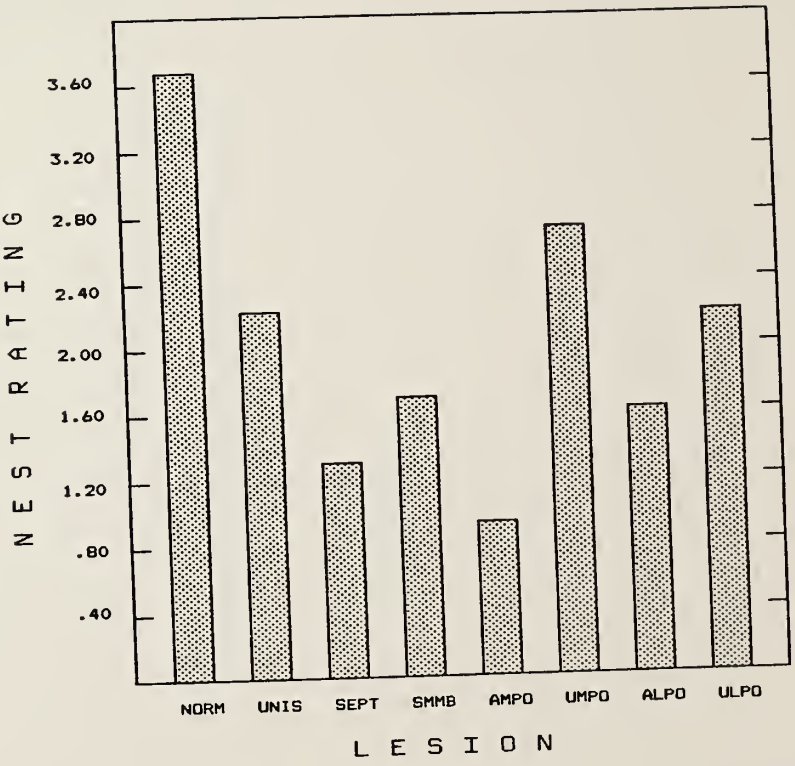
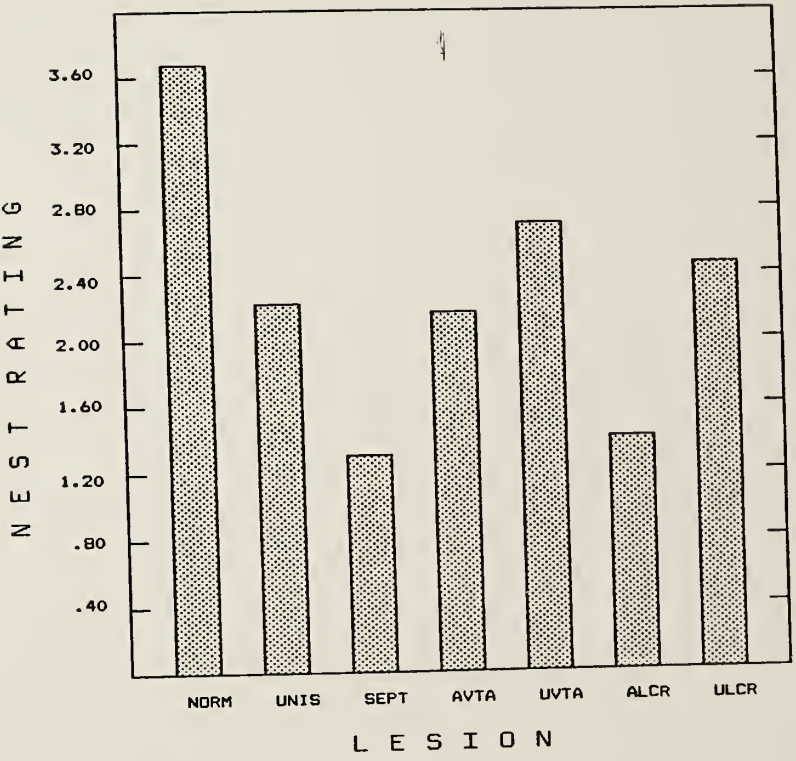

NEST RATING
3.60
3.20
2.80
2.40
2.00
1.60
1.20
.80
.40
NORM
UNIS
SEPT
SMMB
AMPO
UMPO
ALPO
ULPO
LESION

Figure 31

Brainstem Group: Effect of lesion status on nest-building.


NEST RATING
3.60
3.20
2.80
2.40
2.00
1.60
1.20
.80
.40
NORM
UNIS
SEPT
AVTA
UVTA
ALCR
ULCR
LESION

animals that built good nests also frequently incorporated home cage bedding (wood chips) into their nests to make a fuller and more protective nest. These animals also spent a considerable amount of time in their nests and were often very difficult to remove from the home cage because they had to be extracted from the nest. Animals that constructed poor nests either ignored the twine altogether or shredded it haphazardly and left the remnants scattered across the cage floor. Occasionally animals with low ratings built several inadequate nests in the home cage. Furthermore, these animals spent very little time in the nests that they did construct and tended to sleep on the cage bedding.

Statistical data for nest-building can be found in Table 10.

Table 10

ANALYSIS OF VARIANCE FOR NEST-BUILDING

Septal Group

Source	MS	df	F	p
Lesion	7.38	5	7.45	.001
Error	.99	36		

Hippocampal Group

Source	MS	df	F	p
Lesion	7.49	7	12.61	.001
Error	.59	45		

Hypothalamic Group

Source	MS	df	F	p
Lesion	6.75	7	6.73	.001
Error	1.00	48		

Brainstem Group

Source	MS	df	F	p
Lesion	5.17	6	4.86	.001
Error	1.06	38		

Experiment 6: Defensive Burying

Only the data on burying of the target prod (source of air blast) will be considered here as there was no significant effect of lesion status on burying of the control prod. This was true for all clusters/groups.

Septal group

As Figure 32 indicates, normal animals spent more time burying the target prod than animals with lesions in any part of the septal region. Hence, lesion status had a significant effect on time spent burying ($p < .05$). Post hoc analyses revealed that the only significant difference was between normal animals and those with bilateral septal lesions ($p < .05$).

With respect to the burying index (height of highest pile divided by distance from target prod), Figure 3 indicates that lesion status did have a significant effect ($p < .01$). Figure 33 and post hoc analyses reveal that normal animals achieved a significantly higher rating than animals with unilateral septal lesions, bilateral septal lesions, lateral septal lesions, and combined medial septum/columns fornix lesions ($p < .05$).

Hippocampal group

In the hippocampal group, the effect of lesion status

Figure 32

Septal Group: Effect of lesion status on time spent burying the target prod.

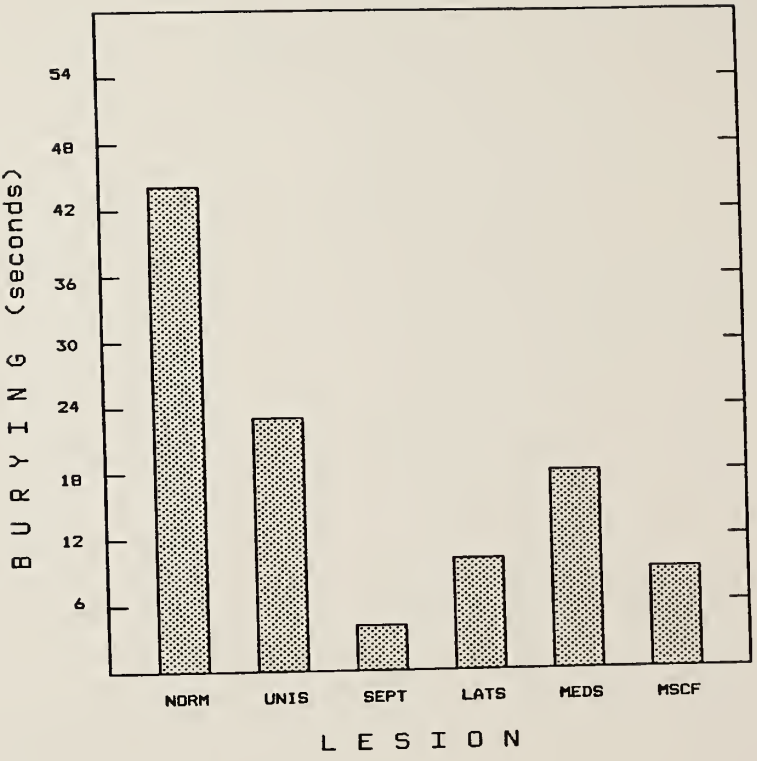
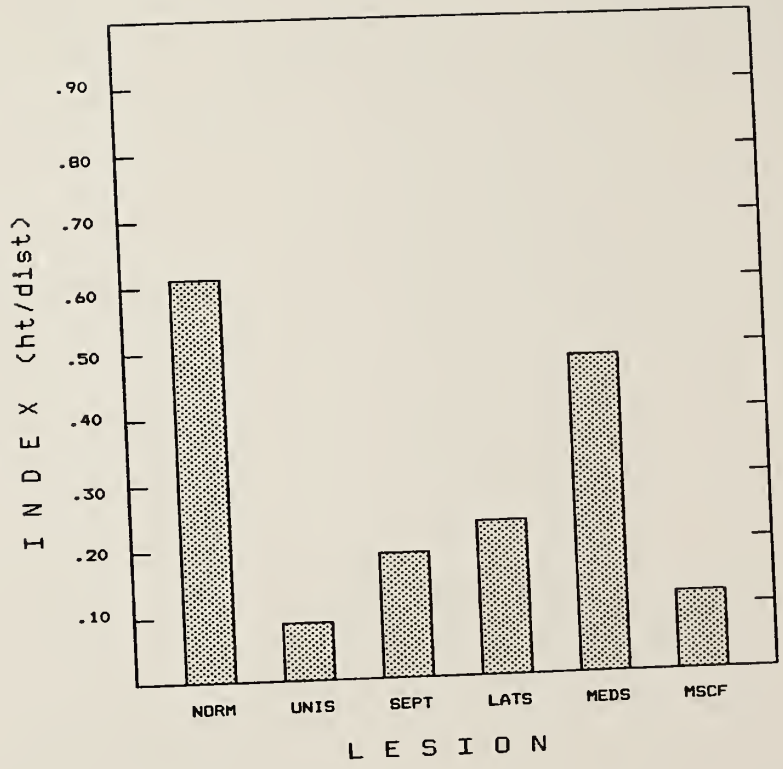

BURYING (seconds)
54
48
42
36
30
24
18
12
6
NORM
UNIS
SEPT
LATS
MEDS
MSCF
LESION

Figure 33

Septal group: Effect of lesion status on burying index.


.90
.80
.70
.60
.50
.40
.30
.20
.10
INDEX (ht/dist)
NORM
UNIS
SEPT
LATS
MEDS
MSCF
LESION

on time spent burying the target prod was not significant. These data are summarized in Figure 34. However, Figure 35 indicates that lesion status had a small but significant effect on the burying index ($p < .05$). Post hoc analyses indicate that the only significant comparison was between normal animals and animals with unilateral septal lesions ($p < .05$).

Hypothalamic group

Figure 36 indicates that animals with no lesions or UMPO lesions spend considerably more time burying than other animals. However, these differences were not significant due to large within-group variability. Lesion status did have a significant effect on the burying index ($p < .01$). Figure 37 and post hoc analyses reveal that normal animals achieved a significantly higher rating than mice with lesions of the mammillary bodies, unilateral septum, and unilateral lesions of the lateral preoptic area and septum ($p < .05$).

Brainstem group

Again, lesion status had no significant effect on time spent burying (see Figure 38). However, there was a significant effect of lesion on burying index ($p < .05$). As indicated in Figure 39 and post hoc analyses, the only significant comparison was between normal animals and those

Figure 34

Hippocampal Group: Effect of lesion status on time spent burying the target prod.

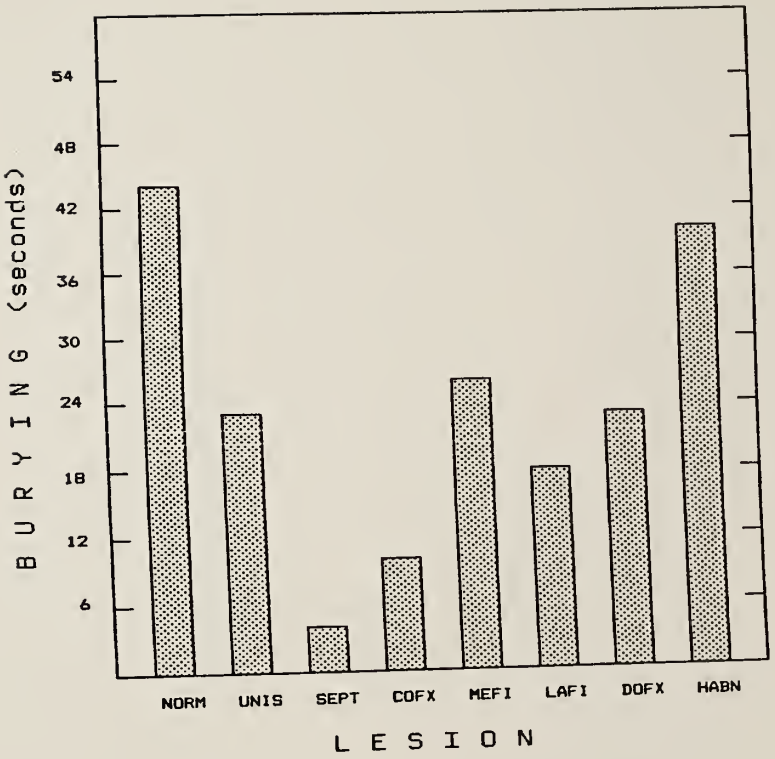

BURYING (seconds)
54
48
42
36
30
24
18
12
6
NORM
UNIS
SEPT
COFX
MEFI
LAFI
DOFX
HABN
LESION

Figure 35

Hippocampal Group: Effect of lesion status on burying index.

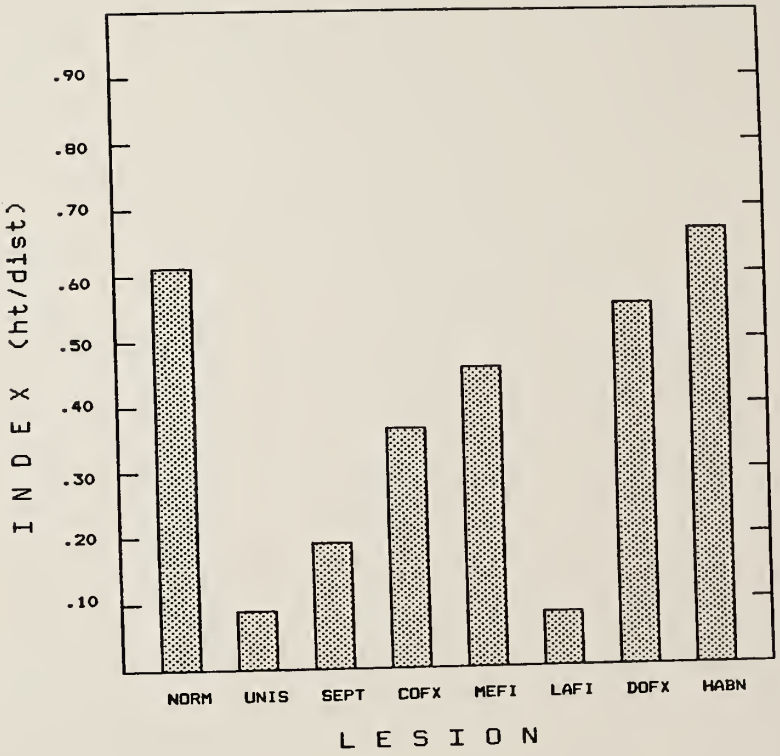

.90
.80
.70
.60
.50
.40
.30
.20
.10
INDEX (ht/dist)
NORM
UNIS
SEPT
COFX
MEFI
LAFI
DOFX
HABN
LESION

Figure 36

Hypothalamic Group: Effect of lesion status on time spent burying the target prod.

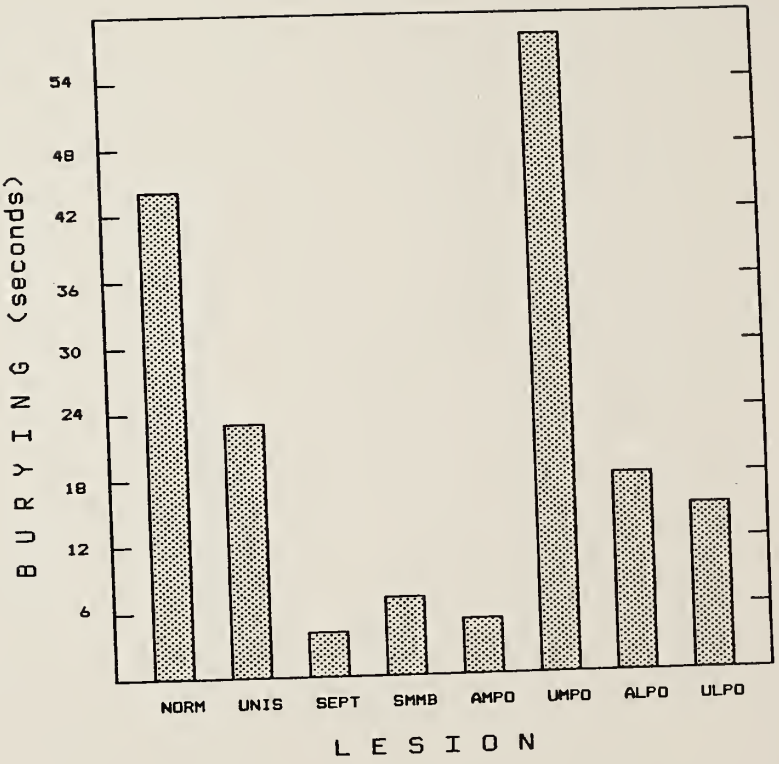

BURYING (seconds)
54
48
42
36
30
24
18
12
6
NORM
UNIS
SEPT
SMMB
AMPO
UMPO
ALPO
ULPO
LESION

Figure 37

Hypothalamic Group: Effect of lesion status on burying index.

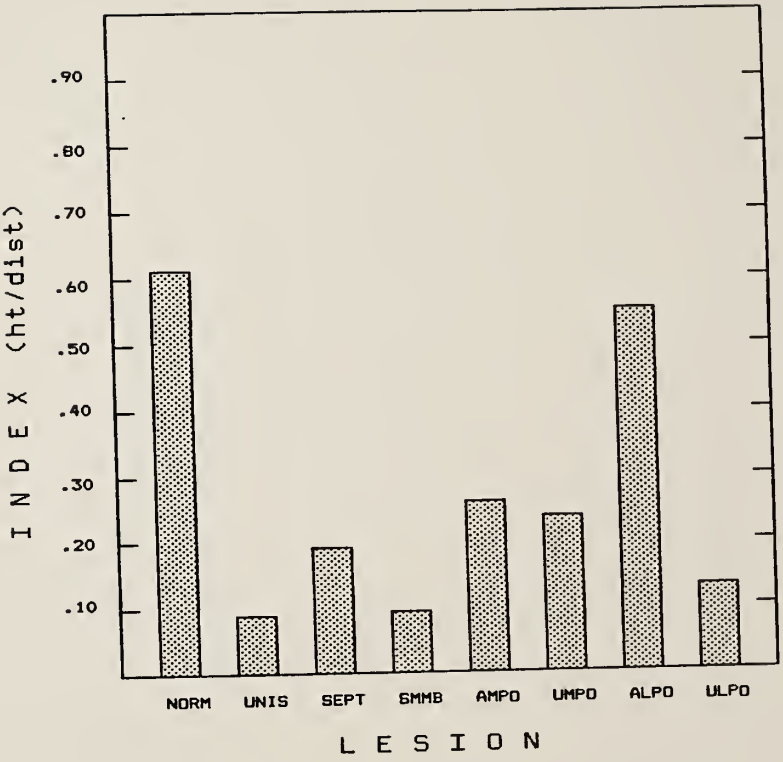

.90
.80
.70
.60
.50
.40
.30
.20
.10
INDEX (ht/dist)
NORM
UNIS
SEPT
SMMB
AMPO
UMPO
ALPO
ULPO
LESION

Figure 38

Brainstem Group: Effect of lesion status on time spent burying the target prod.

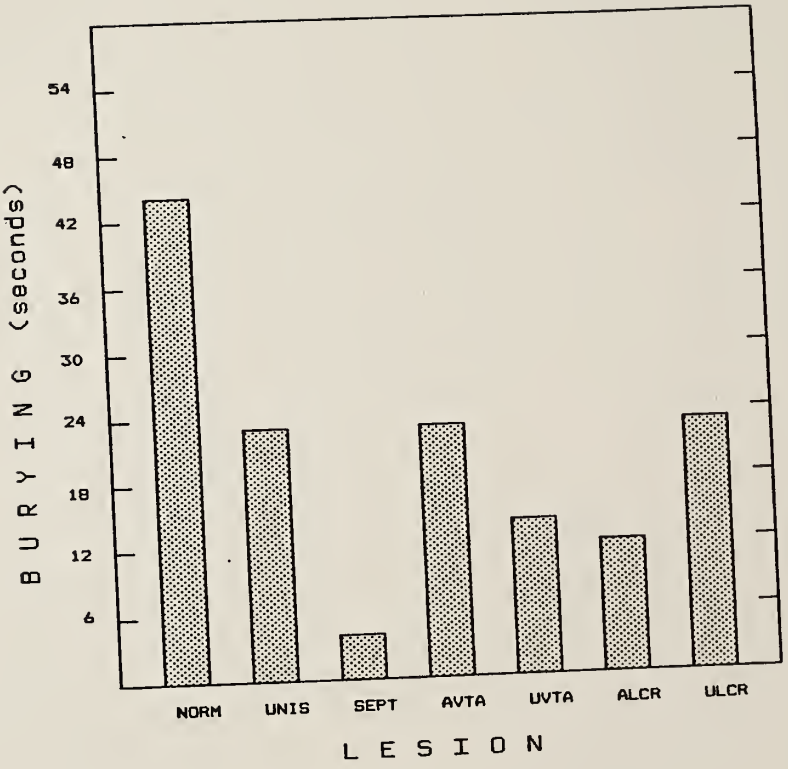
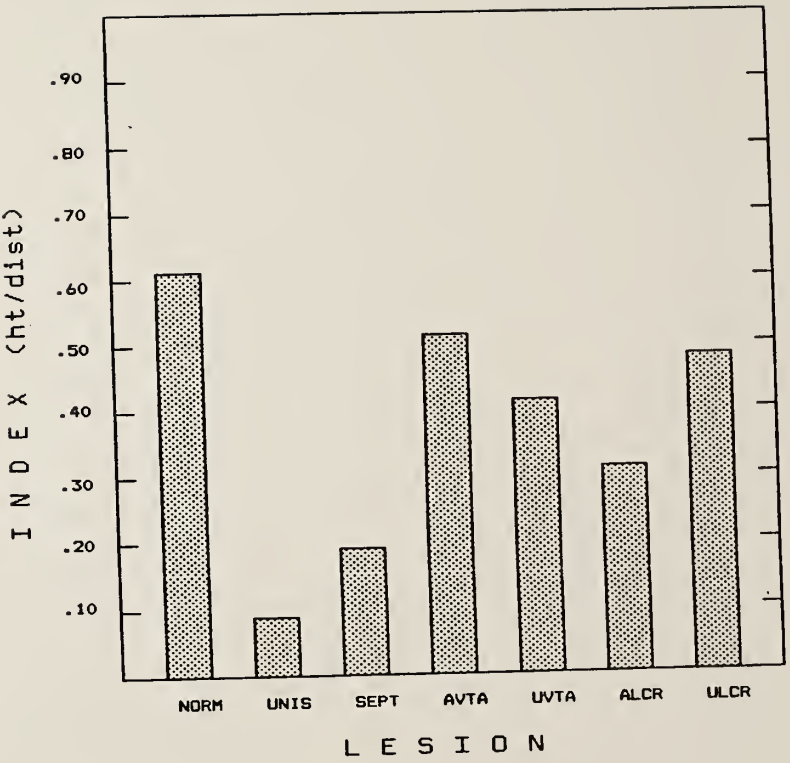

54
48
42
36
30
24
18
12
6
BURYING (seconds)
NORM
UNIS
SEPT
AVTA
UVTA
ALCR
ULCR
LESION

Figure 39

Brainstem Group: Effect of lesion status on burying index.


.90
.80
.70
.60
.50
.40
.30
.20
.10
INDEX (ht/dist)
NORM
UNIS
SEPT
AVTA
UVTA
ALCR
ULCR
LESION

with unilateral septal lesions ($p < .05$).

Statistical data are summarized in Tables 11 and 12.

Table 11

ANALYSIS OF VARIANCE FOR TIME SPENT BURYING TARGET PROD

Septal Group

Source	MS	df	F	p
Lesion	1888.31	5	2.84	.05
Error	665.79	36		

Hippocampal Group

Source	MS	df	F	p
Lesion	1389.93	7	1.63	NS
Error	851.34	45		

Hypothalamic Group

Source	MS	df	F	p
Lesion	2747.57	7	1.13	NS
Error	2439.86	48		

Brainstem Group

Source	MS	df	F	p
Lesion	1331.01	6	1.42	NS
Error	937.30	38		

Table 12

ANALYSIS OF VARIANCE FOR DEFENSIVE BURYING INDEX

Septal Group

Source	MS	df	F	P
Lesion	.38	5	5.25	.01
Error	.07	36		

Hippocampal Group

Source	MS	df	F	P
Lesion	.35	7	2.75	.05
Error	.13	45		

Hypothalamic Group

Source	MS	df	F	P
Lesion	.35	7	3.34	.01
Error	.11	48		

Brainstem Group

Source	MS	df	F	P
Lesion	.26	6	2.82	.05
Error	.09	38		

Experiment 7: Cage Playing

Septal group

Although Figure 40 indicates that normal animals played more than animals with lesions, these differences were not significant. Cage playing, in general, was infrequent.

Hippocampal group

Again, cage playing was not significantly affected by lesion status. However, Figure 41 does indicate that animals with no lesions, medial fimbria lesions, and dorsal fornix lesions exhibited the most cage playing behavior.

Hypothalamic group

Lesion status had a significant effect on cage playing in the hypothalamic group ($p < .05$). As Figure 42 indicates, this is primarily due to the large amount of cage playing observed in the ULPO group. Post hoc analyses revealed that the ULPO animals played significantly more than animals with unilateral septal lesions, or animals with asymmetrical lesions involving either the LPO or MPO area ($p < .05$). Most of this cage playing was exhibited by a single animal in the ULPO group.

Brainstem group

Lesion status had no significant effect on cage playing in the brainstem group. Although Figure 43 reveals a high

Figure 40

Septal Group: Effect of lesion status on cage playing.

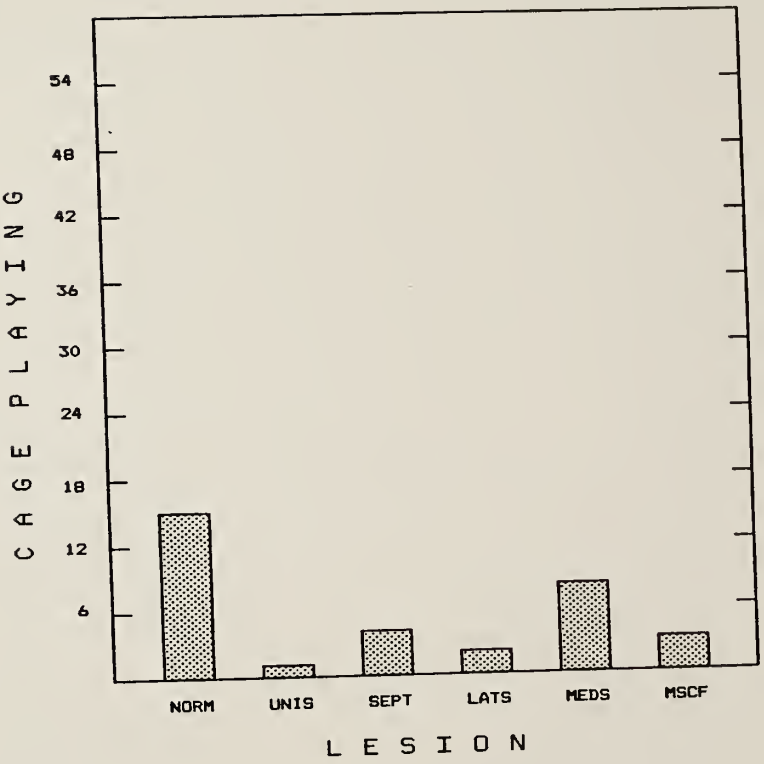

54
48
42
36
30
24
18
12
6
CAGE PLAYING
NORM
UNIS
SEPT
LATS
MEDS
MSCF
LESION

Figure 41

Hippocampal Group: Effect of lesion status on cage playing.

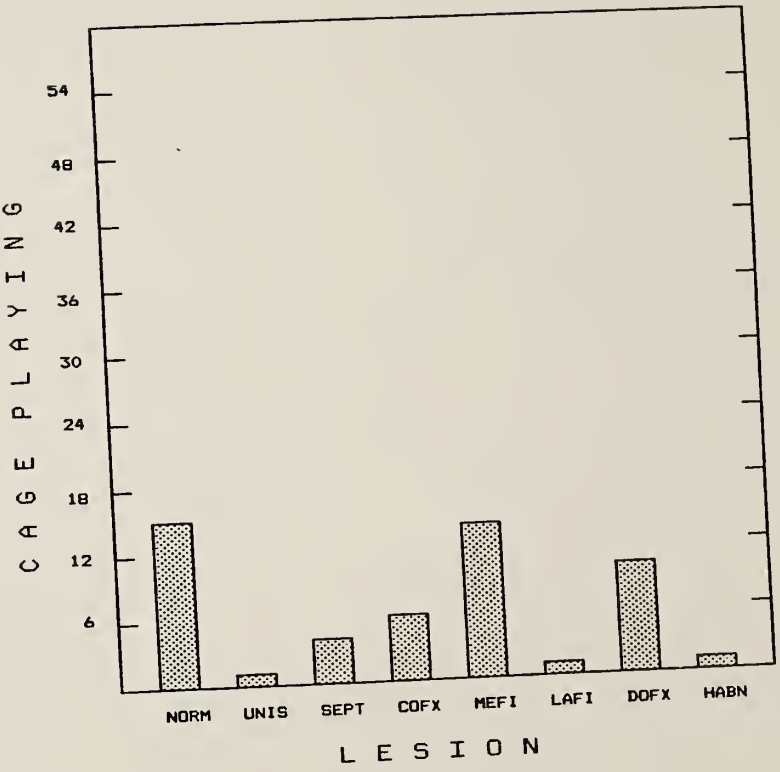

CAGE PLAYING
54
48
42
36
30
24
18
12
6
NORM
UNIS
SEPT
COFX
MEFI
LAFI
DOFX
HABN
LESION

Figure 42

Hypothalamic Group: Effect of lesion status on cage playing.

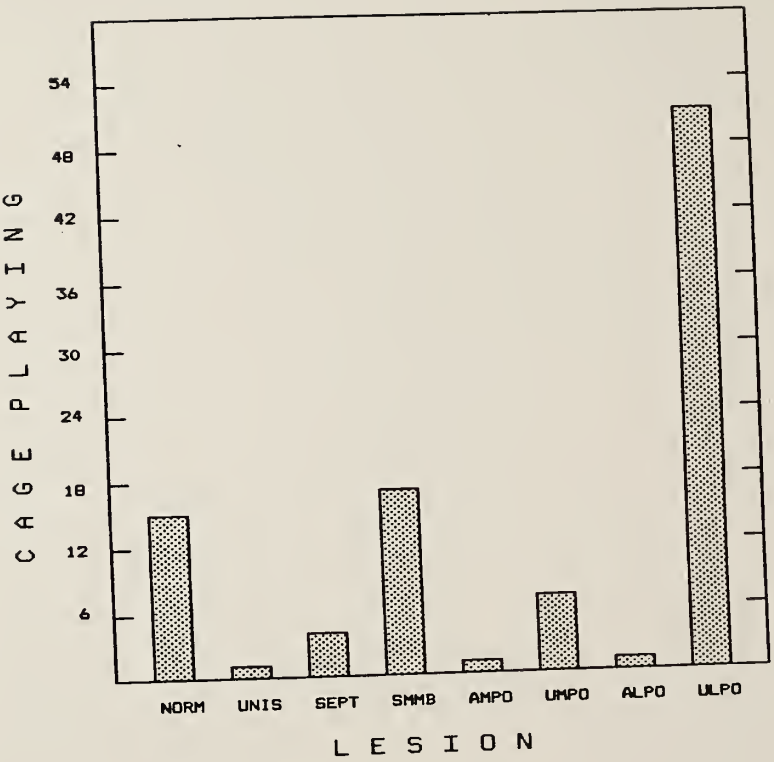
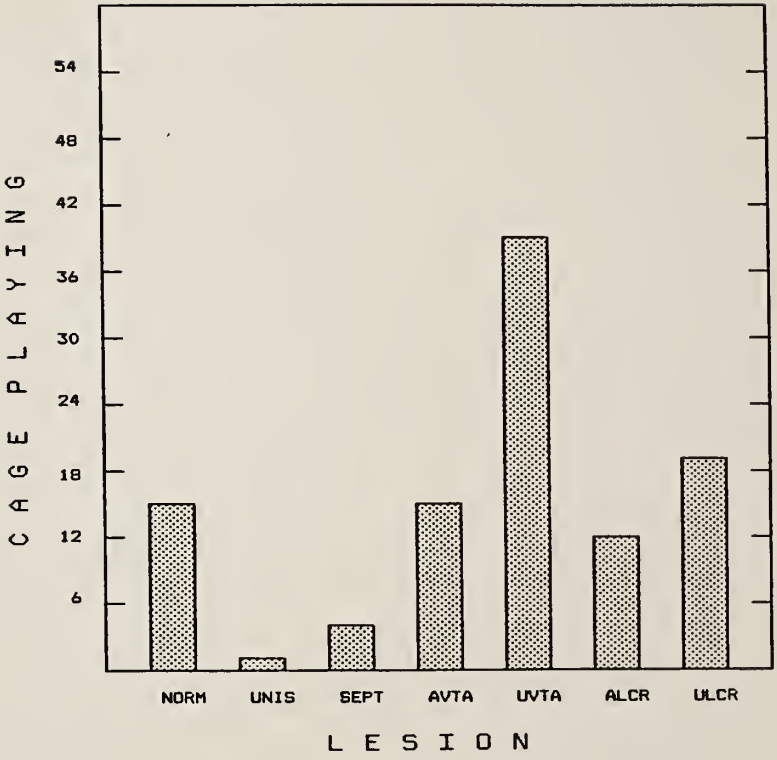

CAGE PLAYING
54
48
42
36
30
24
18
12
6
NORM
UNIS
SEPT
SMMB
AMPO
UMPO
ALPO
ULPO
LESION

Figure 43

Brainstem Group: Effect of lesion status on cage playing.


CAGE PLAYING
54
48
42
36
30
24
18
12
6
NORM
UNIS
SEPT
AVTA
UVTA
ALCR
ULCR
LESION

rate of playing in the UVTA group, this difference was not statistically significant.

Comments

Cage playing was a behavior that was observed infrequently, hence the 10 minute samples per day may be inadequate to determine actual rates of playing. However, data collected at other times during the light/dark cycle produced similar results. Furthermore, animals were remarkably consistent from day to day in terms of the amount of playing exhibited. As with predatory behavior, it seems that some animals are cage-players and some are not, regardless of lesion status.

Statistical data are summarized in Table 13.

Table 15

ANALYSIS OF VARIANCE FOR CAGE PLAYING

Septal Group

Source	MS	df	F	P
Lesion	259.90	5	1.20	NS
Error	216.91	36		

Hippocampal Group

Source	MS	df	F	P
Lesion	251.74	7	.80	NS
Error	315.64	45		

Hypothalamic Group

Source	MS	df	F	P
Lesion	1361.24	7	2.22	.05
Error	614.04	48		

Brainstem Group

Source	Ms	df	F	P
Lesion	869.95	6	1.21	NS
Error	716.80	38		

Experiment 8: Responding on a Variable Interval Schedule

Septal group

As indicated in Figure 44, lesion status significantly affected responding on a variable interval task ($p < .01$). Post hoc analyses reveal that normal animals responded significantly less than animals with bilateral septal or medial septal lesions ($p < .05$). Furthermore, animals with unilateral septal lesions also responded significantly less than animals with bilateral septal or medial septal lesions. There were no significant effects of lesion status on either number of reinforcers earned or number of days required to reach VI-60 (acquisition).

Hippocampal group

Lesion status significantly affected responding on a VI schedule in the hippocampal group ($p < .001$). Figure 45 and post hoc analyses reveal that animals with bilateral septal lesions responded significantly more than animals in all other groups (except LAFI animals) ($p < .05$). There was also a significant effect of lesion status on number of reinforcers earned ($p < .05$). This was primarily due to animals with columns fornix lesions earning more reinforcers than normal animals. There was no significant effect of lesion status on rate of acquisition.

Figure 44

Septal Group: Effect of lesion status on responding on a VI schedule.

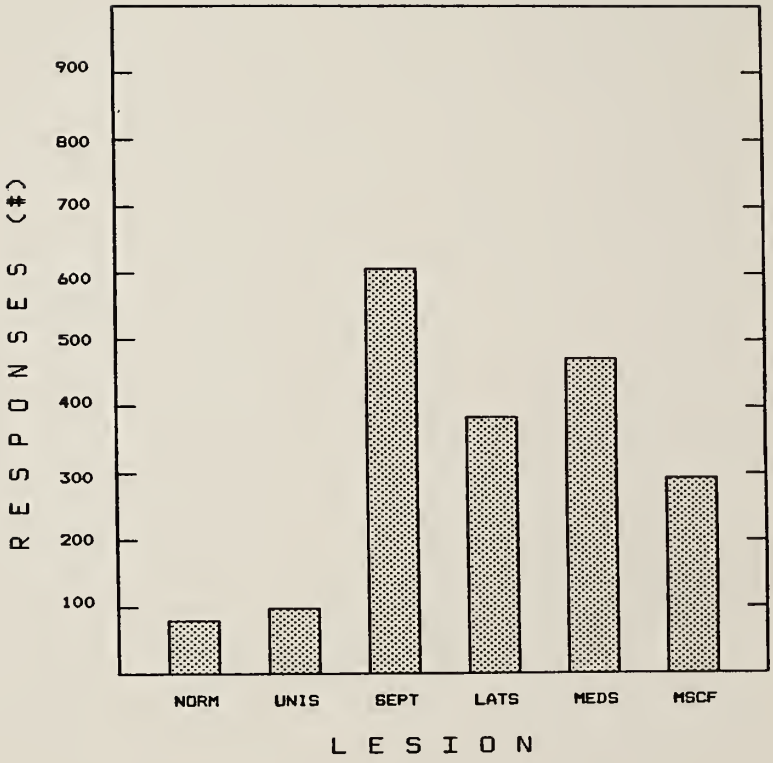
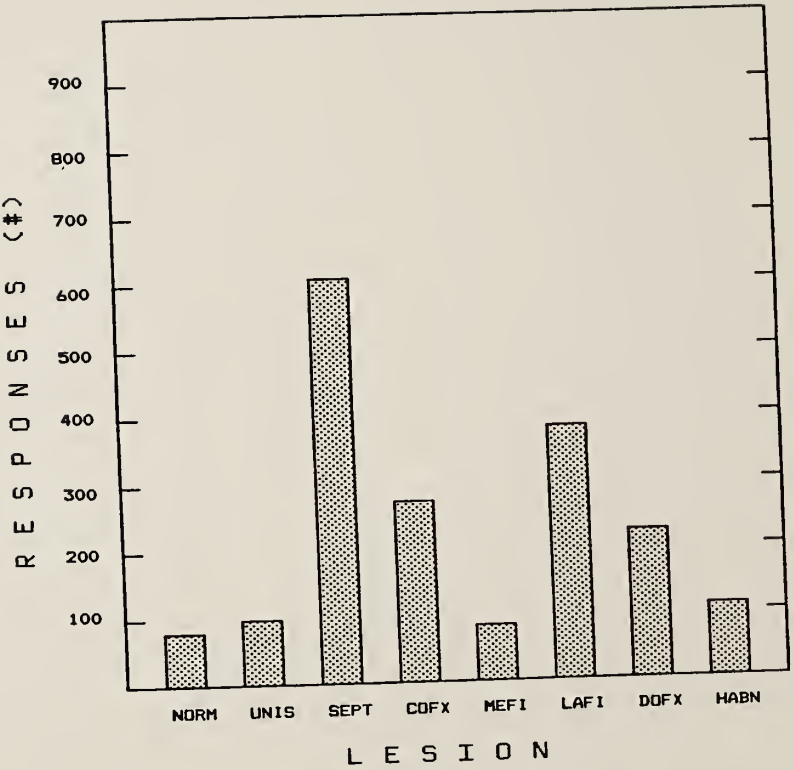

RESPONSES (#)
900
800
700
600
500
400
300
200
100
NORM
UNIS
SEPT
LATS
MEDS
MSCF
LESION

Figure 45

Hippocampal Group: Effect of lesion status on responding on a VI schedule.


RESPONSES (#)
900
800
700
600
500
400
300
200
100
NORM
UNIS
SEPT
COFX
MEFI
LAFI
DOFX
HABN
LESION

Hypothalamic group

Figure 46 indicates that lesion status had a significant effect on responding on a VI task in the hypothalamic group ($p < .001$). Post hoc analyses reveal that animals with septal lesions responded significantly more than normal animals, animals with unilateral septal lesions, and those with unilateral lesions involving the medial preoptic area ($p < .05$). There was no significant effect of lesion status on either number of reinforcers earned or acquisition.

Brainstem group

Responding was significantly affected by lesion status in the brainstem group ($p < .001$). Figure 47 and post hoc analyses indicate that septal lesioned animals responded significantly more than mice with no lesions, unilateral septal lesions, and unilateral lesions involving the locus coeruleus ($p < .05$). Furthermore, animals with asymmetrical lesions involving the VTA responded significantly more than normal animals ($p < .05$). There was no significant effect of lesion status on either number of reinforcers earned or acquisition.

Comments

Although there were no significant effects of lesion status on acquisition rate, there was a definite tendency

Figure 46

Hypothalamic Group: Effect of lesion status on responding on a VI schedule.

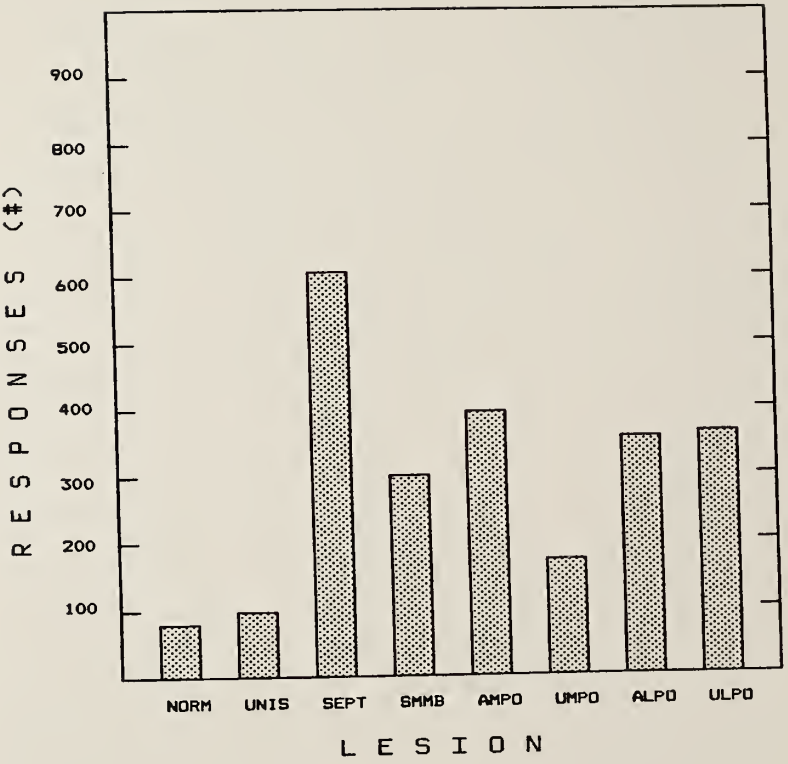
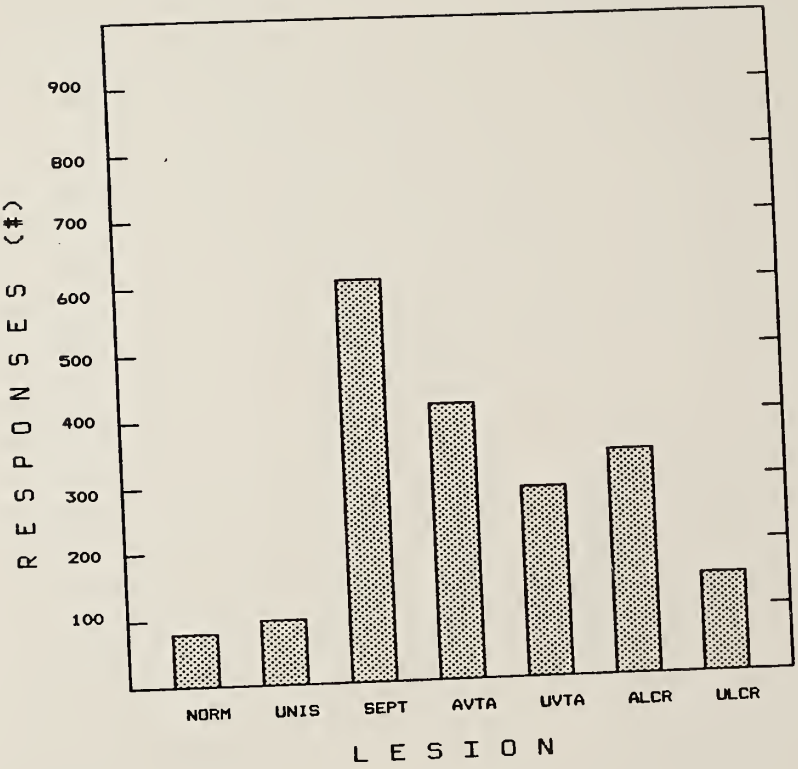

RESPONSES (#)
900
800
700
600
500
400
300
200
100
NORM
UNIS
SEPT
SMMB
AMPO
UMPO
ALPO
ULPO
LESION

Figure 47

Brainstem Group: Effect of lesion status on responding on a VI schedule.


RESPONSES (#)
900
800
700
600
500
400
300
200
100
NORM
UNIS
SEPT
AVTA
UVTA
ALCR
ULCR
LESION

for normal animals to require more time to reach VI-60. The majority of animals achieved VI-60 in less than 10 days. Some normal animals required over 50 days to learn this task. Furthermore, while it could be argued that normal animals are more efficient on the VI task because they emit fewer responses than lesioned animals for the same number of reinforcers it is important to look at the trend in the reinforcement data. This trend reveals that normal animals do in fact earn fewer reinforcers than animals with lesions, even though this difference is not statistically significant.

The statistical data appear in Table 14.

Table 14

ANALYSIS OF VARIANCE FOR RESPONDING ON A VI SCHEDULE

Septal Group

Source	MS	df	F	p
Lesion	310134.00	5	4.85	.01
Error	63956.80	36		

Hippocampal Group

Source	MS	df	F	p
Lesion	195608.00	7	5.21	.001
Error	37523.10	45		

Hypothalamic Group

Source	MS	df	F	p
Lesion	209932.00	7	4.87	.001
Error	43128.80	48		

Brainstem Group

Source	MS	df	F	p
Lesion	236996.00	6	5.28	.001
Error	44898.50	38		

Experiment 9: Two-Way Active Avoidance Behavior

Septal group

Lesion status had a significant effect on both total number of avoidances ($p < .001$) and latency to avoid the conditioned stimulus ($p < .001$). Figure 48 and post hoc analyses reveal that normal animals made significantly fewer avoidances than animals with lesions in any part of the septal region ($p < .05$). Furthermore, when normal animals did avoid, they took significantly longer to shuttle, as indicated in Figure 49 ($p < .05$). Normal animals also made fewer spontaneous crosses than animals with lesions, but this difference was not significant.

Hippocampal group

Lesion status did not significantly affect number of avoidances or latency to shuttle in the hippocampal group, as can be seen in Figures 50 and 51. However, normal animals, animals with columns fornix lesions, and those with dorsal fornix lesions did cross significantly less than animals in the other groups ($p < .05$).

Hypothalamic group

Lesion status had a significant effect on both number of avoidances ($p < .001$) and latency to shuttle ($p < .001$) in the hypothalamic group, as seen in Figures 52 and 53.

Figure 48

Septal Group: Effect of lesion status on total number of avoidances.

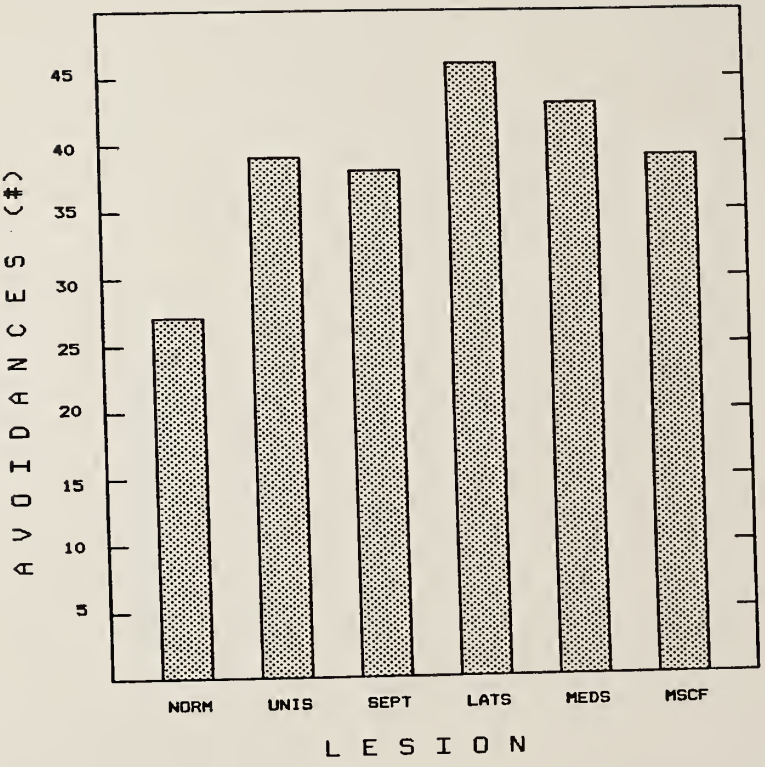

AVOIDANCES (#)
45
40
35
30
25
20
15
10
5
NORM
UNIS
SEPT
LATS
MEDS
MSCF
LESION

Figure 49

Septal Group: Effect of lesion status on latency to avoid.

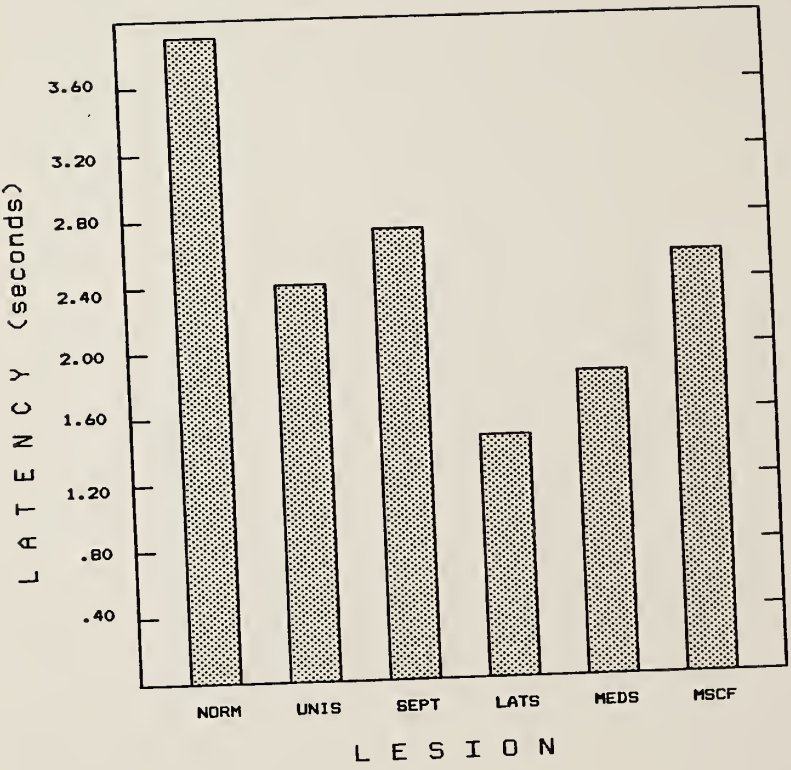

LATENCY (seconds)
3.60
3.20
2.80
2.40
2.00
1.60
1.20
.80
.40
NORM
UNIS
SEPT
LATS
MEDS
MSCF
LESION

Figure 50

Hippocampal Group: Effect of lesion status on total number of avoidances.

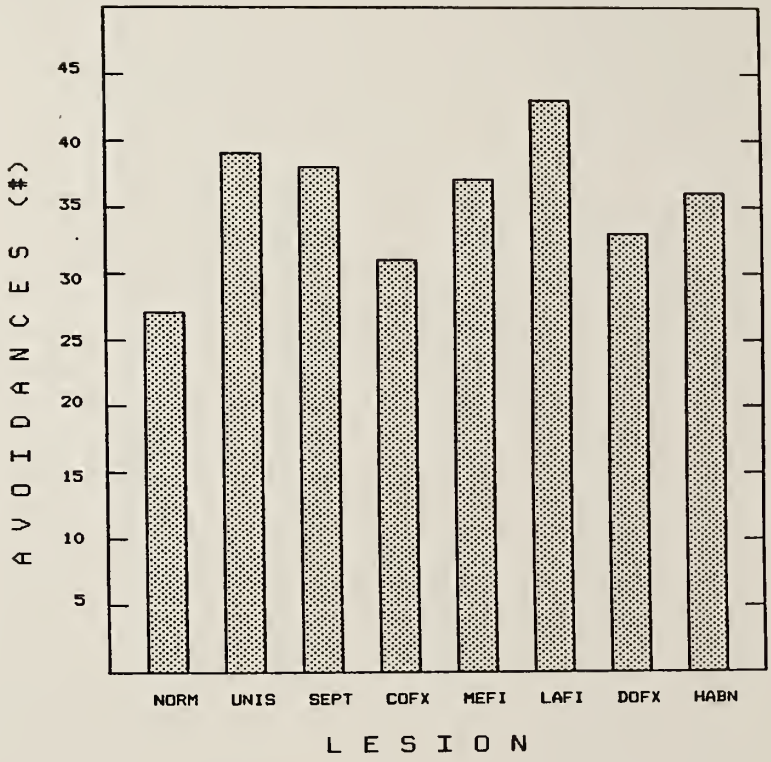

AVOIDANCES (#)
45
40
35
30
25
20
15
10
5
NORM
UNIS
SEPT
COFX
MEFI
LAFI
DOFX
HABN
LESION

Figure 51

Hippocampal Group: Effect of lesion status on latency to avoid.

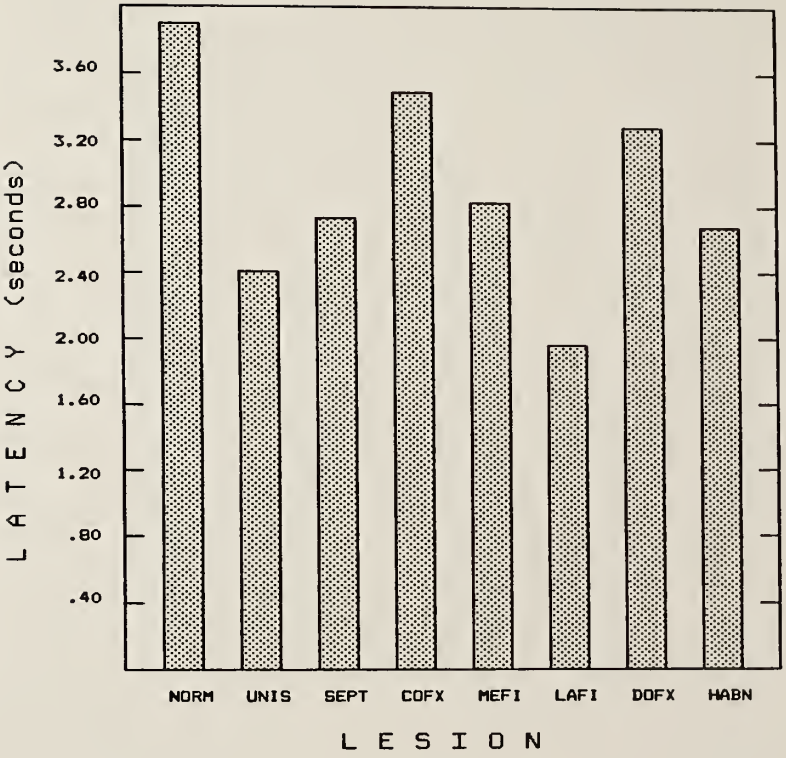

LATENCY (seconds)
3.60
3.20
2.80
2.40
2.00
1.60
1.20
.80
.40
NORM
UNIS
SEPT
COFX
MEFI
LAFI
DOFX
HABN
LESION

Figure 52

Hypothalamic Group: Effect of lesion status on total number of avoidances.

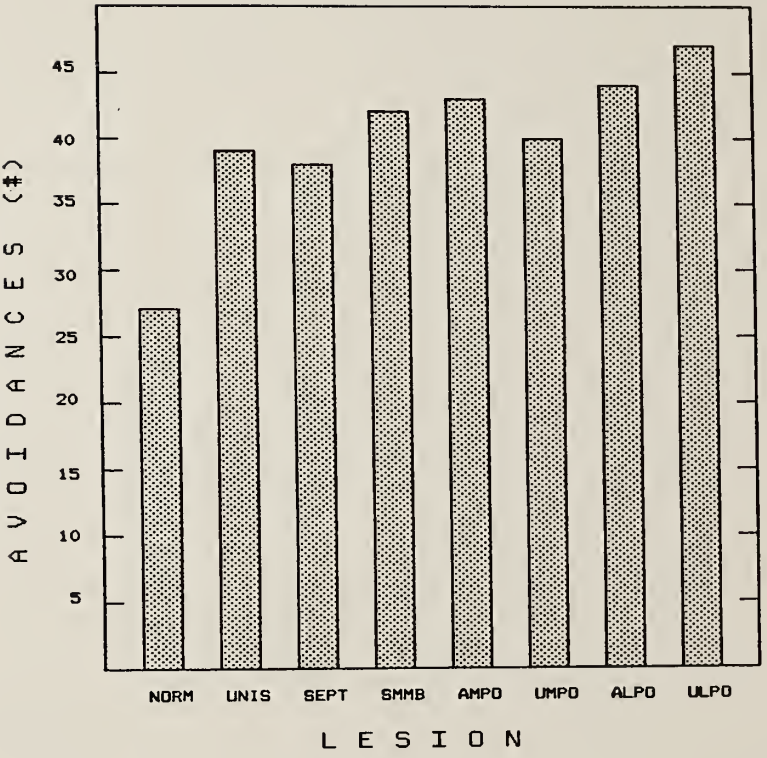
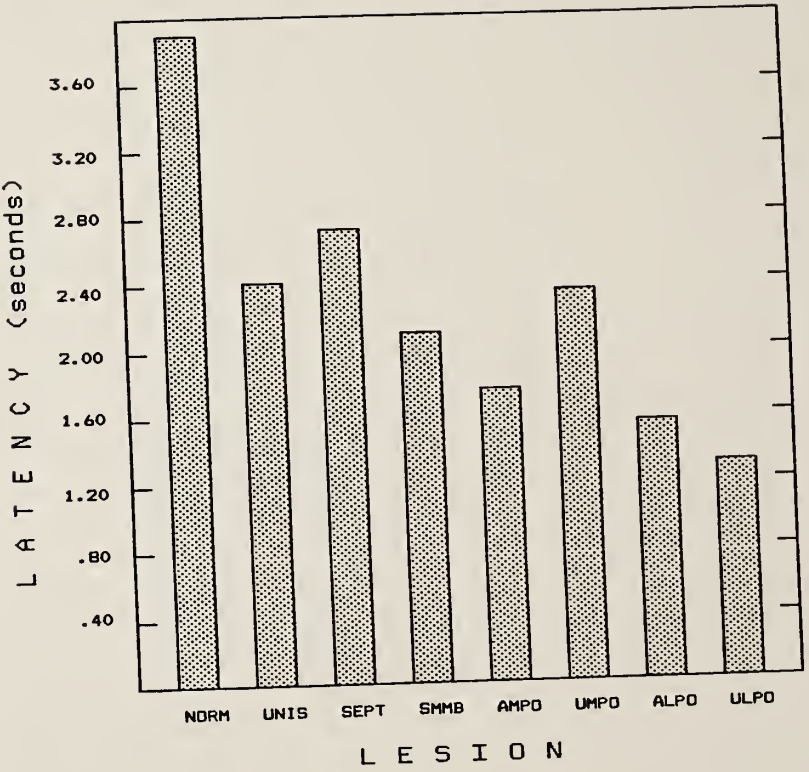

AVOIDANCES (#)
45
40
35
30
25
20
15
10
5
NORM
UNIS
SEPT
SMMB
AMPO
UMPO
ALPO
ULPO
LESION

Figure 53

Hypothalamic Group: Effect of lesion status on latency to avoid.


LATENCY (seconds)
3.60
3.20
2.80
2.40
2.00
1.60
1.20
.80
.40
NORM
UNIS
SEPT
SMMB
AMPO
UMPO
ALPO
ULPO
LESION

Again, normal animals made significantly fewer avoidances and took significantly longer to shuttle than animals with lesions ($p < .05$). Again, normal animals also crossed less frequently between trials than animals with lesions, but this difference was not significant.

Brainstem group

Lesion status again had a significant effect on number of avoidances ($p < .05$) and latency to avoid ($p < .05$), as seen in Figures 54 and 55. Normal animals emitted fewer avoidance response than animals with lesions. Furthermore, normal animals took longer to avoid than animals in other groups. However, post hoc analyses revealed that the only significant difference was between normals and the AVTA group ($p < .05$). Lesion status also significantly affected number of spontaneous crosses ($p < .01$). Post hoc analyses showed that normal animals crossed significantly less than animals in the AVTA, ALCR, and ULCR groups ($p < .05$).

Behavioral descriptions

Observations of the behavior of normal animals during a trial revealed that the typical response to the conditioned stimulus was to freeze and/or jump repeatedly in the "unsafe" chamber. On the other hand, lesioned animals simply crossed into the "safe" chamber in response to the CS without emitting other "competing" responses.

Figure 54

Brainstem Group: Effect of lesion status on total number of avoidances.

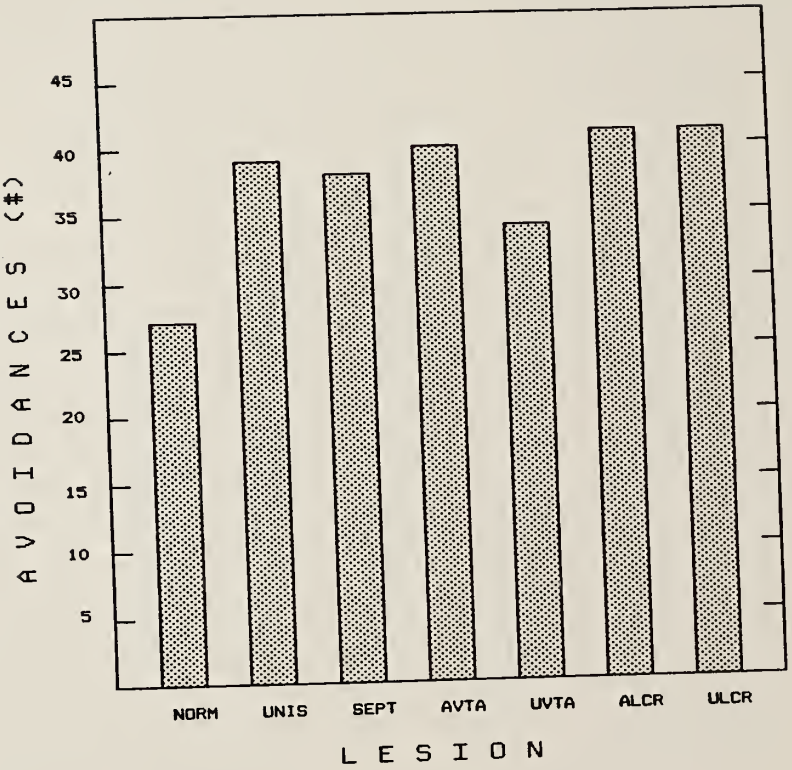
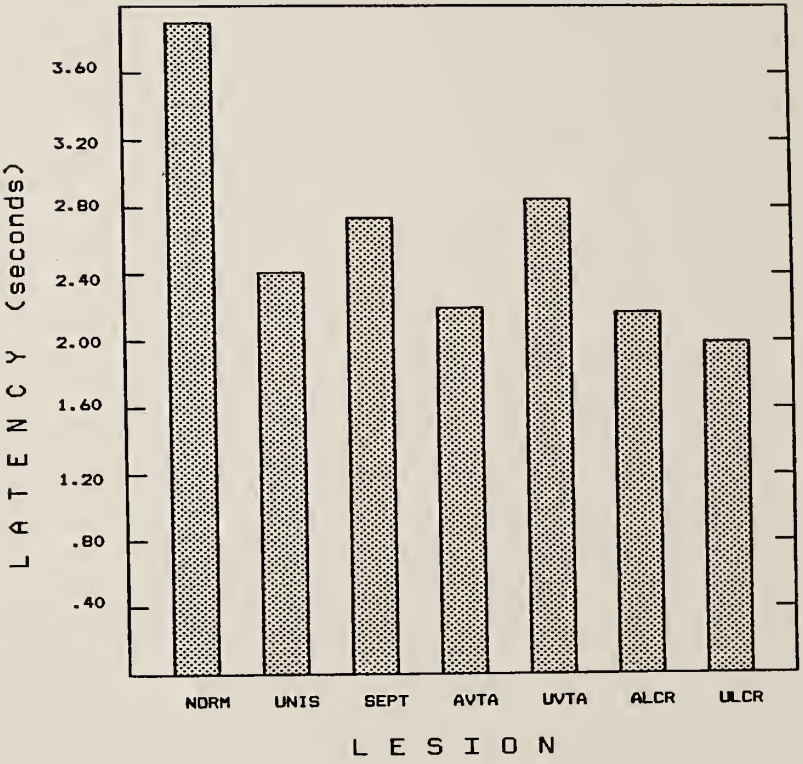

AVOIDANCES (#)
45
40
35
30
25
20
15
10
5
NORM
UNIS
SEPT
AVTA
UVTA
ALCR
ULCR
LESION

Figure 55

Brainstem Group: Effect of lesion status on latency to avoid.


LATENCY (seconds)
3.60
3.20
2.80
2.40
2.00
1.60
1.20
.80
.40
NORM
UNIS
SEPT
AVTA
UVTA
ALCR
ULCR
LESION

Statistical data are summarized in Tables 15 and 16.

Table 15

ANALYSIS OF VARIANCE FOR TOTAL NUMBER OF AVOIDANCES

Septal Group

Source	MS	df	F	p
Lesion	423.85	5	5.66	.001
Error	74.88	36		

Hippocampal Group

Source	MS	df	F	p
Lesion	197.48	7	2.14	NS
Error	92.25	45		

Hypothalamic Group

Source	MS	df	F	p
Lesion	360.64	7	4.79	.001
Error	75.24	48		

Brainstem Group

Source	MS	df	F	p
Lesion	257.84	6	2.55	.05
Error	100.94	38		

Table 16

ANALYSIS OF VARIANCE FOR LATENCY TO AVOID

Septal Group

Source	MS	df	F	p
Lesion	6.59	5	6.79	.001
Error	.97	36		

Hippocampal Group

Source	MS	df	F	p
Lesion	2.82	7	2.20	NS
Error	1.28	45		

Hypothalamic Group

Source	MS	df	F	p
Lesion	5.85	7	5.52	.001
Error	1.06	48		

Brainstem Group

Source	MS	df	F	p
Lesion	3.85	6	2.76	.05
Error	1.40	38		

Overall Results

The overall results from the previous experiments are summarized in Tables 17 through 20.

Results of Correlational Analyses

Performance on the nine behavioral tasks was correlated to determine if animals that showed deficits on one task also showed deficits on another task, regardless of lesion status. Animals that failed to dig sand also failed to hoard food pellets ($r = .447$, $p < .01$) . Animals that were inefficient hoarders tended to construct nests of poor quality ($r = .465$, $p < .01$). However, inefficient hoarders responded more on the VI task ($r = -.363$, $p < .05$) and made more avoidances in the shuttlebox task ($r = -.424$, $p < .01$). Animals that constructed poor quality nests also performed well on the active avoidance task ($r = -.398$, $p < .05$). Defensive burying and shuttlebox performance were also correlated ($r = -.359$, $p < .05$). Within the shuttlebox task, animals that crossed frequently between trials also were more successful avoiding the shock ($r = .371$, $p < .05$). Furthermore, not surprisingly, number of avoidances and latency to avoid were inversely correlated such that mice that made more avoidance responses also avoided more quickly ($r = .979$, $p < .01$).

Table 17

SUMMARY OF RESULTS FROM THE SEPTAL GROUP

	UNIS	SEPT	LATS	MEDS	MSCF
Sand Digging	-*	--*	--*	--*	--*
Hoarding	-*	--*	--*	--*	--*
Predation	0	0	0	-	-
Wheels	0	0	0	0	0
Nests	-*	--*	--*	--*	--*
Burying	--*	-*	-*	0	-*
Playing	-	-	-	0	-
VI Task	0	++*	+	+*	+
Avoidance	+*	+*	+*	+*	+*

*significant at .05 level.

+ indicates increase in behavior compared to controls
- indicates decrease in behavior compared to controls
0 indicates no change

Table 18

SUMMARY OF RESULTS FROM THE HIPPOCAMPAL GROUP

	COFX	MEFI	LAFI	DOFX	HABN
Sand Digging	--*	-	-	+	0
Hoarding	--*	-*	--*	0	0
Predation	-	-	-	0	-
Wheels	0	-	-	-	0
Nests	-*	0	--*	0	0
Burying	0	0	-	0	0
Playing	-	0	-	0	-
VI Task	+	0	+	0	0
Avoidance	0	0	0	0	0

*significant at .05 level.

+ indicates increase in behavior compared to controls
- indicates decrease in behavior compared to controls
0 indicates no change

Table 19

SUMMARY OF RESULTS FROM THE HYPOTHALAMIC GROUP

	SMMB	AMPO	UMPO	ALPO	ULPO
Sand Digging	0	0	0	0	0
Hoarding	-*	--*	-*	-*	-*
Predation	-	-	0	--*	-
Wheels	0	0	0	+	0
Nests	-*	--*	0	-*	0
Burying	--*	-	-	0	--*
Playing	0	-	-	-	+
VI Task	+	+	0	+	+
Avoidance	+*	+*	+*	+*	+*

*significant at the .05 level.

+ indicates increase in behavior compared to controls
- indicates decrease in behavior compared to controls
0 indicates no change

Table 20

SUMMARY OF RESULTS FROM THE BRAINSTEM GROUP

	AVTA	UVTA	ALCR	ULCR
Sand Digging	0	0	-	-
Hoarding	-	0	--*	-*
Predation	-	-	-	-
Wheels	+	+	+	0
Nests	-*	0	-*	0
Burying	0	0	0	0
Playing	0	+	0	0
VI Task	+*	+	+	0
Avoidance	+	+	+	+

*significant at the .05 level.

+ indicates increase in behavior compared to controls
- indicates decrease in behavior compared to controls
0 indicates no change

General Histological Results

The lesions were evaluated in terms of per cent destruction to target tissue. The average destruction in each lesion group can be found in Appendix D. Also included is information on whether extraseptal structures were damaged or not. Sample lesions can also be found in Appendix D. In general, the success rate for bilateral lesions was high (near 90%), whereas success rate for asymmetrical and unilateral lesions was considerably lower (near 65%). Success rate was determined by the number of animals that had lesions of an appropriate size in the target area. Brainstem lesions were particularly difficult to produce accurately, because of the lack of a brainstem atlas for mice and because of the small size of the target structure.

C H A P T E R I V

DISCUSSION

Review of Anatomy

The connections between the septal region and other limbic structures are listed in Table 21. In addition, the relevant neurotransmitters are included, if known.

Species-Typical Behavior

Sand digging

The behavior of sand digging is most disrupted by lesions in the septal area. Connections with hypothalamic areas (MPO/LPO/MMB) and with the midbrain (VTA) do not seem to be of major importance. Septo-hippocampal connections are most involved, as indicated by the disruption seen after lesions of the medial and lateral fimbria. The most disruption was observed following lesions of the medial fimbria. Damage to the fornix columns also disrupted sand digging, indicating a possible role for the postcommissural fornix. The postcommissural fornix carries fibers to the preoptic area, hypothalamus, and mammillary bodies; it does not enter the septal region. However, sand digging was not disrupted following lesions of the preoptic areas or mammillary bodies; hence this is a perplexing finding.

Table 21

SUMMARY OF CONNECTIONS WITH THE SEPTAL REGION

Structure	Connection	Direction	Transmitter
Hippocampus	Dorsal Fornix	Reciprocal	??
	Medial Fimbria	Reciprocal	ACh
	Lateral Fimbria	Reciprocal	ACh
Habenula	Stria Medullaris	Reciprocal	??
Preoptic Area	Medial Forebrain Bundle	Reciprocal	Several NE, DA
Mammillary Bodies	Medial Forebrain Bundle	Mostly Outputs*	??
Ventral Tegmental Area	Mesolimbic Pathway	Reciprocal	DA
Locus Coeruleus	Dorsal Tegmental Bundle	Mostly Inputs**	NE

* Outputs of septum
** Inputs of septum

ACh Acetylcholine
NE Norepinephrine
DA Dopamine

There is also a possibility that the locus coeruleus plays a role in this behavior as sand digging was disrupted following asymmetrical and unilateral lesions involving this brainstem structure.

Comparisons to other investigators' findings is not possible, as the effect of lesions on this behavior has been relatively unstudied to date.

Food hoarding

Not surprisingly, food hoarding is most disrupted following lesions of the septal region, especially the medial septum. All connections studied appear to play a role in this behavior. Again, disruption of septo-hippocampal connections affected food hoarding (lateral and medial fimbria), as did lesions of the locus coeruleus. Furthermore, lesions in any part of the preoptic area (MPO/LPO) and damage to the mammillary bodies also disrupted food hoarding. In addition, lesions involving the ventral tegmental area also disrupted food hoarding. In terms of connections with the septal region, the most disruption occurred following lateral fimbria lesions. About the only lesions that did not disrupt food hoarding were lesions of the dorsal fornix and habenula.

These findings are consistent with those observed by Wishart et al. (1969), Knight (1970), and Shipley and Kolb

(1977) regarding the effects of septal lesions. Shipley and Kolb (1970) also observed deficits following hippocampal lesions, consistent with the deficits found in this study after fimbria lesions. Furthermore, Simon and LeMoal (1978) noted food hoarding deficits following lesions of the ventral tegmentum. Similar disruption was noted following lesions of the ventral tegmental area in the present study. The nature of these deficits is also strikingly similar to that described by Knight (1970) and Shipley and Kolb (1977). These authors viewed the problem as an inability to properly sequence chains of behavior. In the present study, mice with lesions in the areas mentioned above behaved in an inefficient "self-defeating" manner. If they hoarded pellets at all they used the most costly strategy of carrying individual pellets in the mouth. Efficient hoarders moved quantities of pellets at a single time by pushing or kicking the pellets with their front and back paws. Inefficient hoarders were also observed to carry pellets in both directions (to the home cage, and back to the hoarding box); occasionally home cage bedding was carried into the tube as well. Furthermore, inefficient hoarders also ate frequent small meals in the tube or hoarding box whereas efficient hoarders typically hoarded all their pellets and then settled down to eat in the home cage. This behavior suggested that the inefficient hoarder

did not have a clear sense of what was the home cage and what was not the home cage.

Predatory behavior

Contrary to expectations, lesions of the septal region did not enhance predatory behavior in mice. This prediction was based on observations of cockroach killing in septal lesioned animals and on the literature on muricide. Lesions (just about anywhere) generally had the effect of suppressing cricket killing. However, the only significant finding was that animals with asymmetrical lesions of the lateral preoptic area and septum took much longer to kill than normal animals. Most other groups showed deficits, but these were not significant. Slight facilitation of killing was observed in mice with bilateral septal lesions and in animals with dorsal fornix lesions; these differences were also not significant.

These results are not consistent with the literature on muricide which shows that septal lesions enhance interspecies aggression (Albert & Brayley, 1979; Albert et al., 1981; Wallace & Thorne, 1978). The results are also in conflict with the study by Albert and colleagues (1982) that showed that medial hypothalamic lesions enhance muricide. The present study noted the most disruption of cricket killing following lesions involving the LPO, anterior to the

hypothalamus. These discrepant results could be explained by stating that muricide involves different neural circuits than cricket killing. Predatory behavior has not been extensively studied in the mouse. Another explanation concerns the distinction in the literature between "spontaneous killers" and "nonkillers." Some rats are simply more apt to kill prey, regardless of experience. It is possible that this applies to mice as well, and perhaps subjects in the present study should have been evaluated prior to surgery to determine their "killer status." However, it is important to note that only one out of twelve normal animals was a "nonkiller" in the present study. This is probably not a biased group, as normals were selected from all batches of animals that arrived from Jackson Laboratory.

Wheel running

Wheel running was not significantly affected by any of the lesions performed. There was a trend for decreased wheel running following lesions of the septal region and fimbria. On the other hand, high rates were recorded from individual animals in certain groups (DOFX, AVTA, UVTA, ALCR). As a result, the means are not truly representative of the group as a whole (medians might be better).

With the exception of the individual animals just

mentioned, overall rates of running were quite low (means did not exceed 100 and normals averaged around 33). Previous studies in this laboratory have recorded quite different rates from normal animals (averaging around 250 revolutions per 30 minute period) and mice with septal lesions (averaging around 50 revolutions per 30 minute period). The overall low rates in the present study may be due to the use of progesterone pellets. The implants were used to maintain a constant hormonal state, because wheel running normally fluctuates across the estrous cycle (Wade, 1976). However, Wade also notes that activity is depressed by progesterone in nonovariectomized females. Hence, it may be desirable to observe lesion effects on wheel running across the estrous cycle in females (no progesterone) or it may be preferable and simpler to study these effects in male mice.

Nest-building

Nest-building was significantly disrupted by many of the same lesions that disrupted food hoarding. Clearly, lesions in the septal region disrupted nest building as noted in the past by several investigators (Carlson & Thomas, 1968; Shipley & Kolb, 1977; Slotnick & Nigrosh, 1975). Hippocampal connections seem to be important in this behavior, as lateral fimbria lesions dramatically disrupted

nest-building. This is consistent with the findings concerning depressed maternal behavior following hippocampal lesions (Kim, 1960; Kimble et al., 1967; Shipley & Kolb, 1977). Hypothalamic connections also play a role, as nest-building is disrupted following asymmetrical lesions involving the septum and the medial and lateral preoptic areas. This is consistent with the results presented by Numan (1974) and Marques et al. (1979) concerning the effect of medial preoptic lesions on maternal behavior.

Some disruption of nest-building is also seen after lesions involving the ventral tegmental area and locus coeruleus. The findings concerning VTA lesions are consistent with the results of the Gaffori and LeMoal (1979) study which noted severely disturbed maternal behavior following lesions of the ventral tegmentum. The disruption following locus coeruleus damage again suggests the importance of brainstem connections in this behavior.

The disruption in nest-building seen after lateral fimbria and preoptic area lesions may be attributable to different causes. Preoptic area lesions may disrupt nest-building by altering hormonal control of this behavior (Numan, 1983) and/or thermoregulatory mechanisms (Schneider, Lynch, Possidente, & Hegmann, 1982). The effect on thermoregulation is important, because the mice in the

present study were not pregnant and presumably were building nests in response to other factors (possibly in response to temperature). Of course, the nest-building in this study was stimulated by progesterone implants, but progesterone plays a role in both maternal and thermoregulatory nest-building (Schneider, Lynch, & Gundaker, 1983). On the other hand, the nest-building disruption seen after fimbria lesions is possibly due to spatial disorganization, as suggested below by the tendency of lesioned animals to build several nests.

Unfortunately, the nature of the nest-building deficit cannot be described precisely, as nests were rated once a day for five days. It would be instructive to have information on exactly how animals went about constructing nests or not constructing nests. Generally, animals that received poor ratings did so because they either failed to shred twine at all or shredded it but dispersed it haphazardly over the floor of the home cage. Future studies should examine nest-building behavior as well as quality of nests. It would also be sensible to include measures such as time spent in the nest, number of nests constructed, and time to construction of a high quality nest. It is conceivable that all animals would build nests if given enough time to do so.

Defensive burying

The results on defensive burying are perplexing because unilateral septal lesions produce more of a deficit than large bilateral septal lesions, at least according to the burying index. Animals with bilateral lesions do spend less time burying than animals with unilateral lesions, but the latter are unable to effectively bury the prod in the time they spend burying. At any rate, lesions in the septal region (except medial septal lesions) do disrupt defensive burying as predicted from the study by Gray and colleagues (1981). Some disruption is seen after lateral fimbria lesions, but other hippocampal connections do not seem to be involved. Hypothalamic connections appear to play more of a role, with clear disruption occurring after damage to the mammillary bodies and preoptic area. Finally, lesions of either the ventral tegmental area or locus coeruleus have very little effect on this behavior.

Cage playing

Cage playing is in general disrupted by lesions in the septal region, but overall the incidence of cage playing is low. Most other lesions also depress cage playing, with the exception of unilateral lesions involving either the lateral preoptic area or ventral tegmental area. These high rates can be explained by individual animals who always exhibited

cage playing throughout the observation period. After observation of several hundred animals it is apparent that some animals are "players" and some are "nonplayers", much as some rats are "killers" and some are "nonkillers." To confirm this, it would be prudent to take longer and more frequent samples of the animals' cage playing behavior.

Conditioned Behavior

Responding on a variable interval schedule

As expected, lesions in the septal region enhanced responding on a variable interval schedule. This is consistent with the results of several studies cited earlier (for example, Ross & Grossman, 1975). Hippocampal connections play a role in this facilitation, particularly the lateral fimbria and postcommissural fornix. Grossman (1978) also observed enhanced responding following fimbria and hippocampal lesions. The enhanced responding following columns fornix lesions suggests that the postcommissural fornix is also important. Enhanced responding also occurs following lesions in the preoptic area and brainstem, but the only significant elevation occurred in the AVTA group. This finding was not predicted as the literature has emphasized the importance of connections between the medial septum and hippocampus.

It is important to determine whether this overresponding is inefficient or not. Normal animals are clearly able to withhold responses, and at the same time earn about the same number of reinforcers as lesioned animals making two to three times the number of responses. This would suggest that lesioned animals are actually very "wasteful" of their responses. What is most likely going on, as suggested earlier, is that normal animals are able to space their target responses in time because they have available to them a repertoire of time-filling mediating behaviors (species-typical responses). These same behaviors are disrupted in animals with lesions and hence the animal has nothing else to do but make the target response. What still requires explanation, however, is the question of why operant responses are spared and species-typical behaviors are not. It is possible that the animal retains the ability to make one kind of response, a discrete non-continuous response (nose-poking) but is unable to sustain a stereotyped chain of responses (food hoarding) or a continuous response (such as digging or burying).

Support for the idea that lesioned animals are unable to engage in time-filling behaviors comes from a study by Carlson and Rice (unpublished observations) using a DRO (differential reinforcement for other behaviors) schedule. Animals with septal lesions perform very poorly on DRO

schedules; they simply do not engage in behaviors other than the operant even when they are reinforced for engaging in these behaviors. Furthermore, another study by Carlson and Rice indicated that mice with septal lesions are unable to sustain a continued response. In this study, animals were reinforced for maintaining a nose-poke response (for keeping their heads in the poke hole). While animals with septal lesions are superior at making many brief nose-poking responses, they are unable to hold or prolong the response even when being reinforced for such behavior.

Regarding the idea that lesions disrupt chaining, it is possible that species-typical chains are disturbed. However, it is not at all clear that animals are unable to learn chains of behavior. In fact, a study by Carlson and Cole (1970) showed that animals with septal lesions performed better on a sequential lever-pressing task than control animals. Hence, the precise nature of the effect of lesions on conditioned behavior remains unresolved.

Two-way active avoidance behavior

As predicted by the Ross et al. study (1975), virtually any lesion involving damage to the septal area facilitated performance on the shuttlebox task. This was true for all lesions in the hypothalamic group and brainstem group (all included lesions to the septum on one side). Curiously,

lesions that did not involve the septum in the hippocampal group did not significantly affect avoidance responding. Hence, there seems to be something special about damage to septal tissue.

The nature of this facilitation can be described as follows. Animals that avoided readily simply shuttled as soon as the conditioned stimulus was presented. Normal animals tended to engage in incompatible species-typical responses like jumping and freezing. It should also be noted that animals that avoided readily made frequent spontaneous crosses, or crosses between trials. Normal animals rarely crossed. All crosses were punished. Blatt (1976) argues that this punishment adversely affects normal animals and suppresses their shuttling response, whereas lesioned animals are not as affected by the punishment and hence show "nonsuppression" rather than facilitation. Certainly it would be important to examine avoidance responding in lesioned animals when intertrial responses are not being punished. However, it is not clear why lesioned animals are "less punished". Gray and McNaughton (1983) note that septal lesions do not decrease an animal's reactivity to shock; if anything, reactivity is increased and it would seem that lesioned animals should be "more punished." It seems preferable to view the enhanced

shuttlebox performance as being due to the absence of incompatible defensive behaviors, as mentioned above.

Nature of the Behavioral Changes

It is clear from the foregoing experiments that the limbic system plays a pivotal role in species-typical behaviors like nest-building, food hoarding, and so forth. One of the most interesting aspects of this disruption in the nature of the deficit. As mentioned several times, animals with limbic lesions seem singularly unable to sustain continuous responses like sand digging or defensive burying, or chains of responses that are involved in food hoarding and nest-building. This deficit can be seen as a disturbance of orientation in both time and space.

Many of the deficits observed in the present study can be described as impairments in an animal's memory of where it is in space or where it has just been in the last few moments of time. For example, the inefficient food hoarders behaved as if they had no conception of home cage as being different from tube or hoarding box. They carried pellets in both directions, ate pellets in all three areas, and even carried bedding into the tube and hoarding box. Furthermore, they appeared to be unable to chain together various hoarding responses in a reasonable fashion. For example, the efficient animal hoarded virtually all pellets

into the home cage in the first five or ten minutes, piled or buried them in the home cage, and finally settled down to eat. The inefficient hoarder, on the other hand, carried a few pellets back and forth, ate a little, carried a few more, and in general exhibited "unproductive behavior" (for example, crossing many times without pellets). This behavior could be explained as an inability of the animal to remember what it has just done or where it has just been.

This argument can also be applied to nest-building, and perhaps defensive burying and predatory behavior. The nest-building deficits could be explained as an inability of the animal to designate a part of the home cage area as "nest." In many cases, animals with lesions scattered twine haphazardly around the cage or built several nests of poor quality. Normal animals typically had one area designated as a nest, and another as an area to defecate and urinate. Lesioned animals did not exhibit this distinction. The deficits observed on the tests of defensive burying may also be related to an inability to organize responses in space. In many cases lesioned animals dug sand, but either dug all over the field, or buried the control prod. The failure to bury the target prod exclusively may be due to a failure to remember the location of a stimulus that had been the source of aversive stimulation in the past. The predatory behavior

deficits may also be related to an orientation failure. If an animal failed to kill a cricket in the 10 minute test it was usually because the mouse had a great deal of difficulty locating the cricket. The lesioned animals approached the spot where the cricket had been, but failed to shift their approaches when the cricket moved. In fact, the animals often spent a great deal of time piling bedding over nonexistent crickets.

It is more difficult to explain the deficits in sand digging and the minor effects on cage playing and wheel running in these terms.

The effects of lesions on operant behaviors are best explained as being due to an inability of lesioned animals to engage in species-typical behaviors during the task. This would explain why lesioned animals spend so much time making the target response in a VI task; they simply do not have anything else to do but nose poke! Furthermore, lesioned animals do not show the species-typical defensive responses in the active avoidance task that seem to interfere with shuttling in intact animals. This "readiness to shuttle" in lesioned animals could also be explained as an inability of the animal to "remember" the location of a chamber in which it has just been shocked. Hence, deficits in spatial/temporal memory may be involved here as well.

To better assess whether these lesions produce a

spatial memory deficit, a task should be used that measures this more directly than the species-typical behaviors discussed in the present study. To this end, preliminary tests of performance in a swimming pool "milk maze" task have been undertaken. Animals are required to locate a platform hidden in the milk pool, using extra-maze cues only (such as objects in the room or on the wall of the pool). Preliminary results have indicated that many limbic lesions, particularly those involving septo-hippocampal connections, disrupt performance on this spatial memory task. In the present study, lesions that most disrupted species-typical behaviors were also those of the septo-hippocampal system. This was particularly true of lateral fimbria lesions in the following tasks: food hoarding, nest-building, and defensive burying. These are all tasks with an obvious spatial component.

There is a wealth of evidence which suggests the hippocampus plays a critical role in spatial memory. A number of investigators have demonstrated that limbic lesions disrupt spatial memory. Morris, Garrud, Rawlins, and O'Keefe (1982) observed that place navigation in a swimming pool task was impaired following hippocampal lesions in rats. Becker, Walker, and Olton (1980) also observed impairments in memory for a radial arm maze task in

rats with lesions of the fimbria/fornix. Animals with lesions of the amygdala, caudate nucleus, or sulcal frontal cortex did not show these deficits. These findings suggest that an intact septo-hippocampal system is required for performance on spatial memory tasks.

Rawlins and Olton (1982) observed deficits in spatial working memory following lesions of the fornix/fimbria; less permanent deficits were noted following medial or lateral septal lesions. Working memory is defined as operating in situations in which stimulus-response associations change throughout the task. This is contrasted to reference memory which involves unchanging stimulus-response associations (Chozick, 1983). The working memory deficits were observed in an elevated T-maze task in which rats were initially forced to run to one of the goal arms (information run) and were subsequently required to run to the other goal box for reinforcement (choice run). When the procedure was altered so that response-generated cues were not available (the rats were simply placed in one arm or the other on the information run), both control and lesioned rats performed poorly. In a related task, Thomas, Brito, Stein, and Berko (1982) observed working memory impairments following medial septal lesions. These lesions did not disrupt performance on a position task, in which animals learned to always go to the same goal box for reinforcement (this is believed to be

a test of reference memory that involves cues present at the time of the choice). However, performance on an alternation task similar to that described in the Rawlins and Olton (1982) study was disrupted following medial septal lesions. On this task, animals were required to enter the arm of the maze that they had not entered on the previous trial. This was believed to be a test of working memory that is required for the formation of cognitive maps.

Evidence that the hippocampus plays a role in memory for temporal events is provided by Meck, Church, and Olton (1984). These investigators observed that fimbria/fornix lesions disrupted temporal working memory in specific situations; overall sensitivity to time was not affected. These lesions impaired the animal's ability to remember the time of reinforcement and the duration of a gap in a signal that accompanied an FI-20 second schedule. In the latter task, a signal was presented during the FI interval and was terminated by the first response occurring after 20 seconds. On certain interspersed non-reinforcement trials the stimulus remained on for up to 50 seconds, and responding was observed to peak 20 seconds into the interval. When a gap in the signal was introduced, control animals stopped their "internal clocks" and showed that they could remember the duration of the signal prior to the gap. Lesioned

animals apparently did not remember the initial segment of the signal and instead reset their clocks during the gap. In addition to disrupting temporal mapping, these lesions also disrupted performance in an eight-arm radial maze (a spatial memory task, presumably).

Galey, Durkin, Sifakis, Kempf, and Jaffard (1985) described a circuit that they believed to be involved in spatial and temporal memory. They described a system of dopaminergic neurons originating in the A10 cell group (ventral tegmental area) which terminates in the lateral septum and exerts a "tonic inhibition" on the cholinergic septo-hippocampal system. These investigators reasoned that removing this inhibition should facilitate performance on certain memory tasks. They found that animals with 6-hydroxydopamine lesions of the lateral septum (location of the inhibitory interneurons) exhibited better performance than control animals on a spontaneous alternation and spatial discrimination task.

Other studies also support the idea that the septo-hippocampal system is crucial for normal operation of spatial memory. A number of investigators have identified "place neurons" in the hippocampus (O'Keefe, 1976, 1983; Rose, 1983). Place neurons are cells that fire at different rates depending on where an animal is located in space. O'Keefe (1983) has also proposed that place cells may encode

the sequence in which an animal moves from one place to another in the environment. It is likely that these place neurons are regulated by the cholinergic septo-hippocampal system mentioned above, as Whishaw (1985) noted that acetylcholine antagonists such as atropine disrupted place navigation in a swimming pool task. Furthermore, Winson (1978) observed spatial deficits following medial septal lesions that disrupted the hippocampal theta rhythm. The place neurons themselves are not the source of theta rhythm (Kubie & Ranck, 1983). Theta cells are most likely dentate granule cells (and possibly CA_1 pyramids) whereas place cells are complex spike cells found in the pyramidal cell layer of the CA_1 and CA_3 fields of the hippocampus (Rose, 1983). However, theta activity may modulate the excitability of place cells (Winson, 1978). Therefore, because the medial septum controls theta activity, and theta activity in turn influences place neurons, the septo-hippocampal system would appear to play a critical role in behaviors with a spatial component.

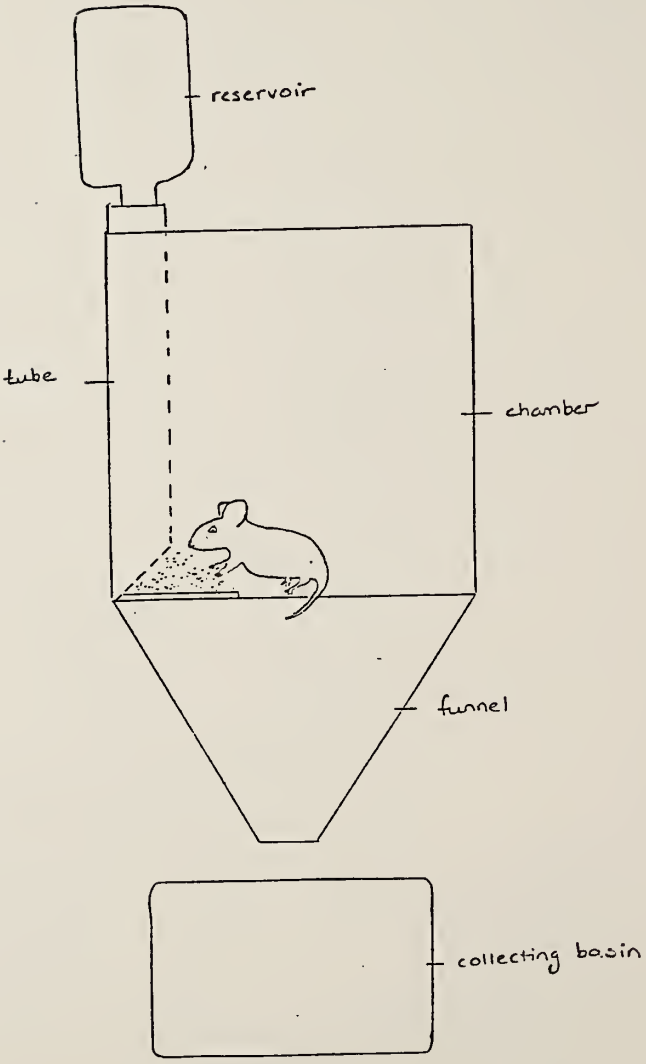
In summary, the limbic system appears to play a critical role in species-typical survival behaviors. Lesions to limbic structures, particularly the septo-hippocampal system, result in disturbances in an animal's ability to locate itself in both time and space. The lack

of species-typical behaviors may further explain why these same animals over-respond on operant tasks. A further examination of the nature of these deficits and the relationship to spatial/temporal memory is indicated.

APPENDIX

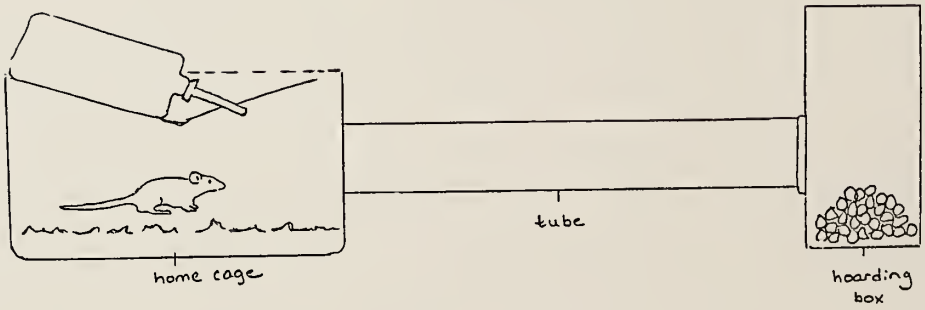
Appendix A

SAND DIGGING APPARATUS



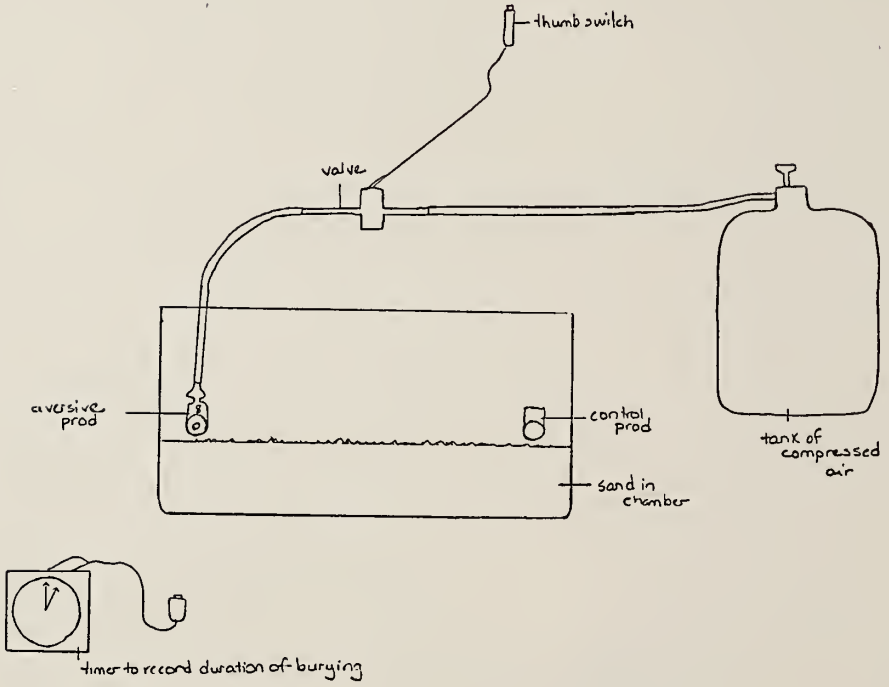
Appendix B

FOOD HOARDING APPARATUS



Appendix C

DEFENSIVE BURING APPARATUS



Appendix D

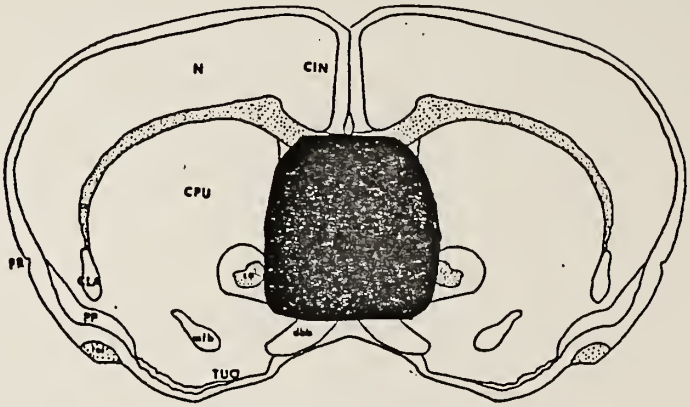
PERCENT DESTRUCTION OF TARGET STRUCTURES

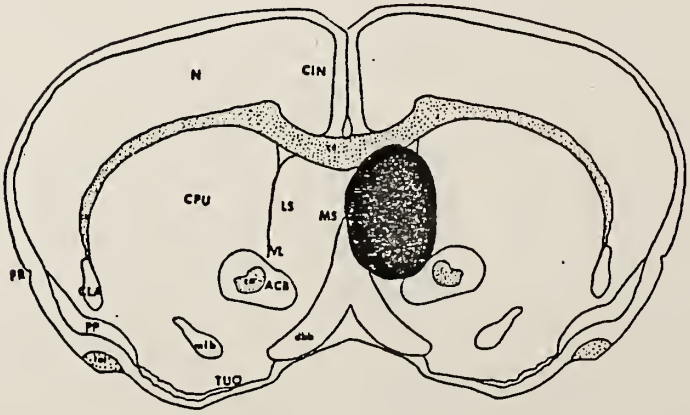
Lesion	Average Destruction	Comments
UNIS	85%	posterior damage 3/7
SEPT-left	86%	
SEPT-right	79%	
LATS-left	82%	
LATS-right	95%	
MEDS	81%	
MSCF-MS	94%	
MSCF-CF	98%	
COFX	86%	thalamic damage 5/8
MEFI	98%	
LAFI-left	78%	
LAFI-right	98%	
DOFX	82%	
HABN-medial	95%	most damage to medial habenular nucleus
HABN-lateral	38%	
SMMB-supra	88%	
SMMB-MMB	73%	
AMPO-sept	87%	damage to AHA in 2/7
AMPO-MPO	86%	
UMPO-sept	94%	damage to AHA in 2/6
UMPO-MPO	89%	
ALPO-sept	93%	
ALPO-LPO	77%	
ULPO-SEPT	88%	
ULPO-LPO	95%	

Appendix D (continued)

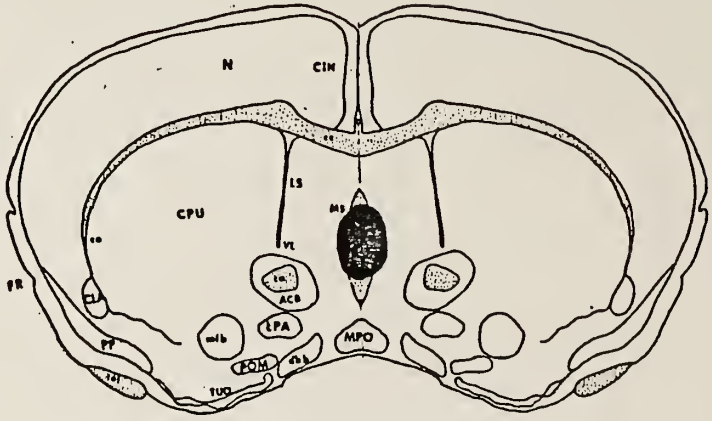
Lesion	Average Destruction	Comments
AVTA-lats	83%	
AVTA-VTA	88%	
UVTA-lats	86%	
UVTA-VTA	93%	
ALCR-sept	83%	
ALCR-LCR	99%	
ULCR-sept	85%	
ULCR-LCR	84%	

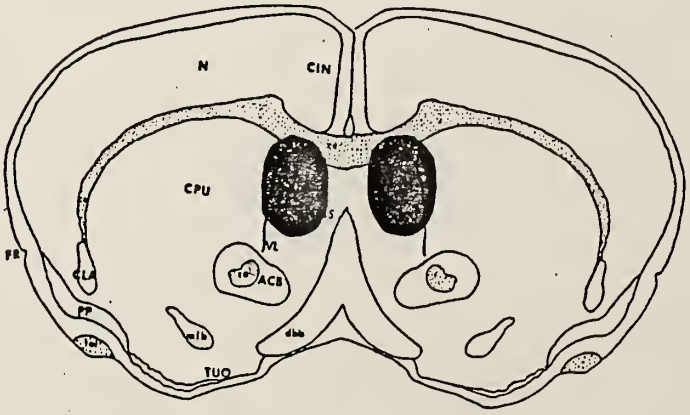
TOP: Typical Bilateral Septal Lesion
BOTTOM: Typical Unilateral Septal Lesion



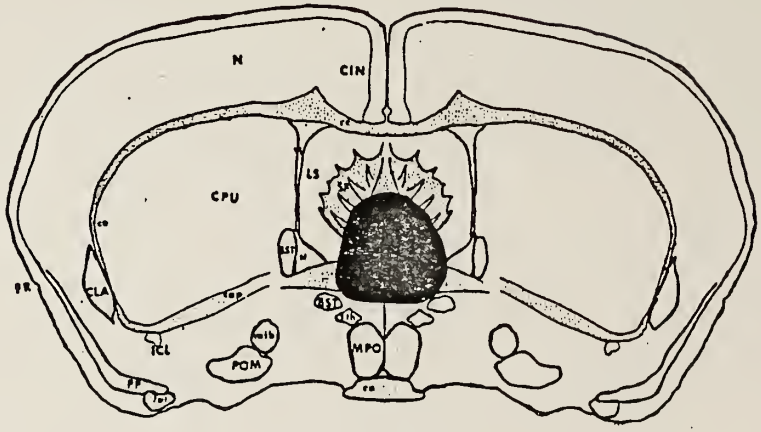


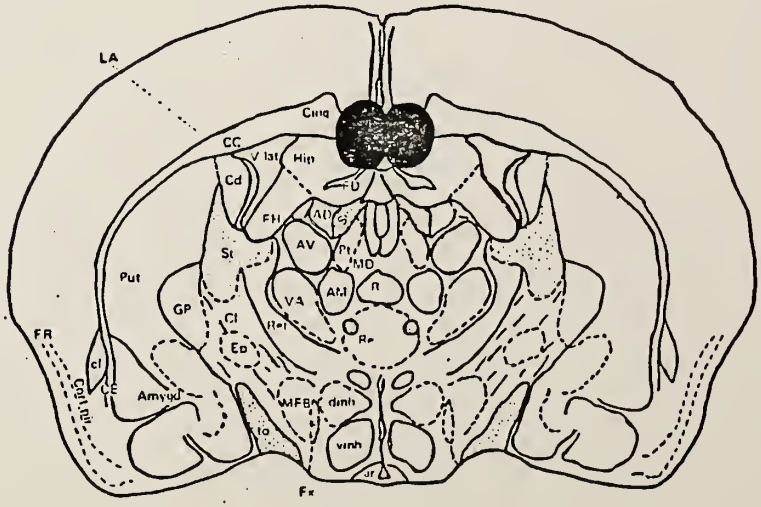
TOP: Typical Medial Septal Lesion
BOTTOM: Typical Lateral Septal Lesion



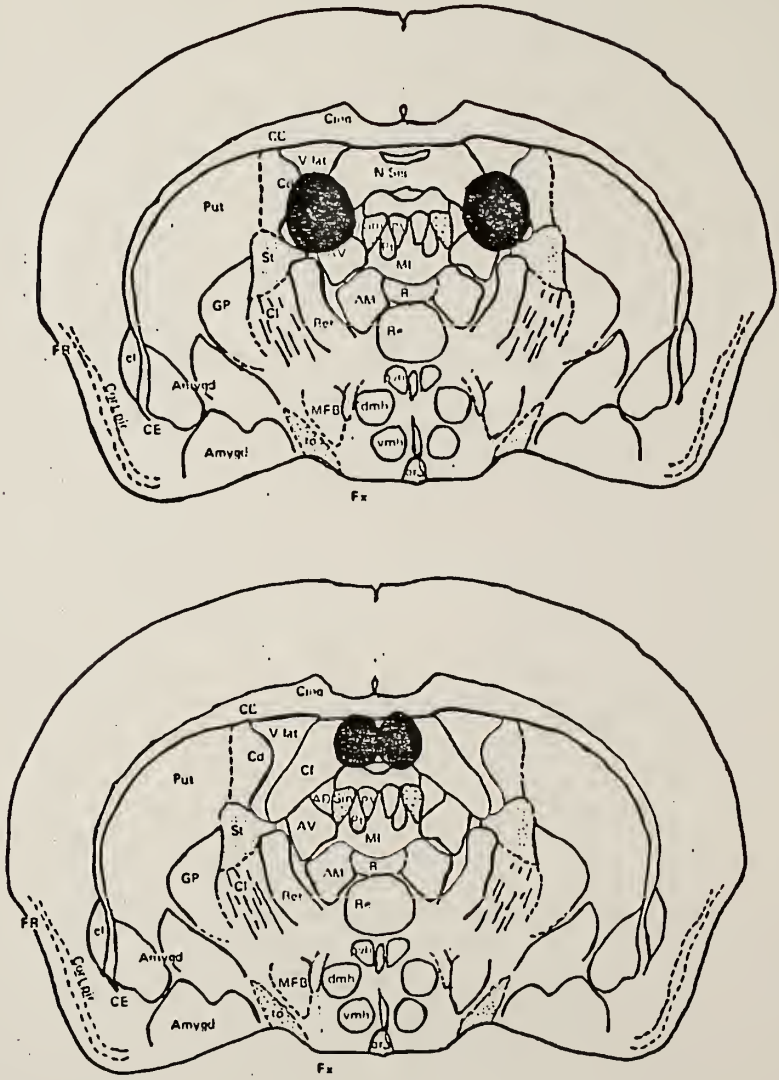


TOP: Typical Columns of the Fornix Lesion
BOTTOM: Typical Dorsal Fornix Lesion

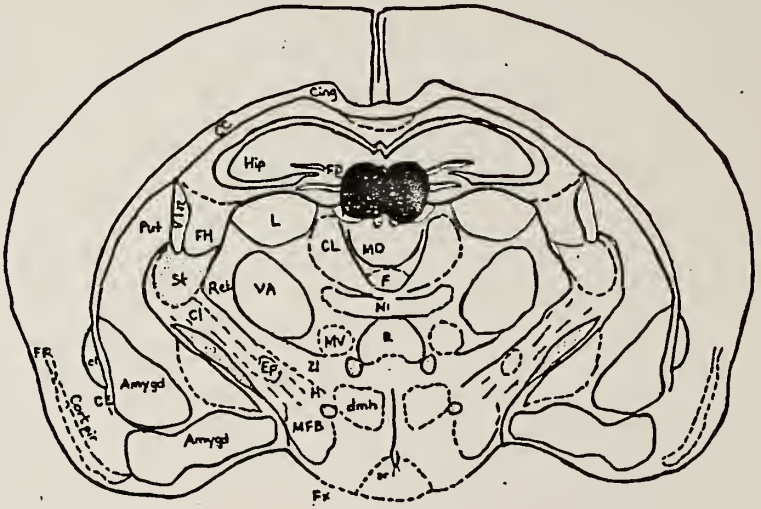


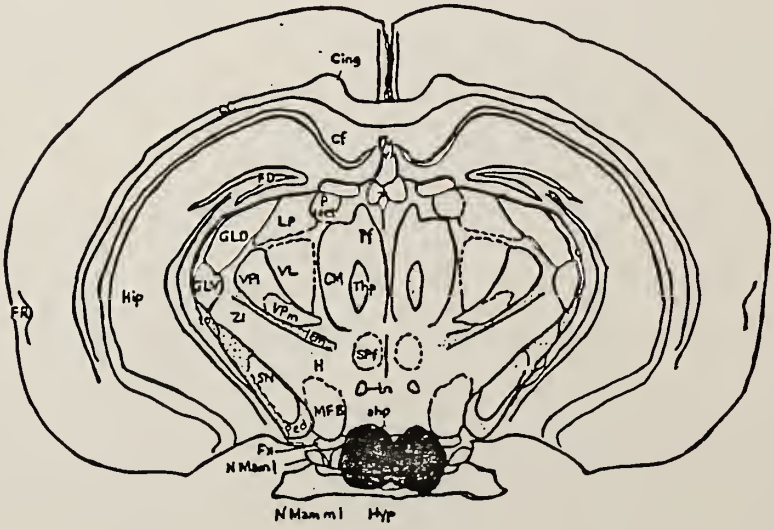


TOP: Typical Lateral Fimbria Lesion
BOTTOM: Typical Medial Fimbria Lesion

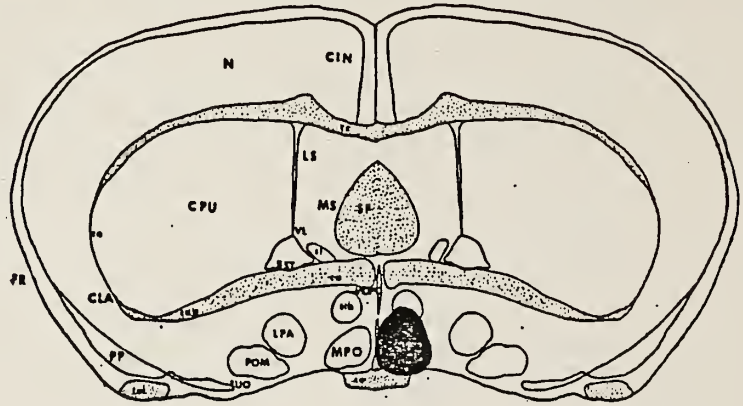


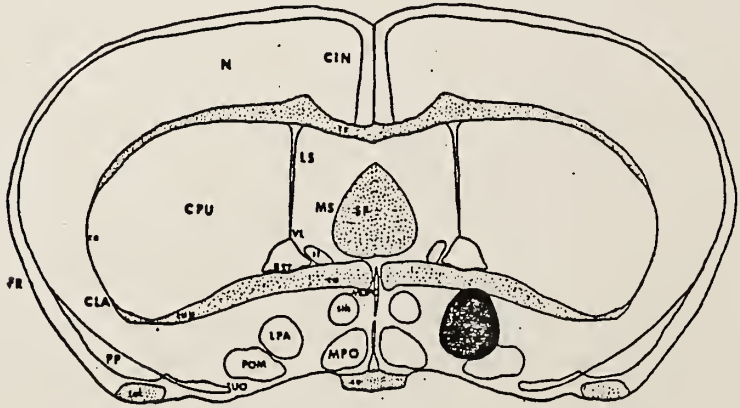
TOP: Typical Habenula Lesion
BOTTOM: Typical Supramammillary/Mammillary Bodies Lesion



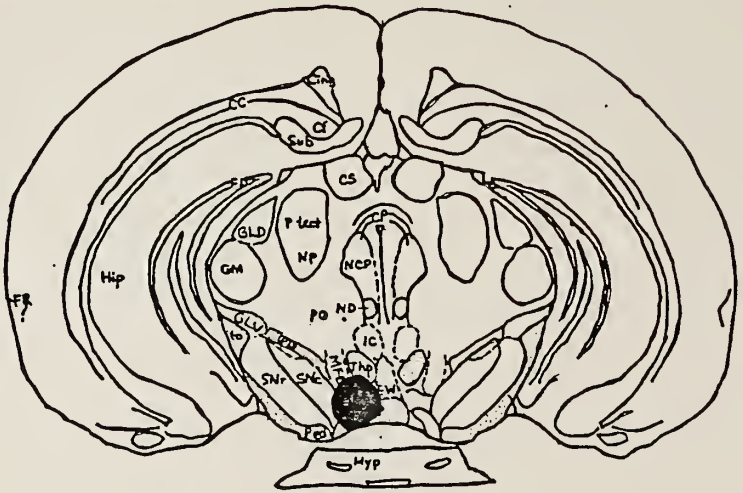


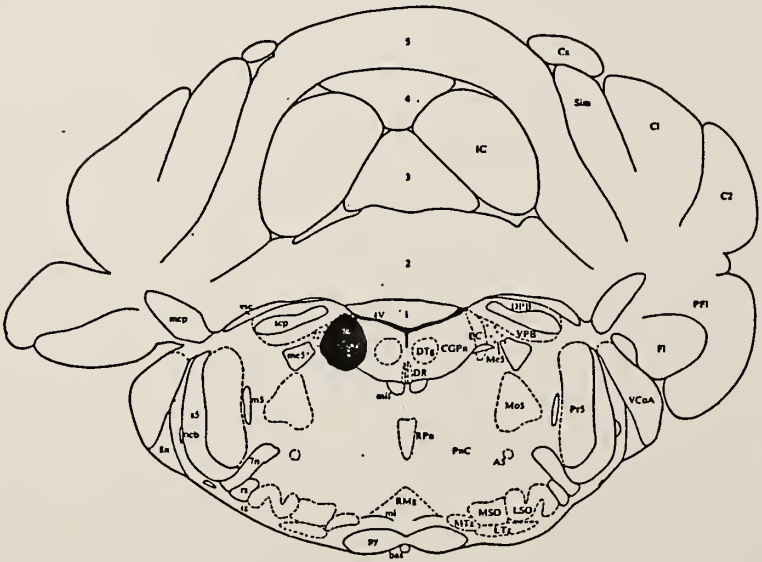
TOP: Typical Medial Preoptic Area Lesion
BOTTOM: Typical Lateral Preoptic Area Lesion





TOP: Typical Ventral Tegmental Area Lesion
BOTTOM: Typical Locus Coeruleus Lesion





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