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The septum and behavior : an experimental analysis of functional anatomy.

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THE SEPTUM AND BEHAVIOR:

AN EXPERIMENTAL ANALYSIS OF FUNCTIONAL ANATOMY

A Dissertation Presented

by

Leanna J. Standish

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ABSTRACT

The Septum and Behavior:

An Experimental Analysis of Functional Anatomy

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Septal lesions in a variety of species have long been known to increase the frequency of operant responding maintained on a variety of schedules of reinforcement. The purpose of Experiment 1 was twofold; first, to determine the relevant anatomical pathways responsible for the abrupt change in the control that the environment has on operant response rates following septal lesions. The second goal was to determine the location of the smallest functionally effective lesion. Following seven days of stable responding on a variable interval 40-second schedule of food reinforcement, male mice received stereotaxic lesions of various sizes and locations within the septal area under brief and light ether anesthesia. During the subsequent seven postsurgical days each subject's response rate and interresponse time distributions were compared with baseline measures.

Fink-Heimer silver terminal and fiber degeneration analyses revealed the following findings. 1) Septal lesions that dramatically increase operant response rates were clearly associated with degenerating fibers and terminals within the lateral fimbria, CA3, CA4, and fascia dentata of the hippocampal formation and the adjacent subiculum. Operant response relevant fibers of septal origin appeared to terminate in the stratum radiatum, the location of basal dendrites of hippocampal pyramidal cells. 2) Lesions within the dorsal diagonal band complex within the medial septal nucleus were sufficient to produce increases in response rates and degeneration within the precommissural fornix, lateral fimbria CA3, CA4, fascia dentata and subiculum. 3) There was a functional relation between postlesion response rate increments over baseline and the amount of terminal and fiber degeneration within the ventral hippocampus. No such relation was found between percent change in response rate and medial forebrain bundle degeneration. The data suggested that neural elements within the dorsal segment of the diagonal band region send fibers into the precommissural fornix that continue caudally through the lateral fimbria into the ventral hippocampus and that this pathway is intimately involved in mediating and modulating operant responding.

Experiment 2 confirmed these findings. Small lesions restricted to the far lateral margin of the lateral fimbria were similarly effective in producing large increments in operant

responding maintained on a VI-40 sec schedule and fiber and terminal degeneration in the ventral hippocampus and fascia dentata. The results from Experiments 1 and 2 are discussed in terms of a general model of limbic system modulation of brain stem motor repertoires and a mathematical interpretation of the relational principle of reinforcement.

The purpose of Part II was to determine through silver degeneration analyses which septal nuclei efferent projections are involved in the hyper-reactivity to tactual stimuli following restricted damage to parts of the septal area ("septal rage"). The anatomical independence of changes in operant response rate and unconditioned emotional behavior was demonstrated. All animals receiving large medial septal lesions displayed large increments in variable interval responding. Only a few of the mice displayed both "septal rage" and increments in operant responding. In these animals heavy degeneration was found in both the hippocampal formation and the dorsomedial nucleus of the thalamus. Thus, the anatomical changes responsible for increases in operant response rates (medial septal/diagonal band complex → CA3, CA4 and the fascia dentata) and those responsible for changes in unconditioned emotional behavior (anterior septal area → dorsomedial nucleus) appear to be quite distinct and independent. Furthermore, the rapid onset of "septal rage" (within 10 minutes) argues against denervation supersensitivity in the dorsomedial nucleus as a likely explanation of septal lesion-induced

hyper-reactivity. These data are discussed in relation to other anatomical findings relevant to septal lesion-induced hyper-reactivity.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

PART I

Limbic System Anatomy and the Operant

The goal of a natural science of behavior is to offer a complete account of the physical variables of which behavior is a function. The behavior of the organism is determined by events occurring both in the public environment and the private environment--the environments outside and inside the skin.

A fundamental assumption of the experimental analysis of behavior is that the behavior of the organism is the result of past and present environments. The relevant events of the past may be further subdivided into phylogenetic and ontogenetic variables. Environments of the very distant past are responsible for the genetic structure of the individual and, hence, the behavior of phylogenetic origin. The controlling variables established in the phylogenetic past have their effects on the present through the genetic structure of the organism. In this way, the behavior of the individual is determined partially by events that occurred millions of years ago. These events responsible for current stimulus control are generally referred to as genetic variables.

The environments with which the tissues of the individual organism have come in contact is the second major source of controlling variables and may be labeled the ontogenetic past. Skinner (1969) concisely summarizes the causal relations between the

organism and the environment as the contingencies of survival (phylogenetic environments) and the contingencies of reinforcement (ontogenetic environments) in the belief that operant conditioning is the major source of ontogenetic behavior change and individuation.

Psychology's important goal is to explain why the behavior of organisms changes. The historian of the future might look upon the last century of psychology and conclude that two important advances were made. First, Darwin explained, through the principle of natural selection, how the behavior of species changes. Second, Thorndike and Skinner explained, in the principle of reinforcement, how the behavior of individuals within a species changes. Clearly, the principle of natural selection and the principle of reinforcement are mutually dependent. The effect that the current environment has on the behavior of an organism is based upon the controlling relation between stimuli and behavior. Such stimulus control is established by phylogenetic environments--the contingencies of survival--and by the ontogenetic environments--the contingencies of reinforcement. The interrelation between the principle of reinforcement and natural selection is no better demonstrated than in learning itself. Through the environmental pressures exerted by the contingencies of survival a class of relations exist between stimuli called biological reinforcers and the responses that immediately precede them. Such reinforcing stimuli are said to have a causal relation with the previously occurring response. In this way, the

behavior of the organism is adapted to the current, ever changing, environment.

Since its inception, the experimental analysis of behavior, as a distinct discipline within psychology, has focused its questions and methods on the analysis of the behavioral effects of variables originating in the public environment--the world outside the skin. The stimuli that originate within the organism have largely been ignored by our current science of behavior. An adequate analysis of private stimuli and behavior has historically been thwarted by other disciplines within psychology, even by the traditional physiological psychology. An important contribution of Skinnerian radical behaviorism has been the insistence that the analysis of private behavior (thinking and feeling) does not require a separate conceptual or methodological framework. The experimental analysis of behavior, both public and private, is the discovery of functional relations between variables (antecedents) and behavior (consequences). Other than technological concerns, the source of these variables, be they public or private, and the consequent behavior, whether overt or covert, has little consequence upon the progress of the science of behavior.

A major objective of physiological psychology is to understand the neural events that mediate operant learning. Changes in the probability of a class of behavior (an operant) are caused by the occurrence of a class of environmental events called reinforcers

that are in causal relation to the previously occurring response. The relation between responses and reinforcers is shown in the paradigm below.

$$\underset{\text{or DEP}}{S^D} \longrightarrow R \longrightarrow S^D \longrightarrow P\uparrow \left(\underset{\text{or DEP}}{S^D} \longrightarrow R\right)$$

A discriminative stimulus (S^D) is usually defined as a state of the public environment that is present when a response (R) is followed by a reinforceing stimulus (S^R). Deprivation (DEP) is an operation defined as the witholding of stimuli (such as food or water) to which the organism has previously had some degree of access. DEP is a short hand means of referring to private discriminative stimuli originating within the organism. An experimental analysis of food deprivation, for example, reveals that metabolic events occurring in the liver may be eliciting stimuli for eating and hunger (Friedman and Stricker, 1976). The symbol S^R indicates a reinforcing stimulus, while P ($\uparrow$) indicates an increase in the probability of whatever is within the parentheses, the "operant response". Thus, the paradigm indicates that when an operant is followed by a reinforcing stimulus, the subsequent probability of that operant is increased. The dependent relation between the three terms of the contingency (S^D, R and S^R) is referred to as the operant (Winokur, 1976).

As yet, it is not known how events occurring within the nervous system change the probability of a response that immediately precedes the occurrence of a reinforcing stimulus. While impressive progress has been made in elucidating the principles by which an organism's behavior is altered by environmental variables, little research has been focused on discovering the class of brain responses that are affected by the same reinforcing stimuli that control the operant. A suitable technology has yet to be fully developed.

A brief overview of the progress made towards understanding the neural bases of learning might include the replicated observations that discrete monoamine pathways are involved in reinforcement (German and Bowden, 1974; Olds, 1977), permanent neuronal changes may be dependent upon simultaneous pre- and postsynaptic activity (Cragg, 1974), and that the establishment of permanent functional changes in the behavior of neurons may depend upon a small class of neurotransmitters, the catecholamines, which may mediate these permanent functional changes through alterations in cyclic AMP levels and subsequent alterations in gene expression (Carlson, 1977; Dunn and Bondy, 1974; Entingh, Dunn, Glassman, Wilson, Hogan and Damstra, 1975).

To date, it is unclear as to which brain structures are affected by reinforcing stimuli and hence underlie the elicitation processes at the heart of conditioning. Because electrical stimulation of the medial forebrain bundle has dramatic reinforcing effects,

these fibers, the cells that give rise to them, their sites of termination and their synaptic biochemistry have been implicated in reinforcement mechanisms (German and Bowden, 1974). Many ascending medial forebrain bundle (MFB) fibers terminate in a group of the midline forebrain structures, the septal nuclei (Lindvall and Björklund, 1974). Efferent fibers from the medial nucleus of the septum heavily contribute to the descending projection of the MFB, as well as projecting many efferent fibers that terminate in the hippocampus. In light of the intimate relations between the MFB and the septum, it is not surprising that electrical stimulation of the septum has reinforcing properties. Similarly, destruction of the medial septal nucleus has profound effects on both the acquisition and asymptotic response rates of positively reinforced behavior (see Fried, 1972 for review). Lesions of the medial septum immediately and permanently increase the response rate controlled by a variety of schedules of reinforcement in a variety of species.

The septal area lies in a special position relative to the rest of the limbic system and is in an excellent position anatomically to integrate and modulate the activity of a large number of brain structures. Raisman (1966) views the septal nuclei as a critical region integrating neural activity between telencephalic limbic structures and the diencephalon and mesencephalon. All parts of the septum receive massive input from a number of limbic regions as well as from the hypothalamus. Its influence over other brain regions is as widespread as its sources of incoming fibers.

The septal area lies below the most anterior portion of the corpus callosum, bounded anteriorly by the hippocampal rudiment and posteriorly by the postcommissural fornix. At the rostral end of the septum lies the medial septal nucleus and the nucleus of the diagonal band of Broca, while lateral to the medial septal nucleus lies the anterior portion of the lateral septal nucleus. Caudally, the medial septal nucleus becomes smaller and finally disappears as the lateral septal nuclei join together at the midline before disappearing at the level of the fornix. The medial septal nucleus is penetrated by fibers of the precommissural fornix which enter the nucleus at an oblique angle. The area between the two bundles of the precommissural fornix is called the nucleus triangularis septi.

The cytoarchitecture of the septal area reveals homogeneous nuclear areas consisting of medium sized neurons. Despite few differences in cytoarchitecture, the septal region has been divided into various subregions. In the anterior portion of the septal area, near the nucleus of the diagonal band, giant cells are found, but only in the medial septal nucleus. These cells project to the hippocampus and undergo degeneration when the fornix is severed (Isaacson, 1974).

Below is a summary of the anatomical connections of the septal nuclei of the rat. This summary is drawn from several sources using a variety of techniques (Chronister and White, 1975; Isaccson,

1974; Powell, 1963; Powell and Hines, 1975; Raisman, 1966; Raisman, Cowan and Powell, 1969).

DIENCEPHALIC AFFERENTS

1. All diencephalic afferents to the septal region travel in the medial forebrain bundle which recruits fibers from areas along the base of the brain as far caudal as the dorsal and ventral tegmental nuclei (midline central gray).

2. The dorsal noradrenergic bundle, originating in the locus coeruleus, joins the medial forebrain bundle and sends fibers into the medial septal nucleus.

3. Some reports have mentioned projections to the septum from the thalamus (midline thalamus, intralaminar nucleus and anteroventral nucleus).

DIENCEPHALIC EFFERENTS

1. All parts of the septal area project fibers through the diagonal band of Broca to terminate diffusely in the lateral hypothalamic area.

2. This diagonal band/MFB pathway seems to send efferents to the preoptic, supraoptic and periventricular nuclei of the hypothalamus. Diencephalic septal efferents through the medial forebrain bundle are said to terminate as far caudally as the tegmental nuclei.

3. Some experimenters report fibers from the septofimbrial nucleus travelling in the stria medullaris to terminate in the medial habenular nucleus. It is clear that lesions of only the very caudal septum send fibers to the habenular nuclei.

4. One degeneration study revealed projections from the ventral medial septum and nucleus of the diagonal band through the medial forebrain bundle and inferior thalamic peduncle to terminate in the dorsomedial nucleus of thalamus.

5. Some believe the septum to send terminating axons into the superior colliculus through the stria medullaris and to the inferior colliculus through the internal capsule and brachium of the inferior colliculus.

6. Lesions of the posterior medial septal area have been reported to result in degenerating terminals in anteroventral and reticular thalamic nucleus. Dorsolateral septum contributes fibers to stria medullaris to terminate in anteromedial, anteroventral, reticular, and reuniens nuclei.

TELENCEPHALIC AFFERENTS

1. All septal nuclei (medial septal nucleus, lateral septal nucleus, nucleus of the diagonal band, septofimbrial nucleus and nucleus trianularis) receive fibers from some area of the hippocampus

2. Hippocampal areas CA3 and CA4 project directly to the medial septal nucleus and the nucleus of the diagonal band and indirectly to these nuclei through the lateral septal nucleus.

3. CA3 and CA4 of the ventral hippocampus projects to the dorsolateral quadrant of the lateral septal nucleus through the lateral margin of the fornix bilaterally.

4. The dorsal hippocampus (CA1) projects to the medial septal nucleus via the medial fornix and precommissural fornix. These fibers also project to the nucleus of the diagonal band. Some of these CA1 fibers travel to the septal area through the dorsal fornix.

5. Posterior CA1 projects to the medioventral quadrant of the lateral septal nucleus.

6. Pyriform cortex, basolateral amygdala and the olfactory tubercle project fibers into the diagonal band of Broca and enter the medial septal nucleus.

TELENCEPHALIC EFFERENTS

1. Some anatomists report septo-hippocampal efferents to only the inferior region of the hippocampus (CA3 and CA4 and the hilus of the fascia dentata). Septo-hippocampal terminals project mostly to the strata oriens and stratum radiatum of CA3 and CA4.

2. Others report the existence of projections from the medial septal nucleus that enter the body of the fornix and the dorsal fornix and terminate in both dorsal and ventral hippocampus over the alveus.

3. Still others report that medial septo-hippocampal projections terminate only in the dorsal hippocampus.

4. Some studies state that the lateral septal nucleus has no hippocampal projections, while others report lateral septal fibers terminating in the ventral hippocampus.

5. The medial septal nucleus has been said to project terminals into the subiculum and adjacent allocortex.

6. Lesions of the dorsal septal area result in degeneration in the dorsal region of the body of the fornix, while posterior midline lesions result in degenerating fibers in the lateral tip of the fimbria/fornix.

Given the extensive interconnections that the septal area has with the rest of the central nervous system it is not surprising that destruction of all or part of this nuclear complex has a variety of profound effects on behavior. Some of these effects are anatomically and behaviorally quite distinct from the effects that medial septal lesions have on operant responding. During the last decade a large literature has accumulated attempting to behaviorally analyze the effects of these lesions (see Caplan, 1973; Fried, 1972

and Isaacson, 1974 for reviews).

Besides changing operant behavior, septal lesions have been reported to change response to appetitive stimuli (Beatty and Schwartzbaum, 1968), increase water intake (Carey, 1969), reduce food intake and decrease body weight (Ross, Grossman and Grossman, 1975), facilitate signalled "two way active" behavior (Carlson, 1970), increase response sensitivity to electrical shock (Lints and Harvey, 1969), increase the emotional response to sensory stimuli (Brady and Nauta, 1955) enhance visual evoked potentials (Golden and Lubar, 1971) and impair a number of species-typical behavior patterns (Carlson and Thomas, 1968).

Thus, the septum appears to be involved in the mediation and integration of a wide range of behavioral repertoires. A review of the literature reveals that the septal area is not a functionally homogeneous structure. Different behavioral effects are produced by varying the location of the lesion within the septal area and damaging selective efferent pathways. The anatomical correlates of each of the behavioral consequences of septal lesions has not been worked out in detail.

This dissertation concerns the specific effect of small medially palced lesions within the septal complex on operant responding maintained by schedules of positive reinforcement. Septal lesions increase the response rates of behavior maintained

by a variety of schedules of reinforcement using a number of reinforcing stimuli (continuous reinforcement, Sagvolden, 1975; fixed ratio, Ellen and Powell, 1962; fixed interval, Lorens and Kondo, 1969; variable interval, Aaron and Thorne, 1975). Stimuli associated with reinforcement have greater secondary reinforcing effects following septal lesions (Carlson, El-Wakil, Standish, and Ormond, 1976). The operant rate-increasing effects of these lesions seem related to damage to the medial septal nucleus (Standish, 1975). Carey (1969) showed that posterior septal lesions produced less responding in operant tasks reinforced by water.

Even when high rates of responding lead to decreased frequency of reinforcement as in differential reinforcement of low rates (DRL) schedules or omission schedules, septal lesions increase response frequency. Destruction of the medial septum impairs DRL performance (MacDougall, Van Hoesen, and Mitchell, 1969) and performance on omission schedules (Aaron and Thorne, 1975). Septal lesions also enhance acquisition of olfactory discrimination (Vom Saal, Hamilton, and Gandelman, 1975) and produce increased resistance to extinction of positively reinforced behavior (Butters and Rosvold, 1968).

These changes in operant behavior are not associated with general increase in motor activity. Rats with septal lesions do

not exhibit an increase in locomotor activity in open field tests (Gotsick, 1969) nor do they run more in running wheels (Anderson, 1970). In fact, animals with septal lesions are hypoactive as measured by running wheel activity. Nor is the change in response rate related to increased "hunger", since septal lesions either have no effect on caloric intake or reduce food intake and body weight (Ross, Grossman, and Grossman, 1975). Although septal animals are not hyperactive, food deprivation and the presentation of stimulus conditions temporally associated with feeding generates more activity in rats with septal lesions than intact subjects (Anderson, 1970).

Since the effects of medial septal lesions appear to profoundly affect operant relations, it is possible to conclude tentatively that the relations among the elements of the three-term contingency, $S^D \rightarrow R \rightarrow S^R$, are altered in some way. Previous research (Carlson et al, 1976) has suggested that the increase in the frequency of operant response emission following septal lesions involves changes in the organism's sensitivity to biological reinforcing stimuli such as food. It is conceivable that destruction of this forebrain region changes the relations between the contingencies of reinforcement and the organism in such a way that reinforcing stimuli (e.g., food) have a greater effect on the probability of the response that immediately preceded. The purpose of this research is to determine the relevant anatomical pathways responsible for the abrupt change

in the control that the environment has on operant response rates following medial septal lesions. A complete anatomical account of the relevant fibers and synaptic terminals associated with this behavior change may prove useful as a step towards isolating the neural events that mediate learning.

Experiment I

Silver Degeneration Analysis of the Efferent Fiber Connections of the Medial Septal Nucleus Following Lesions that Increase Operant Response Rates

The purpose of Experiment 1 was to determine the anatomical connections of the septal area that are involved in the abrupt changes in the control that the environment has on operant response rates following septal lesions. Previous research (Carlson, El-Wakil, Standish, and Ormond, 1976) has indicated that the increase in operant response emission following septal lesions is related to changes in the animals's sensitivity to biological reinforcers. In their experiment changes in caloric value of pellets delivered on a differential reinforcement of low response rate schedule (DRL), during establishment of conditioned reinforcing stimuli and previous extinction modified the effects of septal lesions on response rates in each condition. Their results suggested that septal lesions increase response rate by enhancing the reinforcing properties of food. It is possible that restricted damage to the septum changes relations between contingencies of reinforcement and the animal so that reinforcing stimuli have a greater effect on the probability of the response that immediately preceded. A complete anatomical account of the relevant axonal fibers and synaptic terminals associated with changes in operant behavior following septal lesions may prove useful in isolating the

neural events that mediate learning.

Previous lesion experiments have suggested that disruption of efferent fibers from the septum travelling through the fornix/fimbria and projecting into the hippocampus are responsible for the operant response rate increments observed as a consequence of septal lesions. Ross and Grossman (1975) attempted to delineate anatomically the efferent system of the septal area involved in response rate increases by comparing the effects of transection of the two major efferent pathways of the septal area--the medial forebrain bundle and the fornix/fimbria. A knife cut ventral to the septum transects the diagonal band/medial forebrain bundle fibers that interconnect the septum with the hypothalamus and brain stem. Such a ventral knife cut did not affect DRL, fixed interval or Sidman avoidance performance. A knife cut caudal and dorsal to the septum transects septal interconnections with the hippocampus. Such a dorsal transection of the fornix with minimal direct damage to cellular components of the septum or hippocampus reproduced the effects of septal lesions on performance on DRL, fixed interval (FI) and Sidman avoidance contingencies. Ross and Grossman's experiments suggested that septal connections with the hippocampus are important in mediating normal operant response rates.

The hippocampus itself has been implicated in mediation of operant responding. When rats with hippocampal lesions are subjected to changing reinforcement contingencies their response rate

is greater than intact animals. This has been found in changing from continuous reinforcement schedules to variable interval (VI) and DRL contingencies (Jarrard, 1965).

MacDougall and Capobianco (1976) have described in greater detail the operant functional anatomy of septal-hippocampal connections. Rats with transections of either the total fornix/fimbria bundle, the precommissural fornix or postcommissural fornix were compared on their acquisition and terminal response rates on a DRL-20 and a Sidman avoidance schedule. Total fornix and precommissural fornix transections severely impaired DRL performance and facilitated avoidance acquisition. Postcommissural columns transections had no effect on DRL response rates but did facilitate avoidance behavior. These experiments suggest that septal connections with the hippocampus through the precommissural fornix have important functions in mediating operant response rates controlled by schedules of positive reinforcement. The purpose of the present experiment was to specify further the synaptic termination sites and pathways followed by degenerating axonal fibers responsible for changes in response rate following septal lesions. As the septal area is composed of more than one structurally distinct neural population, the first step was to determine the area of the septum relevant to the lesion-produced increments in operant responding. The second goal was to isolate the critical fiber projections and termination sites responsible for the changes in conditioned

behavior following these lesions.

METHOD

Subjects

Eighteen male B6D2F$_1$/J hybrid mice procured from Jackson Laboratory, Bar Harbor, Maine served as subjects. They were 14 weels of age at the beginning of the experiment. All mice were housed in individual cages and maintained on a 12 hour light-dark cycle. Experimentation occurred during the light cycle. During the experiment body weights were stabilized and maintained by presentation of 3.0 g. of laboratory pigeon grain presented each day following the experimental session described below.

Apparatus

Mice were exposed to a variable interval schedule of food reinforcement in one of four identical operant chambers, each isolated in an insulated chest. These chambers were constructed of Masonite hardboard with a wire mesh floor and perforated harboard lid. Each chamber, 25.4 cm. high, was trapezoidal in its horizontal cross-section. The parallel end walls were 5 cm. and 15 cm. wide. The length of the box (distance between end walls) was 19 cm. Centered on the narrower end wall, 2.8 cm. above the wire mesh floor, was a round aluminum tube (2.5 cm. diameter) which protruded from the chamber. A photocell beam passed through holes in the side of the tube. The operant response consisted of a head poke into the response

tube, breaking the photocell beam. The source of the photocell beam was a red light emitting diode. A light source at the end of the tube provided the only illumination. Reinforcement (20 mg. Noyes pellets, Standard A formula) were delivered directly into the response tube via a plastic hose connected to a pellet dispenser. The presentation of stimuli and the collection of data were controlled by an on-line computer (Modcomp, Inc.).

Procedure

Following three days of restricted feeding (4.0 g. of laboratory grain) mice were placed in operant chambers where reinforcements were delivered on a fixed interval 1 second schedule contingent on a head poke response. The operant level of head poking was sufficiently high to render unnecessary the use of shaping techniques. Over a period of 5 days the schedule of reinforcement was gradually changed from a fixed interval 1 second schedule to a variable interval 10 second schedule (VI-10), VI-20, and finally, VI-40 sec. Number of reinforcements, response rates and interresponse time (IRT) distributions were recorded.

Following the 7th session of stable VI-40 responding (no greater than 10% variation from the mean response rate for those 7 days) stereotaxic lesions of various sizes and locations were produced in the septal area under brief and light ether anesthesia. Mice were placed in a Kopf stereotaxic apparatus equipped with a

mouse head holder which eliminated the need for ear pins (Slotnick, 1972). Thermocoagulations of the septal region were made by passing current from a Grass radio frequency lesion maker through a size 00 (.3 mm. diameter) stainless steel insect pin insulated except for the tip with enamel. Smaller lesions were made through a plastic coated tungsten microelectrode (Spinelli, Bridgeman, and Owens, 1970).

During the 7 days following surgery, each animal's response rate and IRT distribution were recorded as usual. In this way, the effects of brain lesions could be determined 24 hours after surgery and during the subsequenct 6 days without disturbing the animal's normal routine. Following the 14th variable interval schedule session each subject was given an overdose of Nembutal, pericardially with physiological saline followed by 10% formalin, the brain removed and subsequently analyzed for anterograde degeneration throughout the entire brain using a modified silver procedure for the differential staining of degenerating axons and terminals (Fink and Heimer, 1967).

RESULTS AND DISCUSSION

Large septal lesions and behavior

Large lesions invading the medial septal area produced increases in response rate 24 hours after surgery and for the remaining post-surgical period. Mean baseline response rates were compared with mean post lesion response rates to obtain percent behavior change

measures for each subject. Table 1 presents mean baseline response rates, mean post lesion response rates and percent behavior change calculated by the following formula.

$$\frac{\text{Mean baseline rate - mean post lesion rate}}{\text{Mean baseline rate}} \times 100$$

As a result of large septal lesions the percent change in response rates on a variable interval schedule of reinforcement increased from as little as +36% (subject M84) to as great as +189% (subject M89). Larger increments in response rate (189% and 153%; M89 and M56) were correlated with more complete damage of the medial septal area, including the dorsal segment of the diagonal band of Broca and the associated nucleus of the diagonal band embedded within the vertical limb. Generally, less pronounced changes in response rate were correlated with less complete or asymmetrical damage of the medial septal area and its associated nucleus of the diagonal band. Highly effective lesions were found to end just anterior to the precommissural fornix and not to involve the caudal septal area or the columns of the fornix.

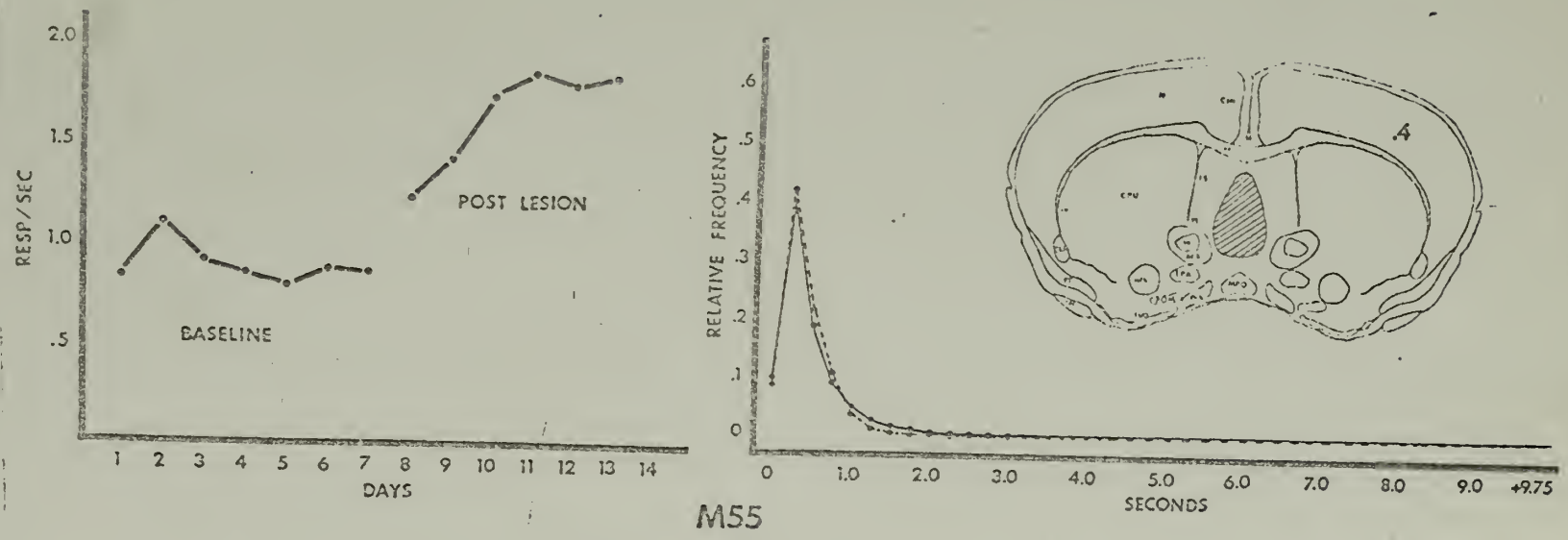
Figures 1 - 10 present, for each experimental animal, response rates, relative response frequency (interresponse time) distributions and appropriate brain sections showing the location of maximal tissue damage in subjects receiving large septal lesions. Data from animal R5 (figure 9), who received a bilateral thalamic lesion, was included to demonstrate that response rate increases are not due to nonspecific

Subject	Mean baseline rate (responses/second)	Mean post lesion rate (responses/second)	% Rate change
M55	.90	1.68	+87%
M56	.66	1.67	+153%
M57	.42	.81	+93%
M60	1.21	1.81	+49%
M83	.42	.98	+93%
M84	.77	1.05	+36%
M88	.94	1.58	+68%
M89	.56	1.62	+189%
R5	.44	.30	-32%
M54	.58	1.01	+74%

Table 1. Baseline and postlesion response rates (responses/second) and behavior change calculated as percent of baseline for subjects in Experiment 1.

FACE PAGE FOR FIGURES 1 - 10

For each subject baseline and post lesion response rates, interresponse time distributions, a diagram of the coronal brain section showing the maximal extent of lesion and the degeneration pattern revealed by the Fink-Heimer procedure are shown. For degeneration patterns DT = degenerated terminals, DF - degenerated fibers. For interresponse time distributions solid lines indicate baseline distributions and dashed line indicates post lesion distribution.

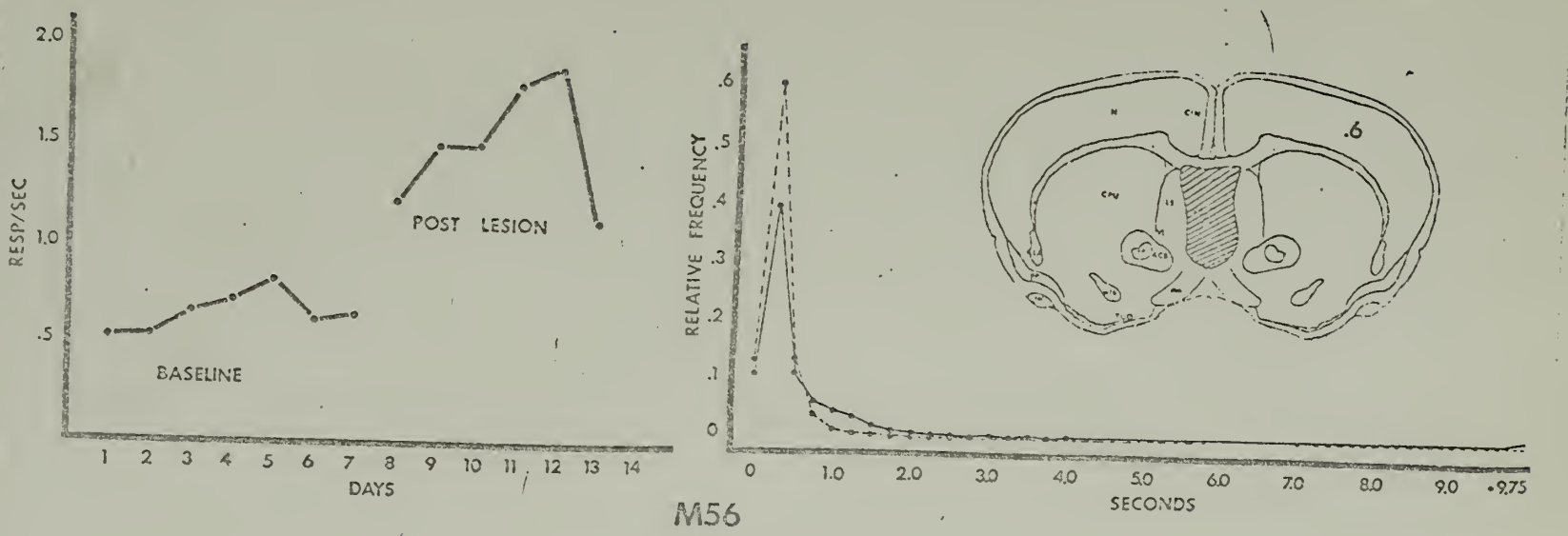


Degeneration Pattern

DF in olfactory bulbs
DF in anterior commissure
DT in n. accumbens septi (minimal)
DF in anterior septum
DF in vertical and horizontal diagonal band
DF in decussation of anterior commissure
DT in lateral caudate n.
DF in medial forebrain bundle
DT in lateral hypothalamus
DF in precommissural fornix
DF in postcommissural fornix
DF in dorsal fornix
DF in lateral fimbria/fornix

DF in stria medullaris
DF and DT in medial and lateral habenular n.
DF and DT in mammillary bodies
DF and DT in anteromedial and anteroventral n. of thalamus
DF in anterior dorsal hippocampus (minimal)
DF in alveus
DF in CA3 and CA4 of ventral hippocampus
DF in fascia dentata (dorsal and ventral)
DF in commissure of fornix
DF in subiculum
DT in subiculum

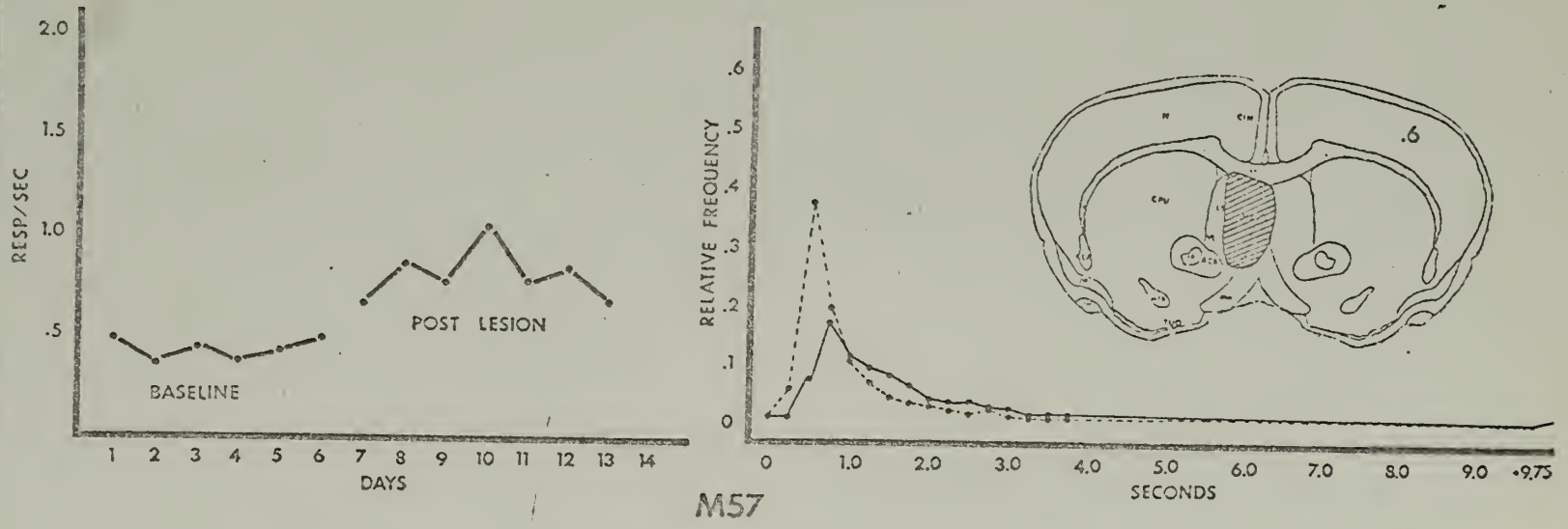
Figure 1



Degeneration Pattern

DT in n. accumbens septi
DF in anterior septum
DF in vertical and horizontal diagonal band
DT in lateral caudate n.
DF in medial forebrain n.
DT in lateral hypothalamus
DT in ventromedial n. of hypothalamus
DF in precommissural fornix
DF in postcommissural fornix
DF in dorsal fornix
DF in lateral fimbria/fornix
DF in stria medullaris
DF and DT in medial and lateral habenular n.
DF and DT in mammillary bodies
DF in paraventricular n. of thalamus
DF in paratenial n. of thalamus
DF and DT in anteromedial and anteroventral n. of thalamus
DF in anterior dorsal hippocampus (minimal)
DF in alveus
DF in CA3 and CA4 of ventral hippocampus
DF in fascia dentata (dorsal and ventral)
DF in commissure of fornix
DF in subiculum

Figure 2

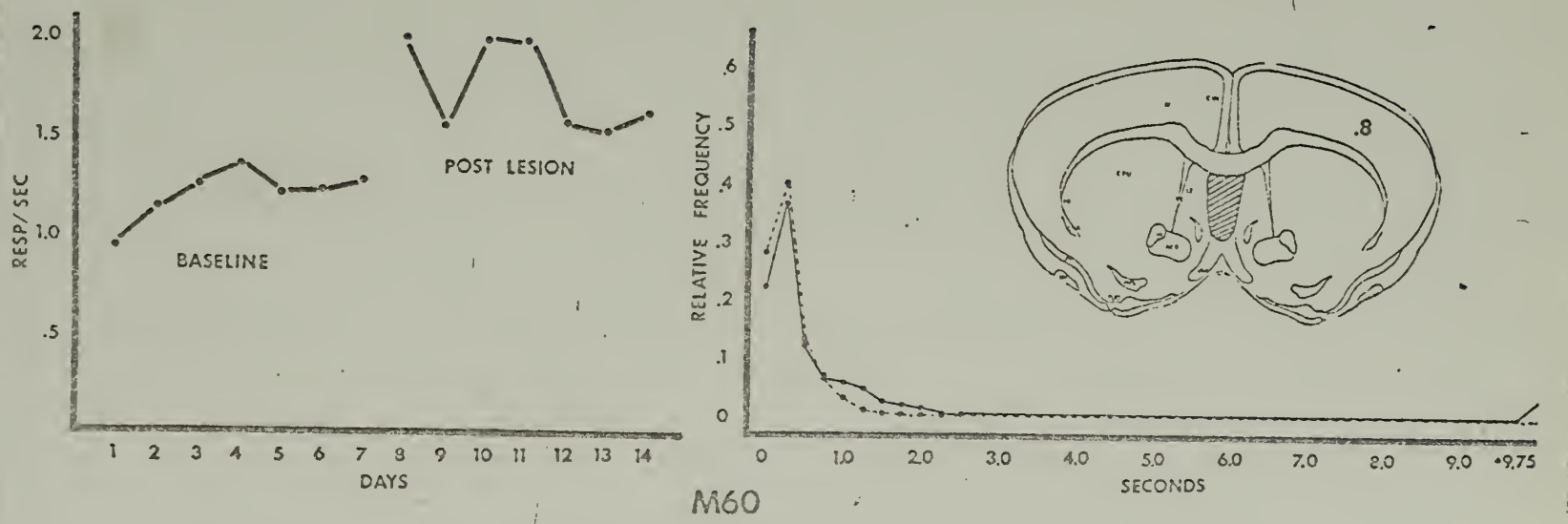


Degeneration Pattern

DT in accumbens septi
DF in anterior septum
DT in lateral septal n. (unilateral)
DF in vertical and horizontal limb of diagonal band
DT in lateral caudate n. (minimal)
DF in medial forebrain bundle
DT in lateral hypothalamus
DF in precommissural fornix
DF in dorsal fornix
DF in lateral fimbria/fornix
DF in stria medullaris (asymmetrical)
DF in medial and lateral habenular n. (asymmetrical)

DF in mammillary bodies (minimal)
DF in alveus
DF in CA3 and CA4 of ventral hippocampus
DF in fascia dentata (dorsal and ventral)
DF in fornix commissure
DF in subiculum

Figure 3



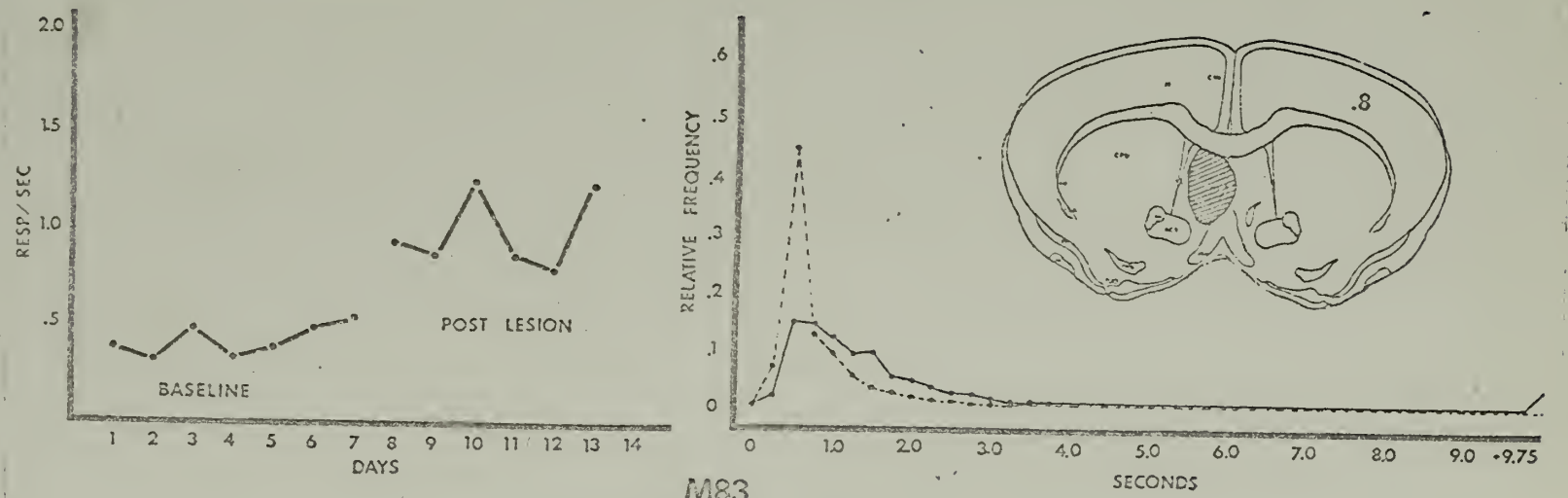
M60

Degeneration Pattern

DT in n. accumbens septi
DF in anterior septum
DF in vertical and horizontal diagonal band
DF in medial forebrain bundle
DF in precommissural fornix
DF in postcommissural fornix
DF in dorsal fornix
DF in lateral fimbria/fornix
DF in stria medullaris (unilateral)
DF in medial habenular n. (unilateral)
DF and DT in mammillary bodies
DF in anterior dorsal hippocampus (minimal)
DF in alveus

DF in CA3 and CA4 of ventral hippocampus
DF in fascia dentata (dorsal and ventral)
DF in commissure of fornix
DF in subiculum

Figure 4



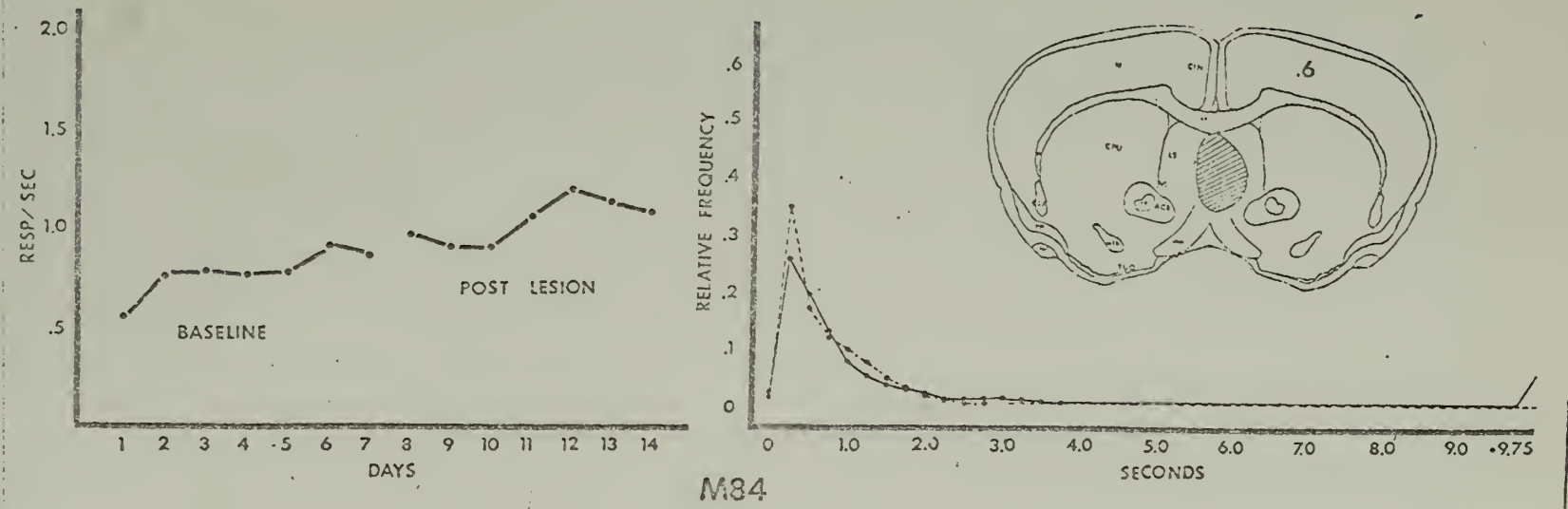
M83

Degeneration Pattern

DT in n. accumbens septi
DF in anterior septum
DT in lateral septal n. (unilateral)
DF in vertical and horizontal diagonal band
DF in medial forebrain bundle
DT in lateral hypothalamus (unilateral)
DF in precommissural fornix
DF in Postcommissural fornix
DF in dorsal fornix
DF in medial fimbria/fornix (minimal)
DF in lateral fimbria/fornix
DF in stria medullaris
DF and DT in medial and lateral habenular n.

DF and DT im mammillary bodies
DF in anterior dorsal hippocampus ((minimal)
DF in alveus
DF in CA3 and CA4 of ventral hippocampus
DF in fascia dentata (dorsal and ventral)
DF in commissure of fornix
DF in subiculum

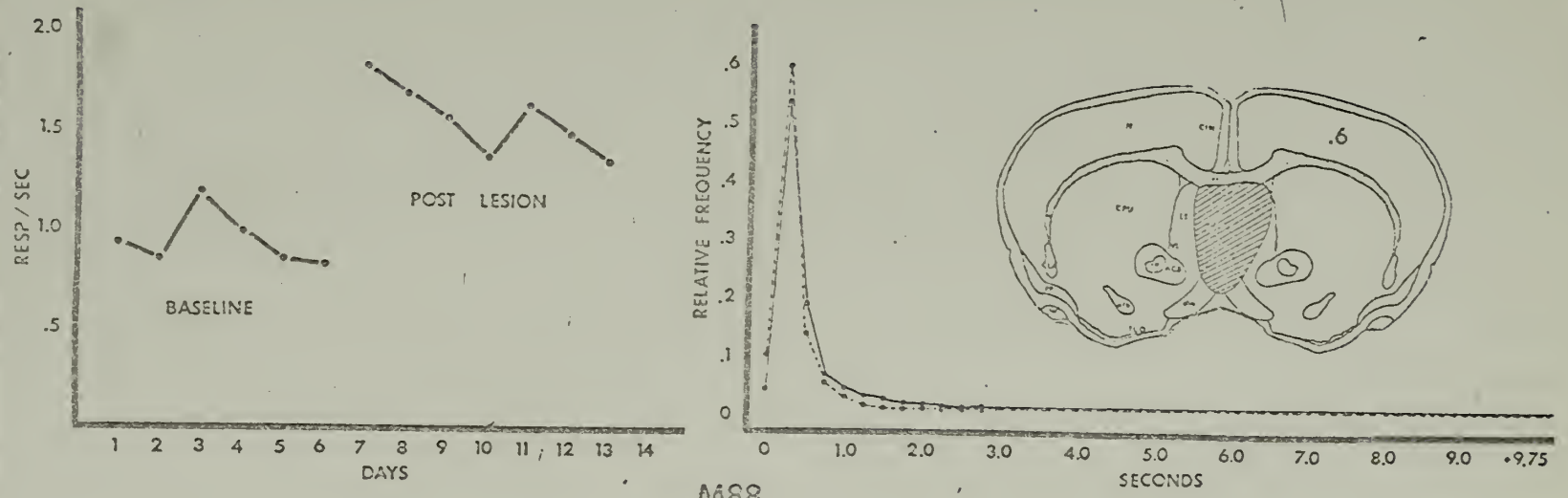
Figure 5



Degeneration Pattern

DF and DT in n. accumbens septi (unilateral)
DF in anterior sptum
DF in vertical and horizontal diagonal band
DF in anterior commissure (unilateral)
DT in lateral caudate n.
DF in medial forebrain bundle
DF in precommissural fornix
DF in postcommissural fornix
DF in dorsal fornix
DF in lateral fimbria/fornix
DF in stria medullaris
DF and DT in medial and lateral habenular n.
DF and DT in anteroventral and anteromedial n. of thalamus
DF and DT in mammillary bodies
DF in anterior dorsal hippocampus (minimal)
DF in alveus
DF in CA3 and CA4 of ventral hippocampus
DF in fascia dentata (dorsal and ventral)
DF in commissure of fornix
DF in subiculum
DF and DT in superior colliculus

Figure 6



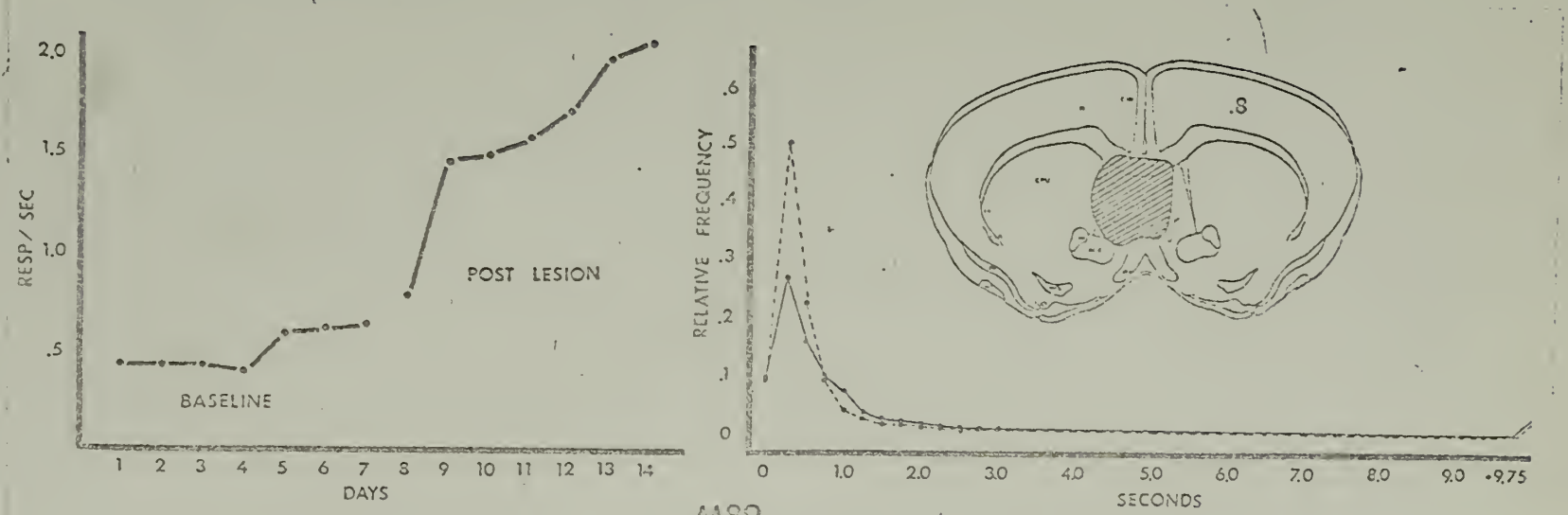
M88

Degeneration Pattern

DF and DT in n. accumbens septi
DF in anterior septum
DF in vertical and horizontal diagonal band
DF in olfactory tubercle (minimal)
DT in lateral caudate n.
DF in medial forebrain bundle
DT in lateral hypothalamus
DT in ventromedial hypothalamus
DF in precommissural fornix
DF in dorsal fornix
DF in lateral fimbria/fornix
DF in anterior dorsal hippocampus (minimal)
DF in alveus

DF in CA3 and CA4 of ventral hippocampus
DF in fascia dentata (dorsal and ventral)
DT on large soma of ventral fascia dentata
DF in commissure of fornix
DF in subiculum
DF in superior colliculus

Figure 7

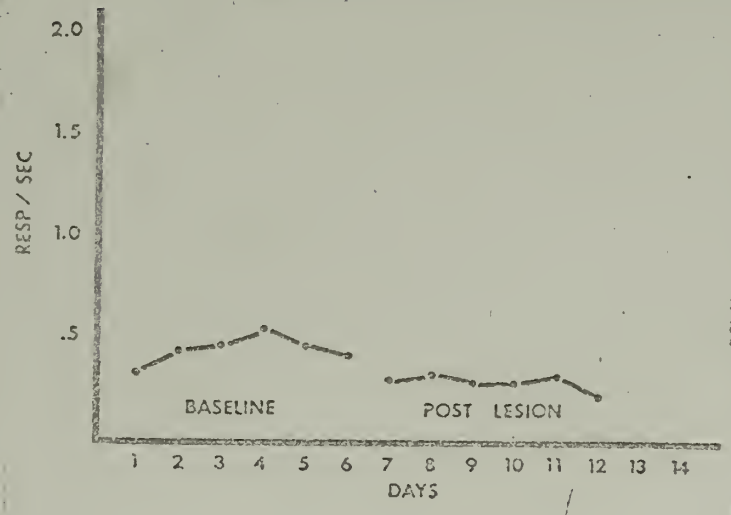


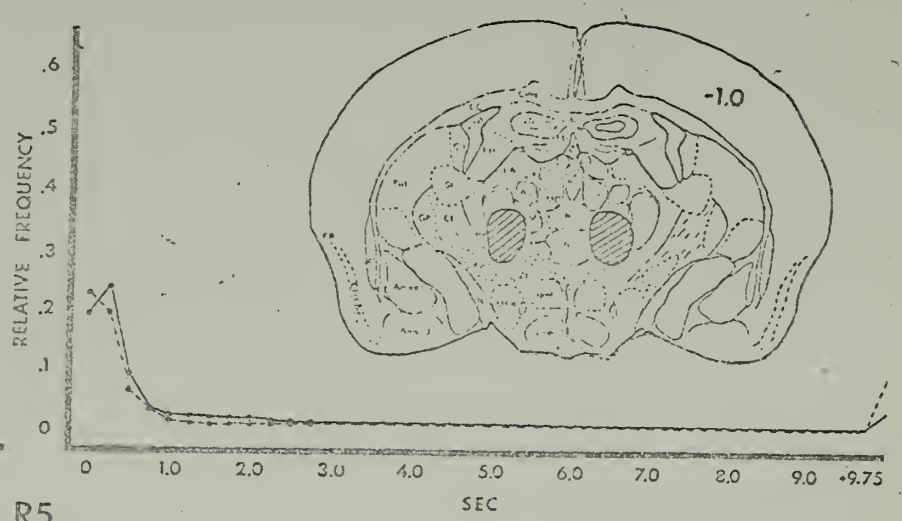
Degeneration Pattern

DF and DT in n. accumbus septi
DF in lateral septal n.
DF in vertical and horizontal diagonal band
DF in anterior commissure
DF in olfactory tubercle (minimal)
DT in caudate n.
DF in medial forebrain bundle
DF and DF in ventromedial n. of hypothalamus
DF in precommissural fornix
DF in postcommissural fornix
DF in dorsal fornix
DF in lateral fimbria/fornix
DF and DT in mammillary bodies
DF in internal capsule

DF and DT in paracentricular n. of thalamus
DF and DT in paratenial n. of thalamus
DF and DT in dorsomedial n. of thalamus
DF and DT in rhomboid n. of thalamus
DT in anterior dorsal hippocampus (minimal)
DT in basolateral amygdala (unilateral)
DF in CA3 and CA4 of ventral hippocampus
DF in fascia dentata (dorsal and ventral)
DT on soma in caudal fascia dentata
DF in commissure of fornix
DF in subiculum

Figure 8



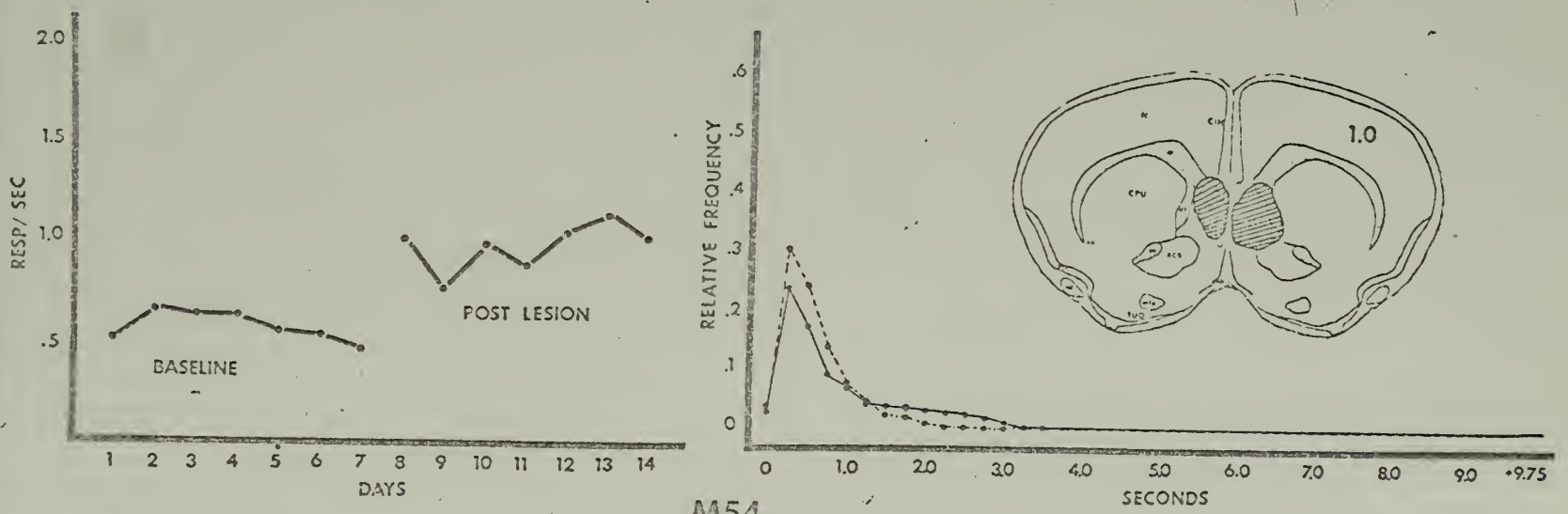


R5

Degeneration Pattern

DF in medial fimbria/fornix
DF and DT in globus pallidus
DF and DT in dorsomedial n. of thalamus
DF and DT in reticular n. of thalamus
DF and DT in reuniens n. of thalamus
DF and DT in rhomboid n. of thalamus
DF and DT in CA1 of hippocampus
DF in dorsal alveus
DF in fascia dentata (dorsal)
DF and DT in lateral n. of thalamus
DF and DT in mammillary bodies

Figure 9



M54

Degeneration Pattern

DF in olfactory bulbs
DT in n. accumbens septi
DF in anterior septum
DF in vertical and horizontal diagonal band
DF in olfactory tubercle (minimal)
DT in lateral caudate n.
DF in medial forebrain bundle
DF in precommissural fornix (minimal)
DF in postcommissural fornix (minimal)
DF in dorsal fornix (minimal)
DF in lateral fimbria/fornix (minimal)
DF in dorsomedial n. of thalamus
DF in rhomboid n. of thalamus
DT in reuniens n. of thalamus
DF in internal capsule
DT in lateral hypothalamus
DT in ventromedial n. of hypothalamus
DF in alveus (light)
DF in commissure of fornix
DF in subiculum

Figure 10

trauma to the brain.

Large lesions, efferent degeneration and behavior

Large lesions confined to the septum resulted in degeneration of axonal fibers and synaptic terminals within limbic forebrain structures, the diencephalon and midbrain. More specifically, degeneration was consistently found in the diagonal band, medial forebrain bundle, precommissural fornix, postcommissural fornix, dorsal fornix, lateral fimbria, stria medullaris, medial and lateral habenular nuclei, lateral hypothalamus, mammillary bodies, alveus, CA3, CA4 and the fascia dentata of the ventral hippocampus, the fornix commissure and the allocortex adjacent to the ventral hippocampus, the subiculum.

Lesions that resulted in considerable response rate increases often did not invade or result in degeneration of the postcommissural fornix or stria medullaris. Only caudal septal lesions result in disturbance in the columns of the fornix or stria medullaris and degeneration in the mammillary bodies or habenular nuclei. By comparing between subject behavioral data and degeneration patterns it was possible to conclude that the system interrelating the postcommissural fornix, anterior thalamus and mammillary bodies was not involved in changes in operant response rates. Likewise, the absence of degenerating fibers within stria medullaris and minimal degenerating terminals in its projection site, the medial and lateral habenular nuclei, within the brains of subjects whose lesion

has produced large increases in response rate (e.g. M54 and M88; figures 10 and 7) suggested that the stria medullaris/habenular pathway is not directly part of the anatomical substrate of operant behavior change.

Large septal lesions that resulted in substantial increments in response rate also produced consistent and marked degeneration in two distinct anatomical systems; the diagonal band/medial forebrain bundle pathway and the precommissural fornix/lateral fimbria/ventral hippocampal pathway. Lesions that were effective in changing operant behavior were also effective in producing heavy degeneration in each of these anatomical systems. The use of large lesions makes the determination of the critical pathway difficult.

A less direct approach to discriminating the more important circuit in the behavior change, however, suggested that the medial septal-hippocampal efferents are involved in increases in response rate during variable interval sessions. If the response rate increases were due to damage of either the medial forebrain bundle or hippocampal pathways then some sort of a functional relation should exist between the magnitude of response rate change and the density of degeneration within the critical efferent structure. By comparing the density of degeneration within the medial forebrain bundle and ventral hippocampus (CA3, CA4 and fascia dentata) in animals with high, moderate and low percent behavior change scores such a functional relation was determined. Animals with the

greatest increments in response rate (M89 with +189% and M56 with 153%) were compared with animals showing moderate increments in rate as a consequence of the lesion (M55 with 87% and M88 with +68%). Degeneration within the ventral hippocampus and medial forebrain bundle of these subjects with high and moderate rate changes were compared with animals whose lesion produced the least amount of behavior change (M60 with +49% and M84 with +36%). Comparative inspection of the concentration of silver impregnation of degenerating fibers within CA3, CA4 and the fascia dentata in these 6 animals revealed a clear, though qualitative, functional relation between changes in response rate and concentration of degenerating fibers within the ventral hippocampus. The same functional relation was observed between the degree of lesion-induced behavior change and concentration of degenerating fibers within the lateral fimbria. Brains of animals (M60 and M84) whose lesion was followed by only small increments in operant responding were found to contain only a small number of degenerating fibers within the ventral hippocampus. Moderate behavior change was correlated with moderate intensities of degeneration within the ventral hippocampus. No such functional relation was found between operant behavior change and the concentration of degenerating elements within the diagonal band/medial forebrain bundle pathway.

Degeneration patterns of animals with large lesions and the consequent changes in behavior suggested that fiber connections

between the medial septal region and the ventral hippocampus are important in mediating operant behavior and that interruption of this pathway by damage to the septum leads to increases in the frequency of response emission. Since the most lateral margin of the lateral fimbria always contained many degenerating axons in brains of animals generating high rates of post lesion responding it was concluded that the relevant connections from the medial septal area to the ventral hippocampus travel through the lateral fimbria. These fibers appeared to terminate in the stratum radiatum within CA3 and CA4. This implies that degenerating fibers terminated on the basal dendrites of pyramidal cells within the area of the fascia dentata containing the dendrites of granule cells composing this structure. These observations are in accord with current data regarding the microanatomical circuitry of the hippocampus (Shepherd, 1974).

Anatomical and behavioral data from most animals who received large septal lesions suggested that degenerating medial septal relations with the ventral hippocampus were necessary for the increases in operant response rates. However, one experimental subject M54 (figure 10), who received a bilateral lesion within the septal area showed a substantial increment in response rate (+74%) but no degeneration in the ventral hippocampus. This animal received a bilateral lesion that completely destroyed the lateral septal nuclei leaving most of the medial septal area intact. Degenerating fibers

were observed to leave the lesion site in the lateral septum, travel ventrally and join the diagonal band below the septum. The medial forebrain bundle contained many degenerating fibers while the lateral fimbria, alveus, CA3, CA4, and fascia dentata were essentially devoid of degenerating terminals or fibers. These results suggested that the lateral septal efferents into the descending medial forebrain bundle have some influence over response probabilities. Hamilton, Kelsey, and Grossman (1970) have shown that lateral septal lesions alone can increase operant response rate. The behavioral and anatomical data from this one subject supports the scheme discussed at greater length below that an operant response-modulating system may depend upon a feedback loop from the medial septal area to the hippocampus, back to the lateral septum and then into the medial forebrain bundle to travel ventrally and caudally to unknown brainstem sites.

Large lesions and interresponse time (IRT) distributions

The mean interresponse time (IRT) distributions were expressed in Figures 1-10 as relative frequency distributions. Mean IRT distributions generated during baseline sessions were highly skewed and unimodal for each subject. Such distributions demonstrated the high degree of behavioral control exercised by the variable interval 40 second schedule.

Most animals generated the majority of their responses within .25 seconds after the last response. Thus, IRT distributions had

Subject	Percent responses made during peak of IRT distribution during baseline	Percent responses made during peak of IRT distribution after surgery
M55	40.36%	41.44%
M56	39.07	61.44
M57	7.79	37.47
M60	36.41	40.93
M83	14.59	45.06
M84	25.84	34.49
M88	53.83	59.77
M89	26.39	50.26
R5	23.69	19.11
M54	23.80	31.27

Table 2. Changes in percent of responses made during the peak IRT bin before and after surgery for subjects in Experiment 1.

Subject	Mean baseline rate (responses/second)	Mean post lesion rate (responses/second)	% Rate change
M87	.47	.33	-5%
R6	.43	.81	+88%
M59	1.31	1.21	-8%
R43	.30	.58	+93%
R9	.74	.79	-7%
R45	.20	.16	-20%
R3	.30	.27	-10%
R7	.47	.33	-30%

Table 3. Baseline and post lesion mean response rates (responses/second) and behavior change measure as percent of baseline for subjects in Experiment 1.

peaks occurring in the .25-.50 second time bin. Two subjects, M57 and M83 made the majority of their responses in the .50-.75 second time bin during baseline, and the peaks of their relative frequency curves occur during the .50-.75 time bin.

Large septal lesions affected IRT distributions in a characteristic way. In most cases, lesions damaging the medial septal area resulted in a steeper peaked .25-.50 second time bin. See figures 1-10 for pre- and post lesion IRT distributions. The change in percent of responses made during the peak baseline time bin as a consequence of surgery is shown for each subject in Table 2.

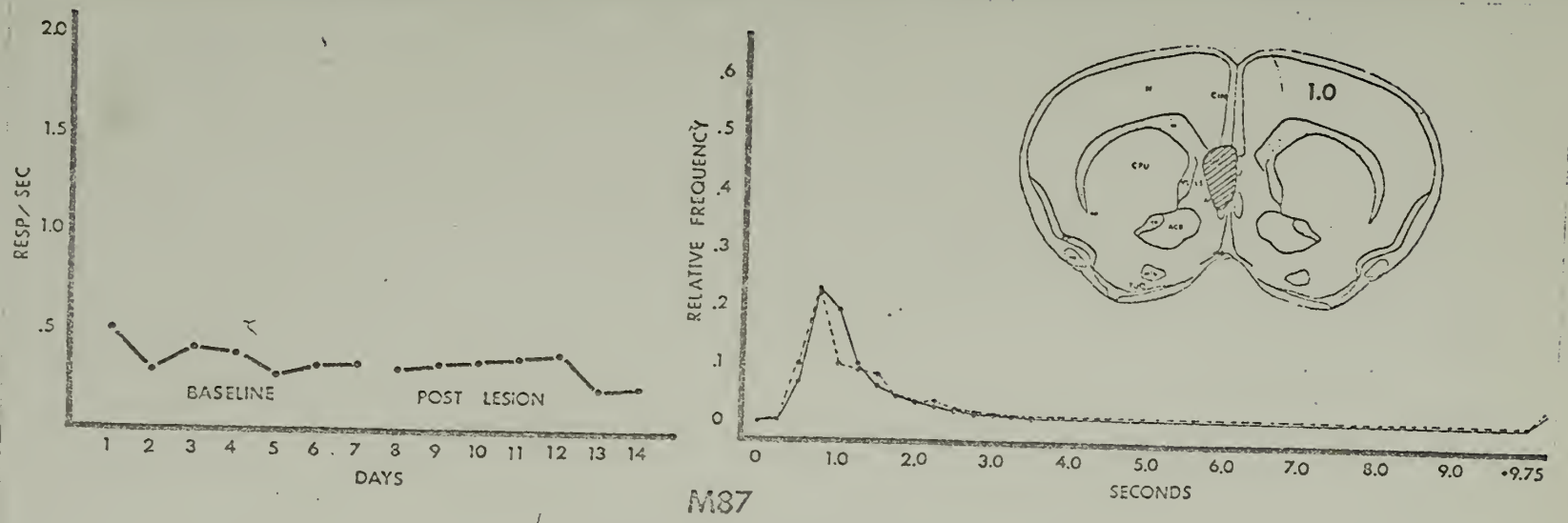
In one animal, M55, a lesion that produced a large increase in response rate had essentially no effect on the IRT distribution (see figure 1). In summary, large septal lesions, if they affected relative response frequency distributions at all, merely increased the percent of responses made during the peak baseline time bin. Responding during IRTs slightly longer than the peak baseline bin tended to decrease following surgery.

Small restricted septal lesions and behavior

The effects of small restricted lesions within the septal area on response rates, IRT distributions and efferent degeneration patterns are shown in figures 11-18. Diagrams of appropriate brain sections indicate the location of the maximal extent of the lesion. Table 2 shows, for each animal, mean baseline and post lesion response

FACE PAGE FOR FIGURES 11 - 18

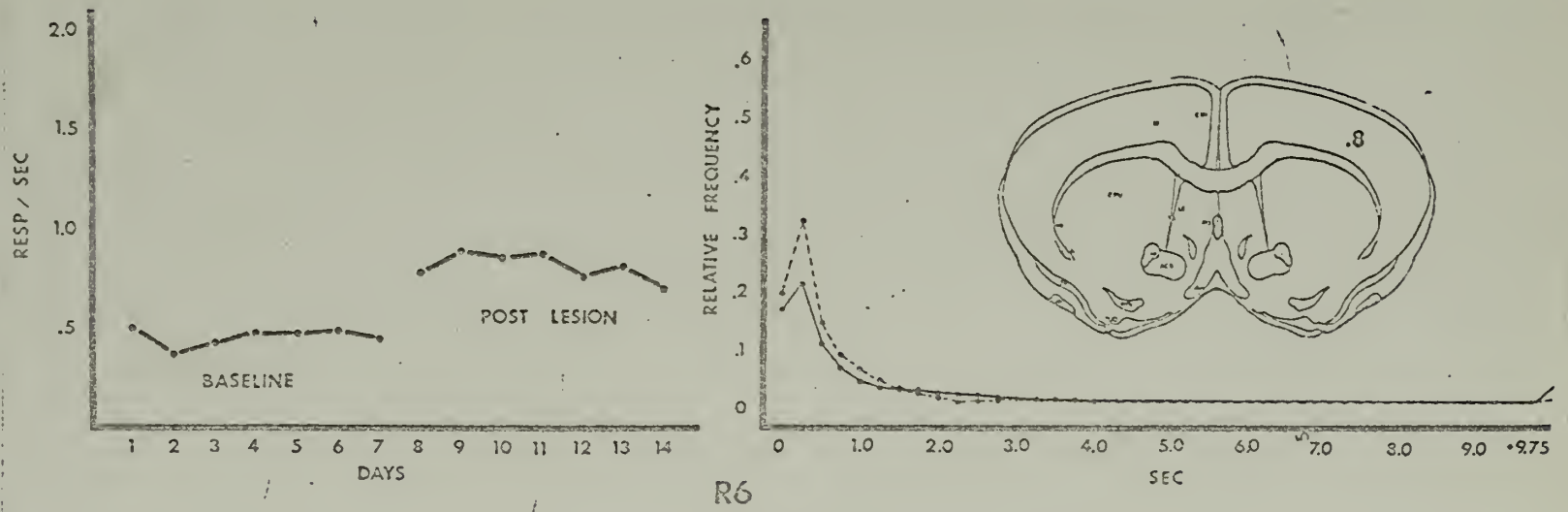
For each subject baseline and post lesion response rates, interresponse time distributions, a diagram of the coronal brain section showing maximal extent of the lesion and the degeneration pattern revealed by the Fink-Heimer procedure are shown. For degeneration patterns DT = degenerated terminals, DF = degenerated fibers. For interresponse time distributions solid lines indicate baseline distributions and dashed lines indicate post lesion distributions.



Degeneration Pattern

DF in anterior septum
DF in vertical and horizontal limb of diagonal band (asymmetrical)
DF in medial forebrain bundle (asymmetrical)
DF in dorsal fornix (minimal)
DF and DT in zona incerta
DF in commissure of fornix (unilateral)

Figure 11

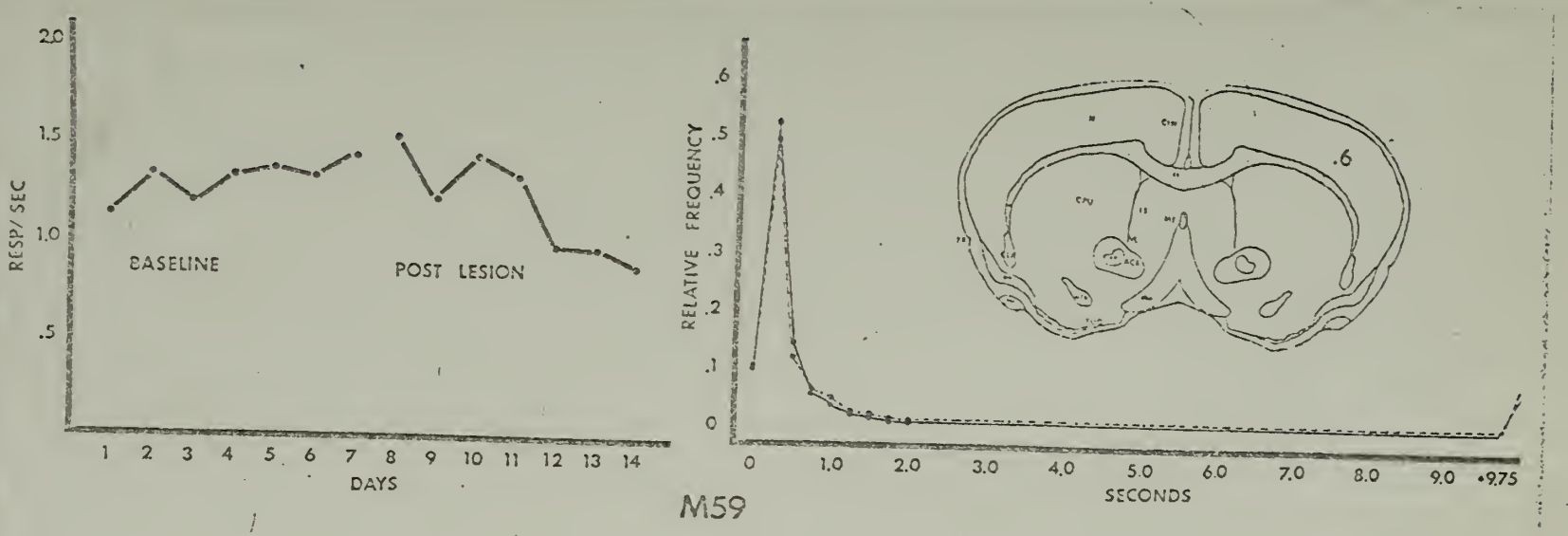


R6

Degeneration Pattern

DF in anterior septum
DF in vertical and horizontal diagonal band
DF in medial forebrain bundle
DF in precommissural fornix
DF in postcommissural fornix (light)
DF in dorsal fornix
DF in lateral fimbria/fornix
DF in stria medullaris (light)
DF in anterior dorsal hippocampus (light)
DF in CA3 and CA4 of ventral hippocampus (light)
DF in dorsal fascia dentata
DF in ventral fascia dentata (light)
DF in commissure of fornix
DF in subiculum (light)

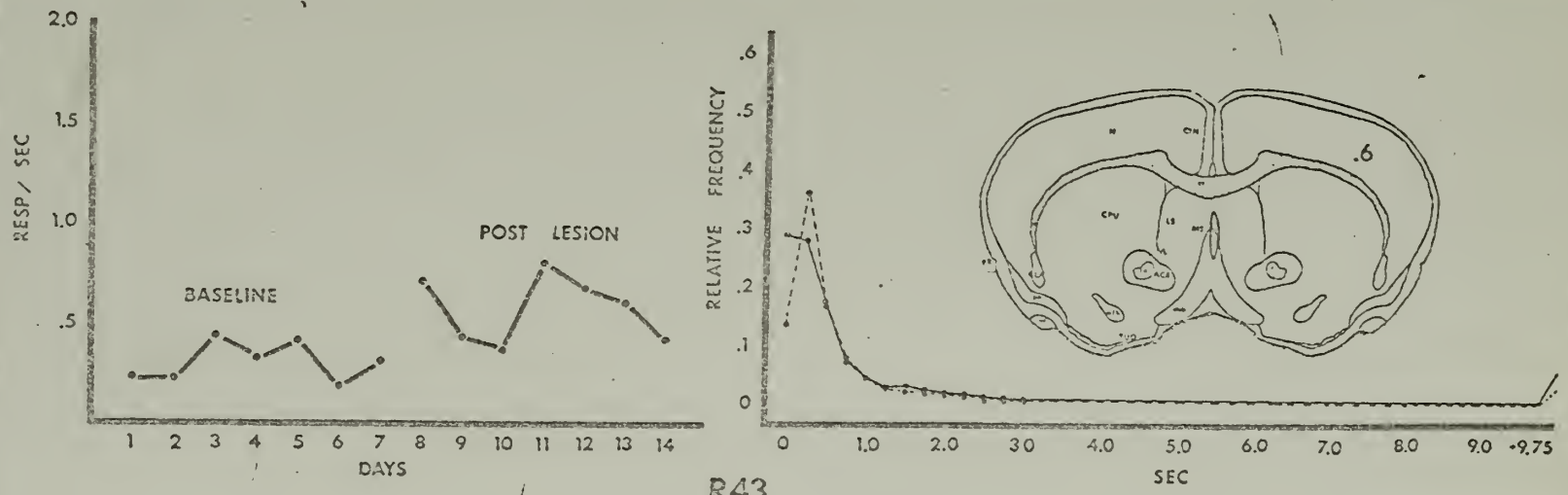
Figure 12



Degeneration Pattern

DF in anterior septum (minimal)
DF in vertical and horizontal diagonal band (light)
DF in medial forebrain bundle

Figure 13

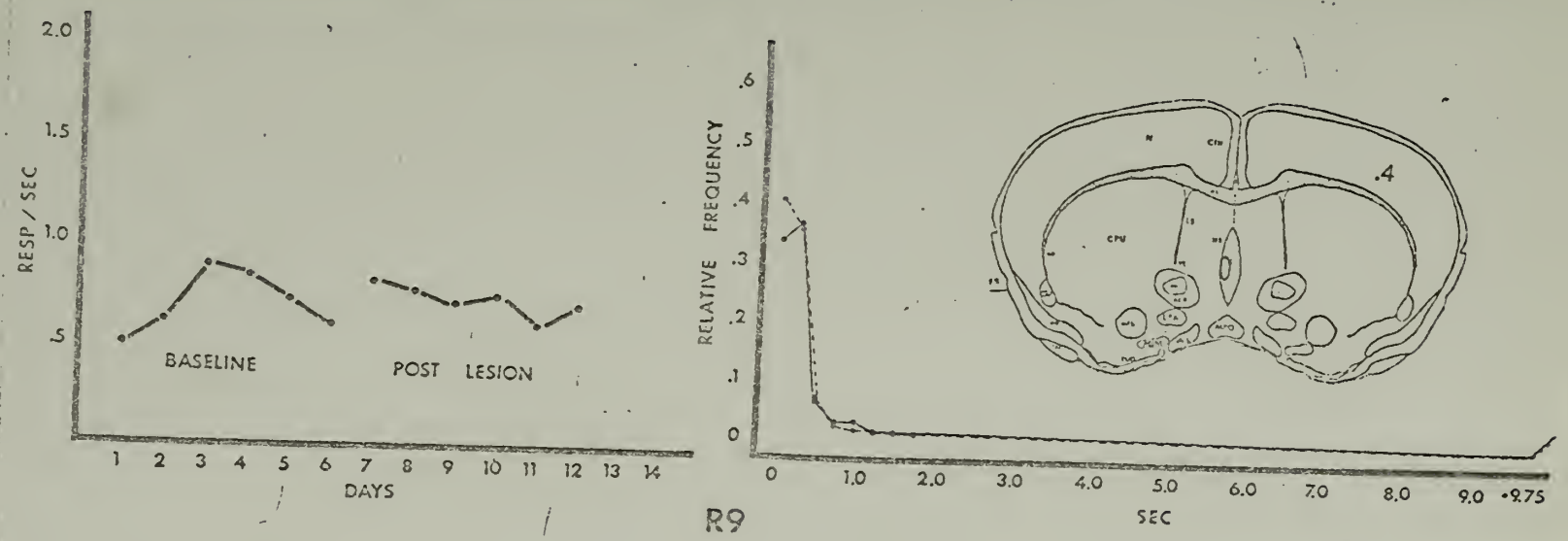


R43

Degeneration Pattern

DF in vertical and horizontal limb of diagonal band (asymmetrical)
DF in medial forebrain bundle (asymmetrical)
DF in precommissural fornix (asymmetrical)
DF in dorsal fornix (light)
DF in lateral fimbria/fornix
DF in anterior dorsal hippocampus (minimal)
DF in alveus (light)
DF in CA3 and CA4 of ventral hippocampus (asymmetrical)
DF in dorsal and ventral fascia dentata (light)
DF in commissure of fornix (light)
DF in subiculum (light)

Figure 14

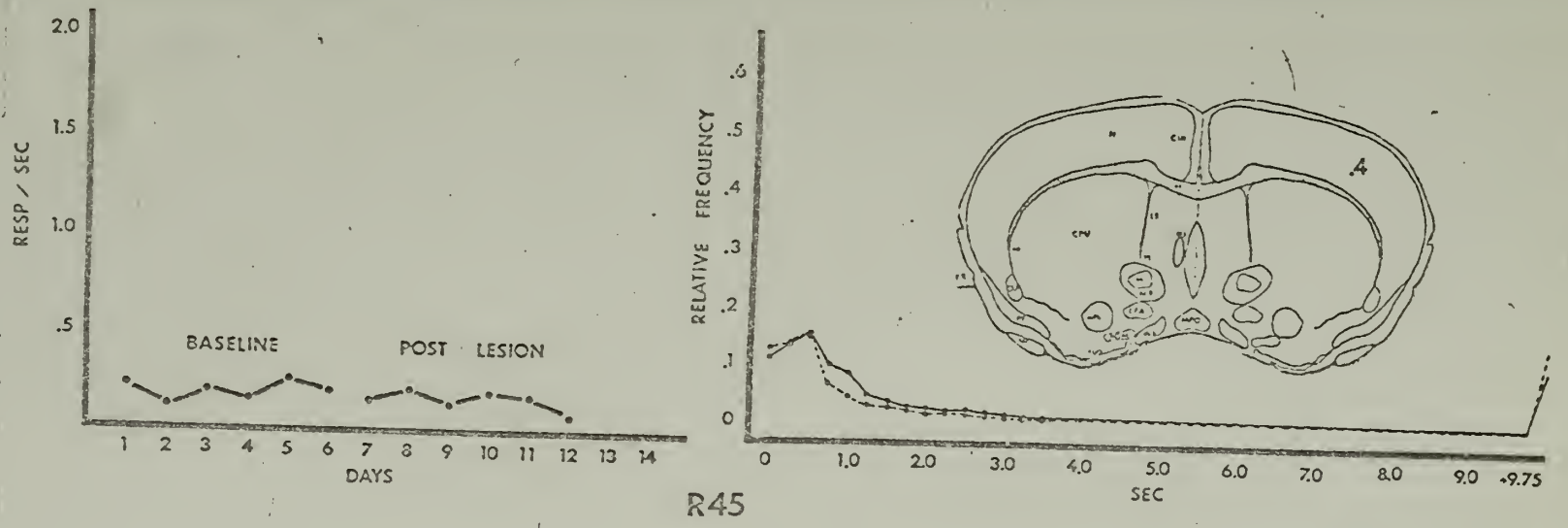


R9

Degeneration Pattern

DF in vertical and horizontal limb of diagonal band (unilateral)
DF in medial forebrain bundle (unilateral)
DF in precommissural fornix (light and unilateral)
DF in anterior dorsal hippocampus (minimal)
DF in alveus (unilateral)
DF in CA3 and CA4 of ventral hippocampus (unilateral)
DF in dorsal and ventral fascia dentata (light)
DF in commissure of fornix (light)
DF in subiculum (unilateral)

Figure 15

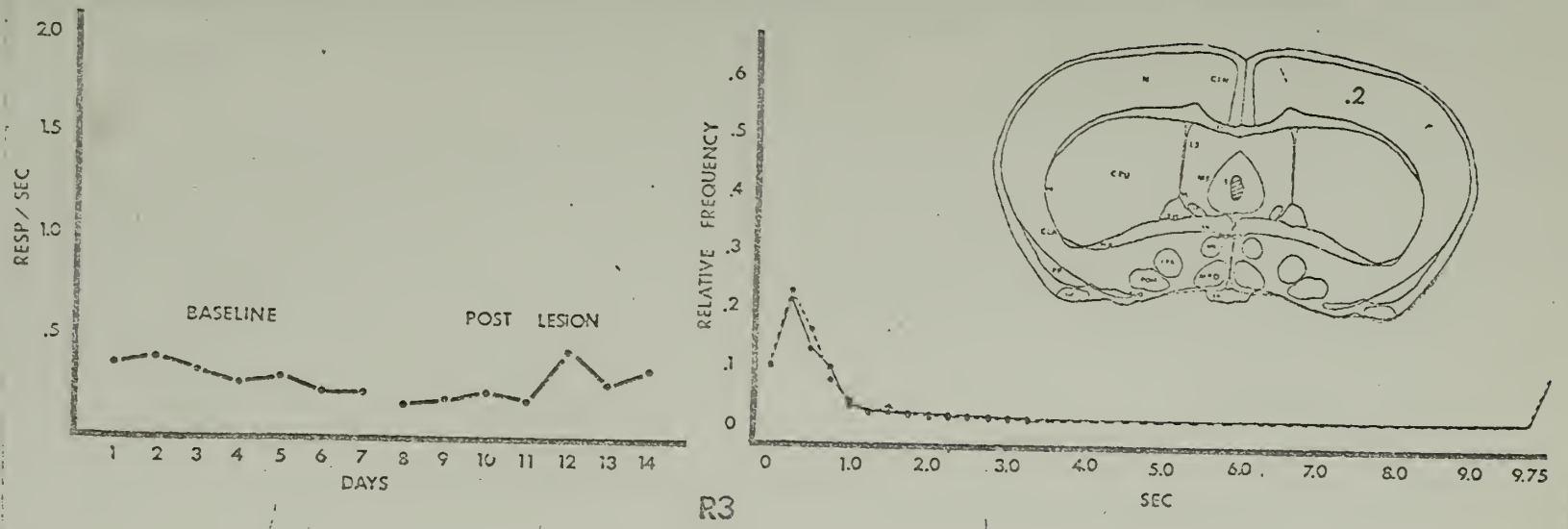


R45

Degeneration Pattern

DF in anterior septum (asymmetrical)
DF in vertical and horizontal diagonal band (asymmetrical)
DF in anterior commissure
DF in medial forebrain bundle (asymmetrical)
DF in precommissural fornix (light)

Figure 16

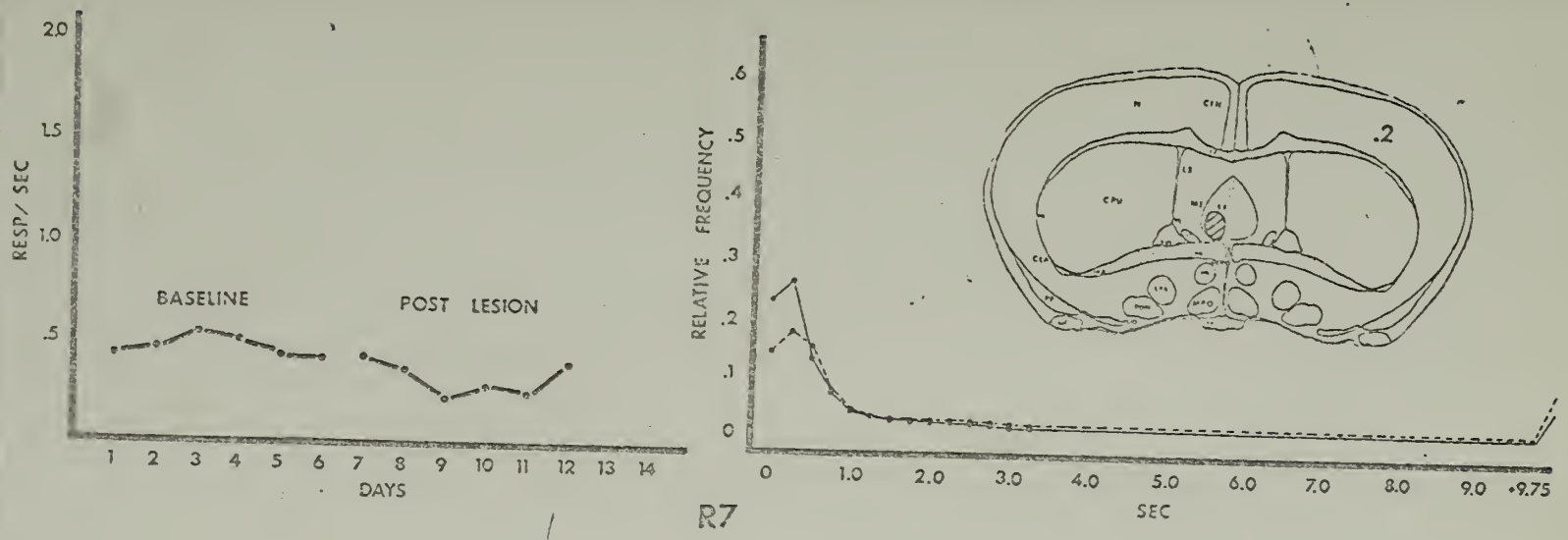


R3

Degeneration Pattern

DF in anterior septum
DF in vertical and horizontal diagonal band
DF in medial forebrain bundle
DF in precommissural fornix
DF in postcommissural fornix
DF in dorsal fornix (light)
DF in anterior dorsal hippocampus (minimal)
DF in alveus (light)
DF in CA3 and CA4 of ventral hippocampus (minimal)
DF in dorsal fascia dentata (light)
DF in ventral fascia dentata (unilateral)

Figure 17



Degeneration Pattern

DF in vertical and horizontal limb of diagonal band
DF in medial forebrain bundle (light)
DF in precommissural fornix (light)
DF in postcommissural fornix (unilateral)
DF in lateral fimbria/fornix (light and unilateral)
DF in stria medullaris (light and unilateral)
DF in medial and lateral habenular n. (light and unilateral)
DF and DT in mammillary bodies (light)
DF in alveus (light)
DF in CA3 and CA4 of ventral hippocampus (light)
DF in dorsal fascia dentata (light and unilateral)

Figure 18

rates and the percent change in response rate as a function of the lesion.

Several important conclusions could be made regarding the location of the lesion and the related change in behavior. The lack of effect of a far anterior septal lesion on operant response rates in subject M87 (figure 11) demonstrated the importance of the medial septal area and, more specifically, the dorsal diagonal band and its associated nucleus, in changes in response rate. The substantial behavior effects of a small symmetrical lesion entirely within the dorsal part of the diagonal band present in subject R6 (figure 11) demonstrated the critical involvement of this area of the septum in increments in rates.

The smaller, more dorsally placed lesion in M59 (figure 13) had little effect on response rates. See Table 3 for quantitative comparisons of baseline and post lesion response rates. The interpretation of data from this subject is unclear. Either the lesion is too small or does not include enough of the diagonal band area to affect a behavior change.

The importance of bilaterality of a lesion in the diagonal band area was demonstrated by the brain and behavior of R43 (figure 14). The lesion in this animal included only one half of the minimal effective area seen in R6 (figure 12). While the lesion tended to increase response rates overall (+93%) the post lesion curve is not monotonic. It was hypothesized that swelling and the varying osmotic

conditions within the lesion site following surgery changed the functioning of the nearby tissue just medial to the lesion. Swelling that interrupted functioning of adjacent tissue could have been responsible for the initial increase in response rate seen during the first few days following surgery.

The relevance of the diagonal band system specifically and not the entire medial septal area in operant behavior was demonstrated in the data from subjects R9 and R45 (figures 15 and 16). Lesions within the midline septal nucleus but caudal to the diagonal band had no effect upon response rates. Moderate lesions within the septofimbrial area, caudal to the diagonal band complex, also were completely ineffective in increasing operant responding.

In summary, not all small medially placed lesions within the medial septal area produced changes in operant behavior. Only exactly midline lesions within the dorsal diagonal band complex including fibers of the vertical limb of the diagonal band and the nucleus of the diagonal band changed behavior to the same degree as large septal lesions.

Small lesions, efferent degeneration patterns and behavior

Brain analyses and behavioral data of subject M87 confirmed that degeneration within the medial forebrain bundle is not a sufficient condition for changes in operant response rates. This animals's lesion (figure 11) was sufficiently anterior so as not to invade the

diagonal band complex. The lesion, however, did cause heavy, if asymmetrical degeneration of fibers within the medial forebrain bundle; yet no change in response rate occurred. No degeneration was observed in the lateral fimbria, CA3, CA4, fascia dentata or subiculum.

While degenerating fibers were always present in the precommissural fornix in the brains of animals receiving rate-increasing lesions small lesions within the precommissural fornix itself were ineffective in changing response frequency. (Refer to figures 15, 17 and 18). Two animals received lesions in very similar locations near or within the dorsal segment of the diagonal band (R6, figure 12 and M59, figure 13), but the behavioral effects of these lesions were quite different. Subject R6 produced many more responses following surgery (+88%) while M59's response did not change significantly (-8%). Degeneration patterns within nearby limbic structures of these two subjects were quite similar except in one respect. There were degenerating fibers within the precommissural fornix in R6, whose lesion produced a higher response rate and an absence of such fibers in M59 whose lesion had little effect on response rates. Thus, the presence of degenerating fibers within the precommissural fornix seemed to be strongly related to post lesion increments in response rates. Furthermore, the origin of these fibers appeared to be within the dorsal segment of the diagonal band complex. Small precommissural fornix lesions were without effect on

response rates. The fiber connections between the critical area in the dorsal diagonal band region and the ventral hippocampus then appear to travel through the precommissural fornix. Small lesions within the precommissural fornix would be expected to have little effect upon behavior because of the diffuse distribution of fibers through the posterior septum.

Conclusions from Experiment 1

Analysis of the effects of small and large septal lesions on operant behavior and efferent silver degeneration patterns suggested the following conclusions.

1) Large septal lesions that dramatically increase operant response rates were associated with degenerating fibers within the lateral fimbria, CA3, CA4 and fascia dentata of the ventral hippocampus and the adjacent subiculum. Fibers of septal origin seemed to terminate in the stratum radiatum, the location of basal dendrites of hippocampal pyramidal cells.

2) Lesions within the dorsal diagonal band complex were sufficient to produce increases in response rates and degeneration within the precommissural fornix, lateral fimbria, CA3, CA4 fascia dentata and subiculum.

3) There was a functional relation between the amount of degeneration within the ventral hippocampus and post lesion response rates. No such relation was found between behavior and medial forebrain bundle degeneration.

4) The data suggested that cells or fibers within the dorsal segment of the diagonal band region send fibers into the precommissural fornix that continue caudally through the lateral fimbria into the ventral hippocampus and that this pathway is intimately involved in mediating and modulating operant responding.

Experiment 2

The Effects of Specific Interruption of Fibers Connecting the Medial Septal Area and the Ventral Hippocampus

The behavioral and anatomical results of Experiment 1 suggested that destruction of neural elements within the dorsal diagonal band region result in increases in response rates controlled by a variable interval schedule of food reinforcement. Such lesions and the resultant behavior were associated with fiber degeneration within the precommissural fornix, lateral fimbria, CA3, CA4, fascia dentata and subiculum of the hippocampal formation. These results made it possible to conclude tentatively that connections between the septum and the hippocampal formation have important functions in determining the effects of contingencies of reinforcement on behavior.

The diffuse degeneration of fibers within the precommissural fornix following such lesions appeared to gather into more discrete bundles in the lateral margin the lateral fimbria. Thus, medial septal connections with the ventral hippocampus appear to travel through the lateral fimbria. If this pathway is involved in the increases in operant response rates following lesions within the dorsal diagonal band complex then damage restricted to the lateral fimbria should have a similar effect on operant response frequency. The purpose of Experiment 2 was to confirm the conclusions drawn in Experiment 1 by determining the effects of small restricted lesions within the lateral fimbria on operant behavior and efferent

degeneration patterns.

METHOD

Subjects

Seven male B6D2F_1/J hybrid mice served as subjects. They were housed in individual cages and maintained on a 12 hour light-dark cycle. Experimentation occurred during the light cycle. During the experiment body weights were stabilized and maintained by the presentation of 3.0 grams of laboratory grain given each day following the experimental session described below.

Apparatus

Mice were exposed to a variable interval schedule of food reinforcement in one of four identical operant chambers, each isolated in an insulated chest. These chambers were constructed of plexiglass with a wire mesh floor and a plexiglass lid. The dimensions of the chamber were 15 cm. x 15 cm. x 25 cm. On one wall of the chamber were three round plexiglass tubes 18 mm. in diameter. These tubes were 3.5 cm. above the wire mesh floor and protruded from the chamber. A photocell was positioned on the outside and bottom of each response tube. A 28 volt lamp centered above the response tubes served as the photocell beam. The operant response consisted of a head poke into the middle response tube, breaking the photocell beam. Reinforcements (20 mg. Noyes pellets, standard A formula) were delivered directly into the middle response tube via

a plastic hose connected to a pellet dispenser. The presentation of stimuli and the collection of data were controlled by an on line computer.

Procedure

Following three days of restricted feeding (4.0 grams of laboratory grain) mice were placed in operant chambers where reinforcements were delivered into the middle response tube on a fixed interval 1 second schedule contingent upon a head poke response. Over a period of 5 days the schedule of reinforcement was gradually changed from a fixed interval 1 second schedule to a variable interval 10 second schedule, variable interval 20 second schedule and finally, a variable interval 40 second schedule. Sessions were 30 minutes long. Number of reinforcements,response rates and interresponse time distributions were recorded each day.

Following the 7th session of stable VI-40 second responding stereotaxic lesions were placed in the area of the lateral fimbria at stereotaxic coordinates posterior -.5 mm., lateral ±1.2 mm., ventral -2.3 mm. under brief and light ether anesthesia. Thermocoagulations of the fibers within the lateral fimbria were made by passing current from a Grass radio frequency lesion maker through the tip of a tungsten microelectrode insulated with plastic except for the tip.

During the 7 days following surgery, each animal's response rate and interresponse distributions were recorded as usual. In this

way, the effects of lateral fimbria lesions could be determined 24 hours after surgery and during the subsequent 5, 6 or 7 days without disturbing the animal's normal routine. Following the 12th, 13th or 14th variable interval schedule session each subject was administered an overdose of Nembutal, perfused through the heart, the brain removed and subsequently analyzed for anterograde degeneration throughout the entire brain using a modified silver procedure for the differential staining of degenerating axons and terminals (Fink and Heimer, 1967).

RESULTS AND DISCUSSION

Lateral fimbria lesions and behavior

Lesions restricted to the far lateral region of the lateral fimbria were extremely effective in increasing operant response rates. The smallest and most effective bilateral lesion was made in subject R1. The tissue damage in this animal was almost completely restricted to the far ends of the lateral fimbria. Response rates 24 hours following surgery more than doubled and remained at this high rate for the remaining 5 days.

Figures 19-25 present baseline and post lesion response rates, IRT distributions and diagrams of appropriate brain sections showing the maximal extent of the lesion. Table 4 lists, for each subject, the mean pre-lesion response rate, mean post lesion rate and the computed percent behavior damage.

Subjects R1, R4, R8, and R42 received lesions that significantly increased response rates. In each case, the lesion invaded most of

Subject	Mean baseline rate (responses/second)	Mean post lesion rate (responses/second)	% Rate change
R1	1.04	2.43	+134%
R4	.31	.84	+171%
R8	.37	.83	+124%
R10	.72	.71	-1%
R41	.32	.33	+3%
R42	.43	.86	+100%
R44	.53	.59	+11%

Table 4. Baseline and post lesion mean response rates (responses/second) and behavior change measures as percent of baseline in subjects in Experiment 2.

the far lateral fimbria. The farther lateral the lesion within the fimbria the greater the behavior change appeared to be. Subject R1 (figure 23) received a lesion that was within the lateral fimbria but not far enough laterally to generate the behavior change in R1 as a consequence of a smaller more lateral lesion (figure 19).

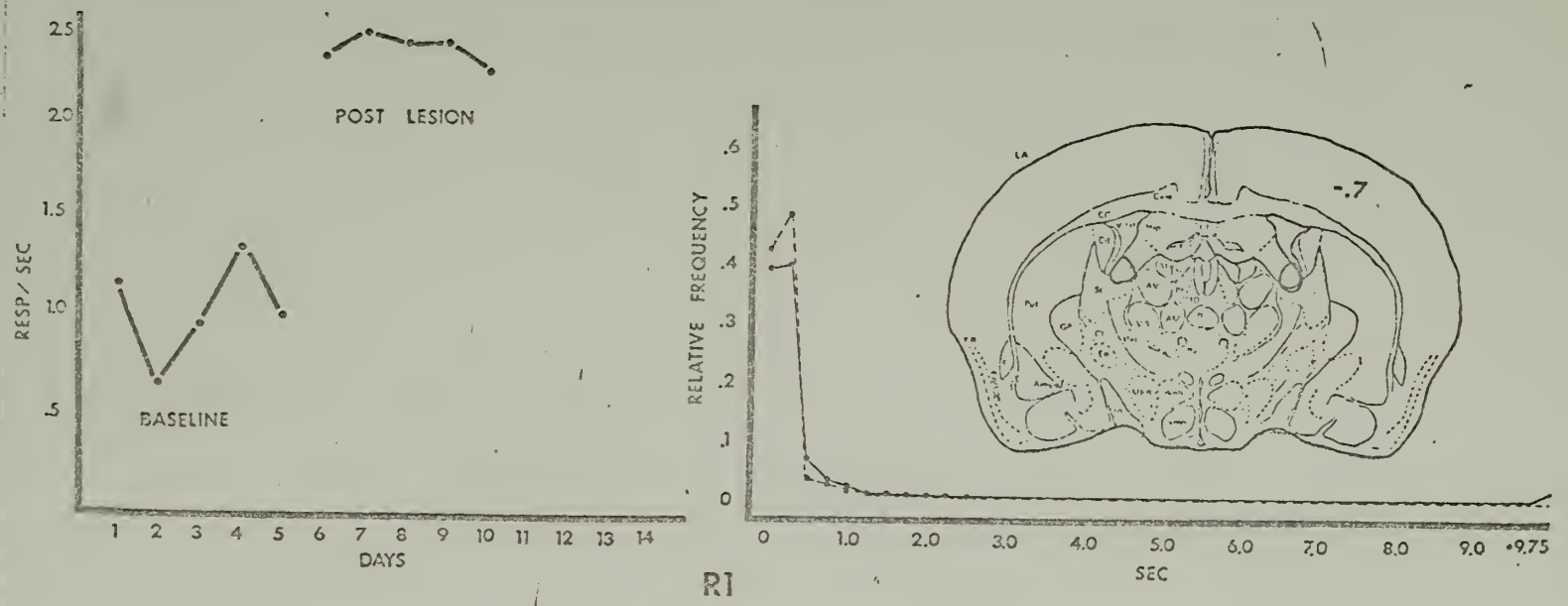
One animal, R42, received asymmetrical lesions within the fimbria. The lesion on the left included the far lateral margin of the fimbria, but the lesion on the right is just medial to the far lateral margin. During the first day following surgery response rate was approximately three times as great as during baseline. However, during the following 4 days this high response rate gradually decreased and by the last experimental day had nearly approached baseline rates. It was hypothesized that this decelerating curve followed the gradual reduction in local swelling around the lesion in the right fimbria. Such swelling could temporarily block transmission of the nearby far lateral fimbria fibers apparently involved in response rate increments. It is possible that as swelling diminished and local osmotic conditions normalized transmission along these fibers returned to normal. As a consequence, so too did response rates gradually return to normal.

Lateral fimbria lesions, efferent degeneration patterns and behavior

Large lateral fimbria lesions resulted in widespread axonal and terminal degeneration within the brain. Following such lesions

FACE PAGE FOR FIGURES 19 - 25

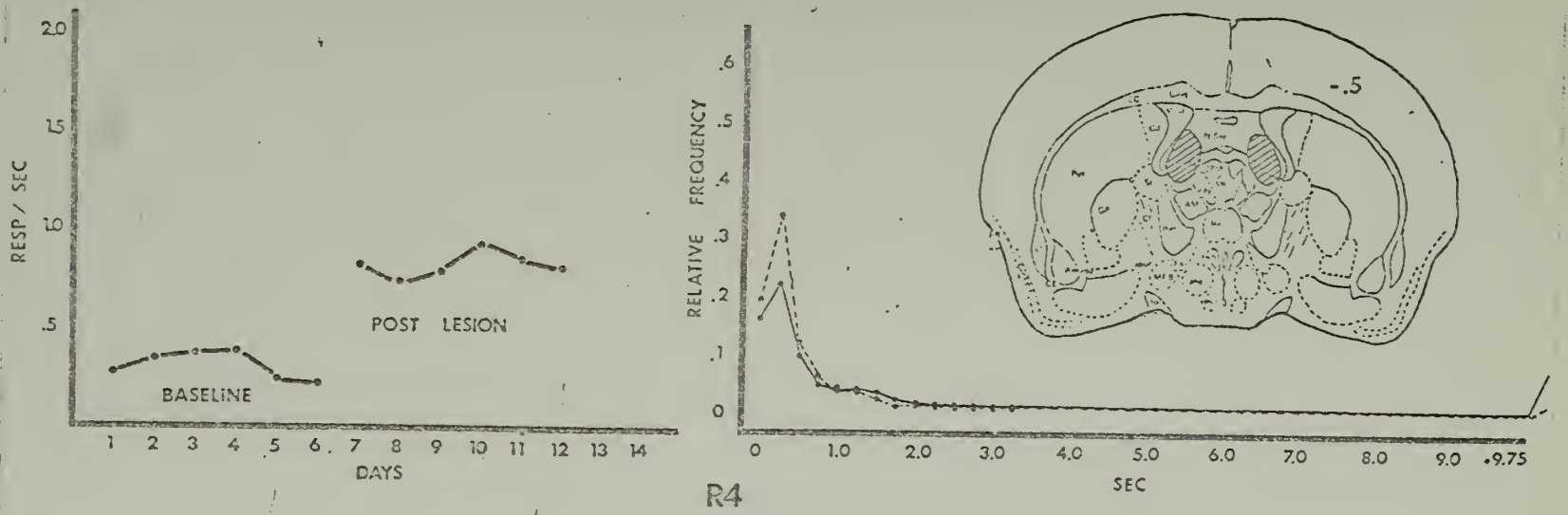
For each subject baseline and post lesion response rates, interresponse time distributions, a diagram of the coronal brain section showing maximal extent of the lesion and the degeneration pattern revealed by the Fink-Heimer procedure are shown. For degeneration patterns DT = degenerated terminals, DF = degenerated fibers. For interresponse time distributions solid lines indicate baseline distributions and dashed lines indicate post lesion distributions.



Degeneration Pattern

DT in accumbens septi
DT in anterior lateral septal n.
DF and DT in lateral septal n.
DF in vertical and horizontal limbs of diagonal band (light)
DF in lateral precommissural fornix
DF in postcommissural fornix (light)
DF in lateral fimbria/fornix
DF in stria terminalis (light)
DF in coritcomedial n. of amygdala
DF in ventral alveus
DF in CA3 and CA4 of ventral hippocampus

Figure 19



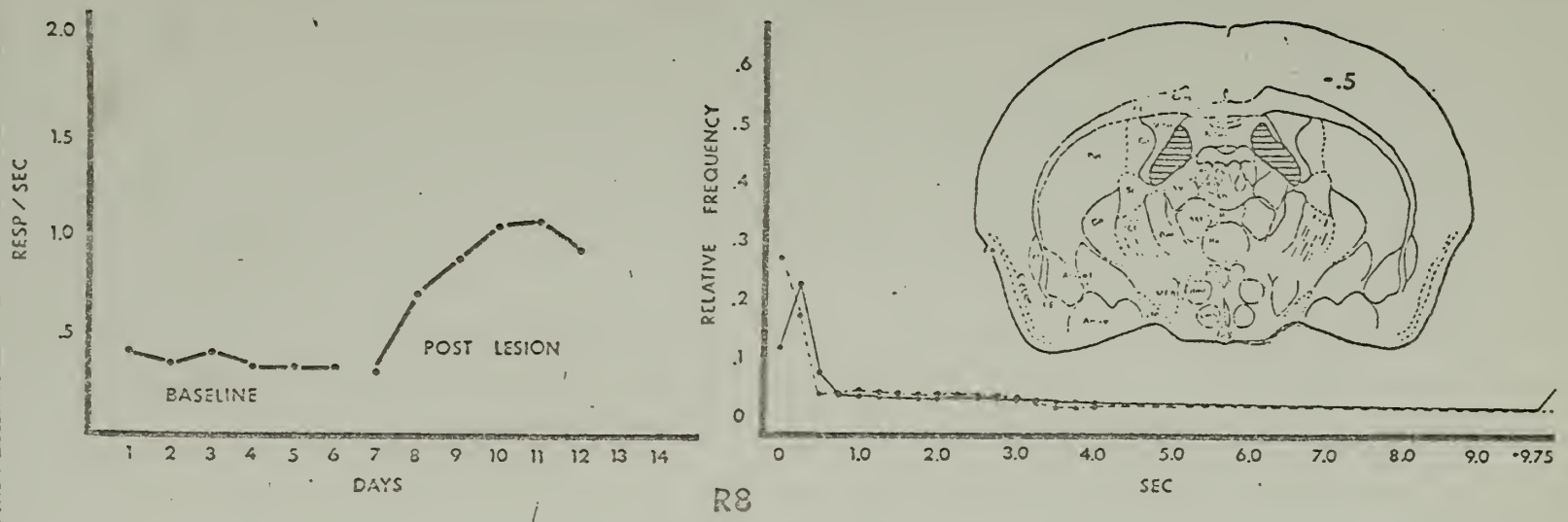
R4

Degeneration Pattern

DT in n. accumbens septi
DT in lateral septal n.
DF in lateral septal n.
DF in vertical and horizontal diagonal band
DF in medial forebrain bundle
DF in lateral precommissural fornix
DF in postcommissural fornix (light)
DF in lateral fimbria
DF in stria terminalis (unilateral)
DF and DT in paraventricular n. of thalamus (unilateral)
DF and DT in paratenial n. of thalamus (unilateral)
DF and DT in anterodorsal n. of thalamus
DF and DT in lateral anterior n. of thalamus

DF and DT in corticomedial n. of amygdala (unilateral)
DF in anterior dorsal hippocampus (minimal)
DT in CA1 of dorsal hippocampus (stratum oriens and stratum radiatum)
DF and DT in CA2
DT in CA4 of ventral hippocampus
DF in CA3 and CA4
DF in ventral alveus
DF in dorsal and ventral fascia dentata
DF in commissure of fornix
DF and DT in subiculum

Figure 20

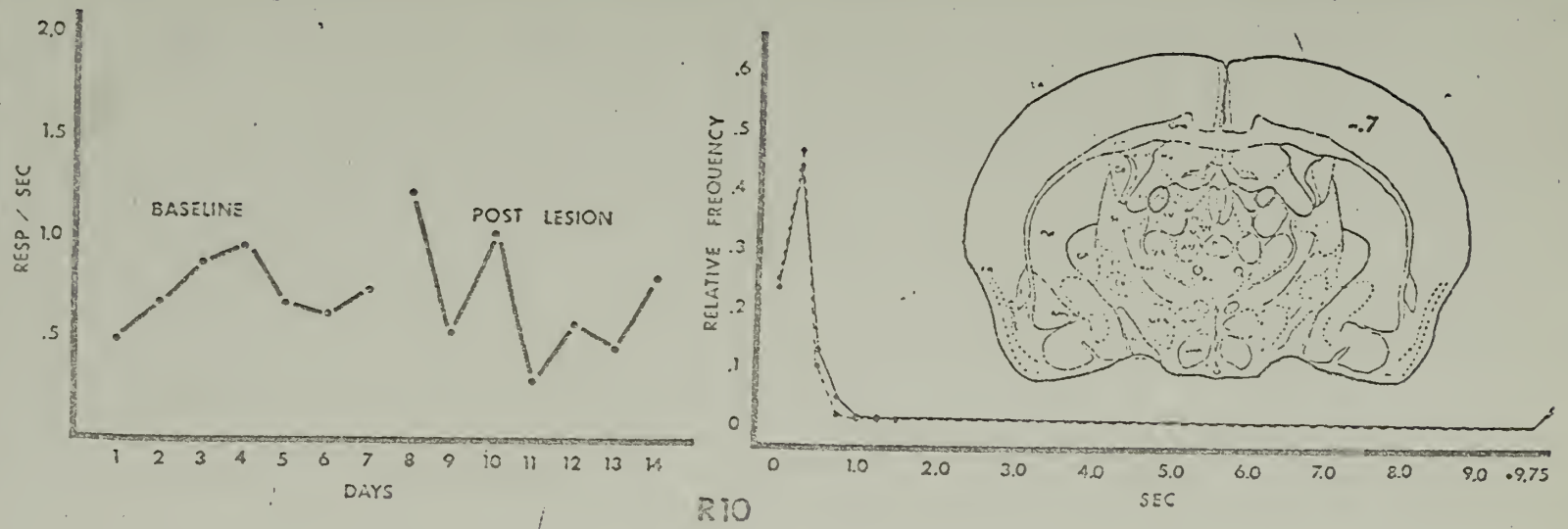


R8

Degeneration Pattern

DT in n. accumbens septi
DT in lateral septal n.
DF in lateral septal n.
DF in vertical and horizontal diagonal band
DF in olfactory tubercle (light)
DF in medial forebrain bundle
DF in lateral precommissural fornix
DF in postcommissural fornix
DF and DT in paraventricular n. of thalamus
DF and DT in paratenial n. of thalamus
DF and DT in anteromedial and anteroventral n. of thalamus
DF and DT in lateral anterior n. of thalamus
DF and DT in rhomboid n. of thalamus
DF and DT in zona incerta
DF and DT im mammillary bodies
DF and DT in CA1 of dorsal hippocampus
DT in CA2 (stratum oriens and stratum radiatum)
DT in CA3 and CA4 of ventral hippocampus (stratum oriens and radiatum)
DF in CA3 and CA4 of ventral hippocampus
DF in alveus
DF in dorsal and ventral fascia dentata
DF in stria terminalis (light)
DF surrounding interpeduncular n.
DF in commissure of fornix
DF and DT in subiculum

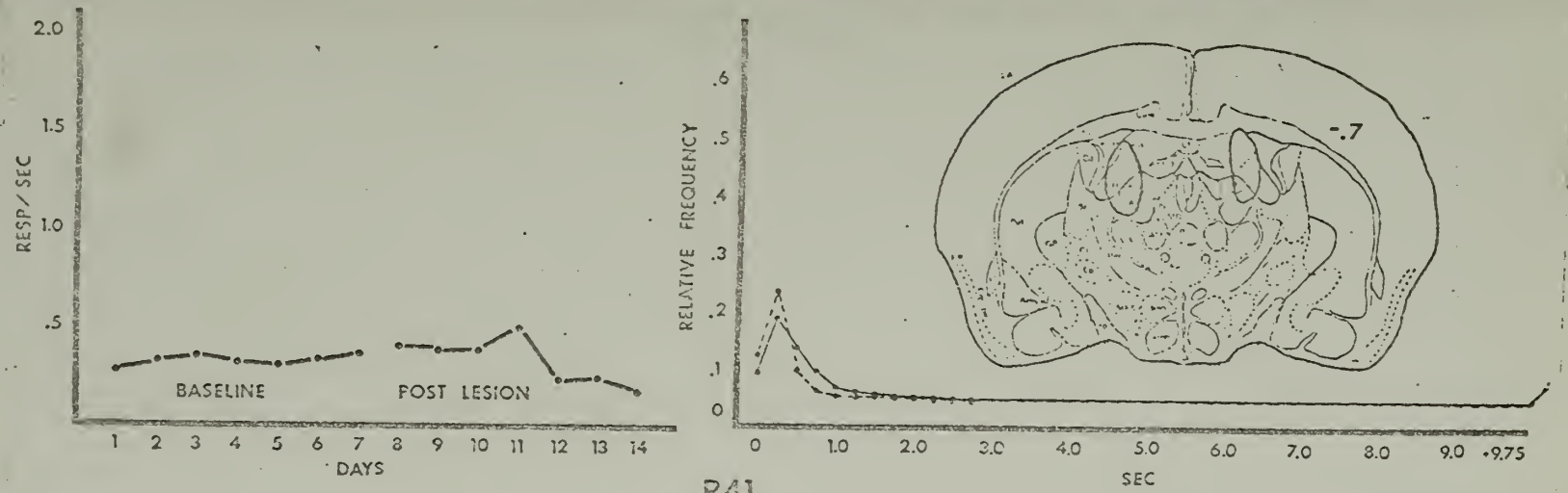
Figure 21



Degeneration Pattern

DT in n. accumbens septi (light)
DF in anterior septum (light)
DF in lateral fimbria/fornix (light and unilateral)
DF in anterior dorsal hippocampus (light)
DF in alveus (light)
DF in dorsal fascia dentata (light)
DF in CA3 and CA4 (minimal)
DF in commissure of fornix
DF in subiculum

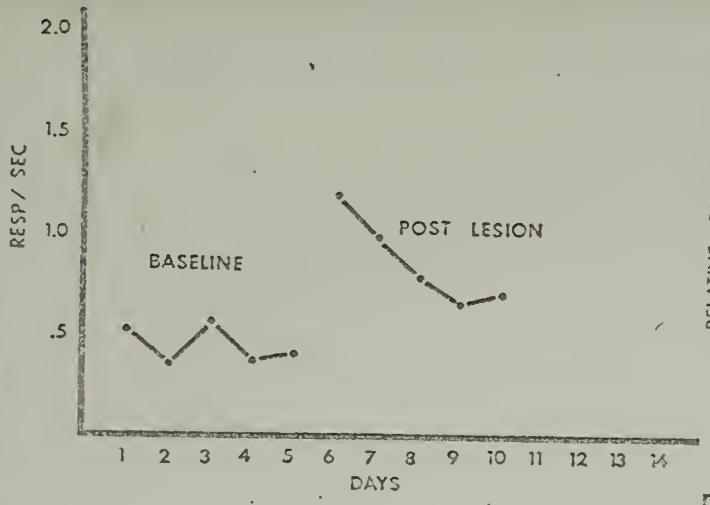
Figure 22

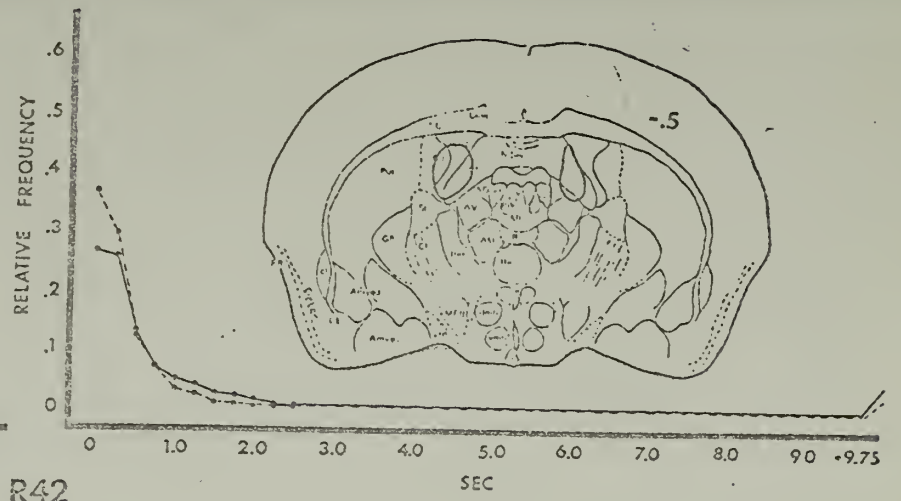


Degeneration Pattern

DT in n. accumbens septi (light)
DF and DT in lateral septal n.
DF in vertical and horizontal limb of diagonal band (light)
DF in medial forebrain bundle (light)
DF in lateral precommissural fornix
DF in postcommissural fornix
DF and DT in anteromedial and anteroventral n. of thalamus
DF and DT in mammillary bodies (light)
DF in stria terminalis (light)
DT in CA1 of dorsal hippocampus
DF and DT in CA3 and CA4 of ventral hippocampus
DF in ventral fascia dentata (light)
DF in subiculum

Figure 23





R42

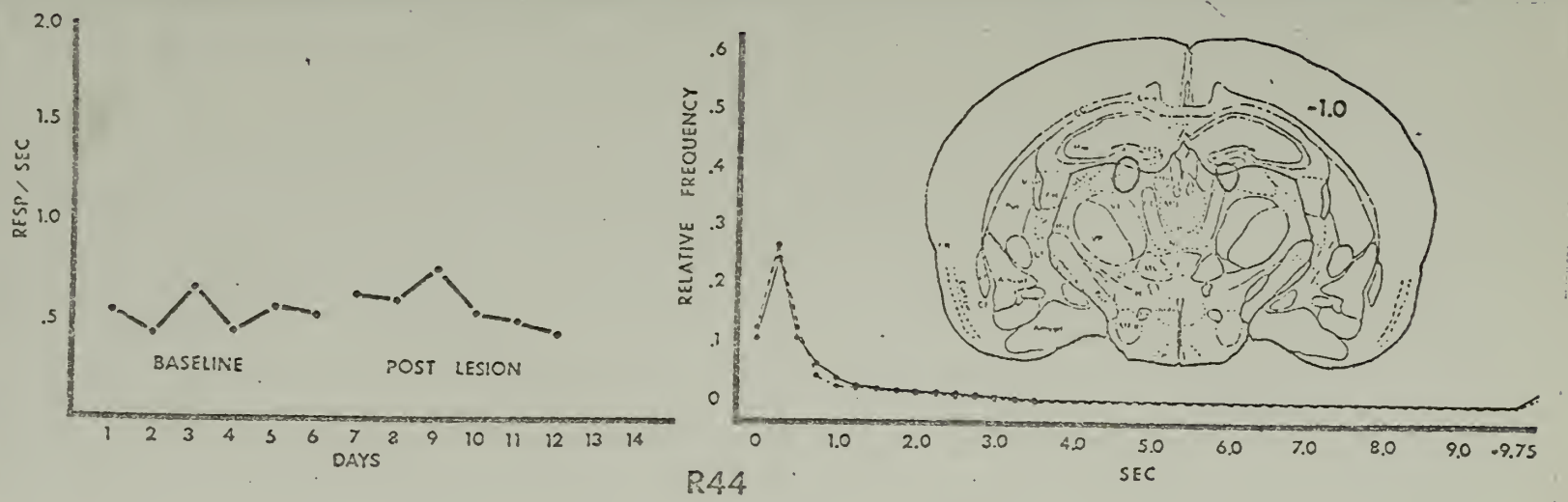
/ Degeneration Pattern

DT in n. accumbens septi (unilateral)
DF in anterior septum (unilateral)
DF and DT in lateral septal n. (unilateral)
DF in vertical and horizontal diagonal band (unilateral)
DF in medial forebrain bundle (light and unilateral)
DF in precommissural fornix (unilateral)
DF in postcommissural fornix (unilateral)
DF and DT in mammillary bodies
DF and DT in medial caudate n.
DT in CA1 and CA2 of dorsal hippocampus (stratum oriens and stratum radiatum)
DT in CA4 of ventral hippocampus
DF in CA3 and CA4 (unilateral)

DF in ventral fascia dentata (unilateral)
DF in dorsal fascia dentata
DF in alveus

DF and DT in anterodorsal n. of thalamus
DF in commissure of fornix
DF and DT in subiculum (light)

Figure 24



R44

Degeneration Pattern

DF and DT in anterodorsal n. of thalamus
DT in CA1 of dorsal hippocampus
DT in CA3 and CA4 of ventral hippocampus (stratum oriens)
DF and DT in subiculum (light)

Figure 25

degeneration was consistently observed in the nucleus accumbens septi, lateral precommissural fornix, lateral septal nuclei, vertical and horizontal limbs of the diagonal band (minimal), in the medial forebrain bundle (minimal), remaining lateral fimbria, ventral alveus, CA1, CA2, CA3, CA4 and the ventral fascia dentata, the commissure of the fornix and the allocortical subiculum. No degeneration was found in the postcommissural fornix or mammillary bodies.

The lack of direct involvement of the medial forebrain bundle in increments in operant responding was confirmed by the data from subject R1. This animal recieved small lesions restricted to the far lateral margin of the lateral fimbria that resulted in heavy degeneration within CA3, CA4 and the fascia dentata of the ventral hippocampus, but no degeneration in the diagonal band or medial forebrain bundle. In this subject degeneration was confined to the ventral hippocampus, lateral precommissural fornix, lateral septal nuclei and the nucleus accumbens septi. Anatomical data from R1 indicated that fibers travelling from the relevant diagonal band region travel through the precommissural fornix and into the far lateral margin of the fimbria to project onto basal dendrites of pyramidal cells in CA3 and CA4 and dendrites of granule cells in the fascia dentata. Disruption of this pathway by small lesions in the lateral fimbria dramatically increased operant response rates.

Further delineation of the important hippocampal efferent site involved in changes in operant behavior derived from analysis of the behavioral data and degeneration pattern in subject R41 (figure 23).

This animal received lateral fimbria lesions that left most of the lateral margin intact. While moderate concentrations of degenerating fibers were present in CA3, CA4 and the fascia dentata no change in response rate occurred following surgery. Unlike the hippocampal degeneration patterns present in R1, R4 or R8, where lesions resulted in response rate increases, degeneration in the far caudal ventral hippocampus within CA3, CA4 and fascia dentata was absent. These differences suggested that degeneration of the far caudal ventral hippocampus was necessary for alteration in response rates within the context of these lesions.

Degeneration analyses made it possible to eliminate the direct role of the dorsal extension of the fascia dentata in changing operant rates. Subject R44 (figure 25) sustained some damage to the dorsal fascia dentata and subsequent degeneration of fibers within the dorsal region of this structure. However, no significant change in response rate occurred. No degeneration was observed in the ventral extension of the fascia dentata or CA3, CA4 or the subiculum.

The importance of bilateral degeneration within the caudal ventral hippocampal formation to changes in operant response rates was demonstrated in subject R42 (figure 24). This animal received a lesion in the left hemisphere that involved the far lateral margin of the lateral fimbria. However, the lesion on the right left the far lateral margin essentially intact. Heavy degeneration was observed in CA3, CA4 and fascia dentata of the ventral hippocampus

but only on the left. Thus, unilateral disruption of the lateral fimbrial connections with the ventral hippocampus was insufficient to increase response rate.

Relative response frequency distribtuions were altered by rate changing lesions. In the case of the animal with lesions restricted to the lateral margin of the fimbria (R1, figure 19) nearly all responses were made within .5 second of the previous response during baseline. The peak of this distribution became even steeper as a function of the lesion. The same result was obtained in R4 and R42. The lesions received by subject R8 had a more marked effect on the IRT distribution. The peak of the curve shifted to the left into the 0 - .25 second time bin following surgery.

Conclusions

The behavioral and anatomical results obtained in Experiment 2 suggested the following conclusions.

1) Bilateral lesions restricted to the far lateral margin of the lateral fimbria were extremely effective in increasing operant response emission.

2) Lesions that generated higher response rates after surgery resulted in heavy neural degeneration within the caudal ventral hippocampal formation (CA3, CA4, fascia dentata and subiculum).

GENERAL DISCUSSION

Anatomical Considerations

The results of Experiments 1 and 2 demonstrated that lesions restricted to the dorsal segment of the diagonal band complex or the axonal projection of this area, the lateral fimbria, result in dramatic changes in the rate of responding of mice on a variable interval schedule of food reinforcement. Furthermore, both types of lesions resulted in degeneration of axons within the caudal aspect of the ventral hippocampal formation. These fibers appeared to terminate on basal dendrites of pyramidal cells and granule cells within CA3, CA4, the fascia dentata and subiculum. This degeneration pattern was consistently correlated with increments in postsurgical response rates.

The results of these experiments are in agreement with other studies in the rat. Ross and Grossman (1975) studied the effects of transection of afferent and efferent connections of the septum with the hippocampus on a variety of behavioral measures. They compared the effects of knife cuts through the fimbria/fornix with the effects of transection of the afferent and efferent connections of the septum with the diencephalon by means of a horizontal knife cut through the diagonal band just ventral to the septal area. Response rates controlled by a differential reinforcement of low rate schedule, a fixed interval schedule or a discriminated Sidman avoidance schedule were unaffected by ventral knife cuts through the diagonal band/medial forebrain bundle pathway. Fimbria/fornix transections increased

response rates on all schedules of reinforcement and punishment. Previously these authors had shown that blocking transmission at cholinergic synapses in various sites in the hippocampus increased responding on a differential reinforcement of low rate schedule (Ross and Grossman, 1974). These results suggested that pathways that mediate or modulate interactions between contingencies of reinforcement and behavior may be components of cholinergic projections from the medial septal area to the hippocampus described by Lewis and Shute (1967).

MacDougall, Van Hoesen and Mitchell (1969) have reported that lesions of the most lateral aspect of the fimbria impair DRL performance, while medial fimbrial lesions do not. The lateral fimbria was consistently observed to contain dense axonal degeneration following effective medial septal/diagonal band lesions that produced increases in operant responding in mice maintained on a variable interval schedule. Lateral fimbria lesions were similarly found to be effective in raising response rates in mice (Experiment 2). The present experimental evidence along with the data from Ross and Grossman (1974, 1975) and MacDougall et al (1969) argue that the disturbance of cholinergic fibers of medial septal origin, travelling through the precommissural fornix and lateral fimbria and projecting to CA3, CA4 and the fascia dentata result in significant changes in operant response rate maintained by a variety of schedules of reinforcement.

More recently, MacDougall and Capobianco (1976) have attempted

to delineate further the relation between operant response rates and the fornix system of the rat. They compared the behavioral effects of total fimbria/fornix transection with the effects of transection of only the pre- or postcommissural extentions of the fornix. Knife cuts severing the total fimbria/fornix or the precommissural fornix caused increases in response rates controlled by a DRL schedule so as to severely impair performance as measured by reinforcement density and response per reinforcement. Transection of postcommissural fornix fibers produced no such impairment. The results of these knife cut experiments are in complete agreement with the present experiments. The composite results of the knife cut experiments and the present silver degeneration studies in the mouse argue that the functional cholinergic efferent connections of the dorsal segment of the diagonal band complex with the fascia dentata, CA3 and CA4 of the hippocampus that travel through the precommissural fornix and fimbria have very direct mediating effects on the relation between environmental contingencies and the operant.

What remains to be explained is how the anatomical relations between the diagonal band complex and the ventral hippocampus are able to modulate the relations among the theoretical elements of the "three term contingency"; $S^D \rightarrow R \rightarrow S^R$. It is not as yet clear how disruption of these connections leads to changes in response probability. Two general possibilities seem to exist.

First, the hippocampal cell fields within the fascia dentata, CA3 and CA4 may exert modulatory control on behavior via projections

to entorhinal cortex. Raisman, Cowan and Powell (1966) have reported reciprocal connections among the medial septal area (MS), hippocampus and entorhinal cortex. Cells within CA3 and CA4 project directly to MS and the nucleus of the diagonal band, and indirectly to the MS and nucleus of the diagonal band through the lateral septal nuclei. The medial septal area, including the nucleus of the diagonal band, in turn, project back to fields CA3 and CA4. Neurons within CA3 are believed to send fibers into entorhinal cortex. The fascia dentata receives fibers from entorhinal cortex, while efferents from the dentate, constituted by mossy fibers, project to CA3 and CA4. There appears to be a cascading output from the fascia dentata to CA3 to CA1 to the subiculum, presubiculum and entorhinal cortex (Shepherd, 1974).

These anatomical relations might suggest that MS damage, resulting in degeneration within CA3 and CA4 and the fascia dentata, modifies the effects that entorhinal inputs have on hippocampal neurons. While this may be true, functional efferent output from the relevant hippocampal neurons is still required for functional changes within the limbic system to influence response rates. An analysis that includes only the limbic system does not allow us to understand how these changes ultimately affect striated muscle contraction through central nervous system motor systems.

It is in keeping with what is known about hippocampal-entorhinal interactions to suggest that neurons within CA3, CA4 and the fascia

dentata exert modulatory control directly via entorhinal connections. Unfortunately, non-hippocampal entorhinal efferent pathways are poorly understood. If the effects of disruption of medial septal connections with CA3, CA4 and fascia dentata on operant response rates are mediated through entorhinal efferents it is unclear which pathways and efferent structures are involved. Entorhinal cortex has no direct relation with motor systems controlling muscle contraction and, unfortunately, operant response data from animal sustaining entorhinal lesions are lacking in the literature. Simply put, however, moving our explanation into neocortex is moving even further away from the neural substrate more intimately involved in skeletal muscle contraction (behavior).

A second and perhaps more plausible possibility may be that altered neural control involved in response rate increments following medial septal or lateral fimbrial lesions is exerted via the descending efferent projections of the hippocampus through the intact fornix. The plausibility of this scheme derives from the fact that efferents from the hippocampus, travelling in the fornix, have more direct access to caudal motor systems within the brainstem. In such a view, degeneration of fibers from the medial septum to CA3, CA4 and the fascia dentata functionally change the axonal output of the hippocampus. Furthermore, relevant axonal efferents travel rostrally through the fimbria back to the septum to then travel ventrally and caudally to terminate in response-relevant motor systems. All

ventral connections of the septum are carried by the medial forebrain bundle. Descending fibers are known to travel in the medial forebrain bundle to terminate in the rostral brainstem area, the ventral tegmental area of Tsai (Wolf and Sutin, 1965).

There seems to exist a continuous system extending from the lateral hypothalamus through the ventral tegmental area of Tsai and into the midbrain and pontine central tegmentum (Berntson and Micco, 1976). Stimulation along this trajectory has been shown to elicit vigorous stimulation bound eating behavior (Wyrwicka and Doty, 1966). Moreover, the ventral tegmental area of Tsai has recently been shown to contain dopaminergic neurons (Kizer, Palkovits and Brownstein, 1976). A review of recent literature (Berntson and Micco, 1976) suggests that the brainstem may play a more fundamental role in the mediation of complex behavior than has previously been assumed. These authors document the substantial behavioral repertoires of decerebrate animals and cite recent findings that electrical stimulation of localized areas in all major levels of the brainstem can elicit complex and coordinated behavior. Behavior elicited from sites in the caudal brainstem evidenced surprising stimulus control over response topography. Additional neuroanatomical and behavioral data implicate caudal brainstem networks in reinforcement and punishment (German and Bowden, 1974). Berntson and Micco conclude that mediating mechanisms for many behavioral repertoires are intrinsic to the lower brainstem. In accord with this view, rostral hypothalamic and limbic mechanisms may contribute little more than refinement of

stimulus control. These forebrain structures might be best viewed as phylogenetically newer control mechanisms that modulate the activity of caudal systems. In such a perspective, medial septal - hippocampal interactions may serve only to modulate the effects of public and private stimuli. Moreover, the response-relevant output of the limbic system feedback loop between septum and hippocampus may be through the ventral septal area into the caudal projecting medial forebrain bundle.

This scheme of neural events has been hypothesized by MacDougall and Capobianco (1976). However, in their experiment, total fimbria/fornix transection produced the same magnitude of effect on DRL response rates as medial septal lesions. This argued that the relevant efferent fibers emerging from the hippocampus cannot be travelling in the fimbria because it has been transected. Inferentially, the rostral efferent flow of hippocampal output would be disrupted by the same transection that produced the change in response rate via septal efferents travelling to the hippocampus through the lateral fimbria. If the critical hippocampal efferents are those travelling rostrally and not those synapsing in entorhinal cortex they are not projecting through the fimbria/fornix. It is conceivable that the efferent fibers of the hippocampus that are necessary to affect the response rate following medial septal damage travel in the dorsal fornix. This small bundle of fibers lies just below the corpus callosum and dorsal to the fimbria. It is possible

that hippocampal efferents mediating increases in response rate following septal lesions travel in this small bundle and are unaffected by knife cuts through the fimbria.

The dorsal fornix is known to contain fibers of both subicular and CA1 origin, both of which have intimate connections with CA3, CA4 and the fascia dentata. However, lesions of the dorsal fornix alone offer little evidence of a role in mediating operant response rates (Myhrer, 1975; Myhrer and Kaada, 1975). If the dorsal fornix is involved in the expression of the effects of medial septal or lateral fimbria lesion it is not involved in any simple fashion. There is no a priori reason to believe that the response rate increases following these lesions derive directly from CA3, CA4 and fascia dentata. First, the fascia dentata has no extrahippocampal projections. It receives its main input from entorhinal cortex through the perforant pathway and from the medial septal area via the fimbrial (alvear) pathway. The efferent output of the dentate, through the mossy axonal fibers of granule cells is directed to pyramidal cells in CA3 and CA4. These former hippocampal fields project much of their output to CA1 and CA2. It is CA1 that primarily sends rostral fibers through the dorsal fornix to the septal area (Raisman, Cowan and Powell, 1966). Thus, if hippocampal efferents through the dorsal fornix are involved in increments in response rate following medial septal and fimbrial lesions they originate in the directly affected CA3, CA4 and fascia dentata. In such a scheme

CA3, CA4 and the dentate effect motor systems indirectly through the output of CA1 through the dorsal fornix into the efferent output of the septal area to caudal brainstem sites.

There are behavioral data to suggest that the effects of medial septal lesions on operant response rates are mediated through the hippocampus in a complex fashion to affect rostrally travelling fibers that possibly project through the dorsal fornix. Ross and Grossman (1975) have reported that undercutting of the medial septum had no effect on DRL performance. If any ventral projections of the septum are critical for increases in operant response rate following lesions they must assume a very lateral course in their descent. Support for this possibility comes from a recent report by MacDougall and Capobiano (1976) that complete undercutting of the septum produced deficits in DRL performance of a magnitude comparable to total fornix transections or medial septal lesions. Their result may imply that at least a portion of a response-modulating system depends upon a feedback loop from the medial septal area to the hippocampus, back to the lateral septal nuclei and then on to some unknown ventral and caudal structure; possibly the ventral tegmental area of Tsai. Some support for this scheme comes from the experiment of Hamilton et al (1970) in which operant response rate increases were produced by restricted lesions of the lateral septum. This finding was replicated in the present Experiment 1. In such a model, the

entorhinal connections might be viewed as supplying a limbic operant response-modulating system with modality-specific or polysensory discriminative stimuli (i.e., the S^D component of the three term contingency).

Electrophysiological analyses of the functional relations between the lateral and medial septal nuclei have revealed that neurons in the medial septal area generate bursts of action potentials during lateral hypothalamic stimulation (McLennan and Miller, 1976). Stimulation of the fimbria inhibits lateral septal neurons. Activity in the hippocampus relayed through the fimbria excites lateral septal interneurons. These interneurons, according to McLennan and Miller, in turn excite medial septal cells as well as recurrent inhibitory interneurons in the lateral septal nuclei. The result of this hippocampal-lateral septal afferent input to medial septum is to produce phasic burst responding of medial septal neurons to hypothalamic (medial forebrain bundle) stimulation. A recurrent collateral system involving interneurons containing gamma-aminobutyric acid in the lateral septum is hypothesized by these authors to regulate the discharge of medial septal cells. The state of these lateral septal interneurons depends upon the frequency of output from fimbrial fibers of hippocampal origin. If medial septal cells do not receive phasic inhibitory input from lateral septal relay neurons they will discharge in an irregular pattern controlled only by the tonic activity ascending in the medial forebrain bundle. This description is supported by Chronister and

White's (1975) report that neurons in the medial septal area have bilateral dendritic arborizations and respond to medial forebrain bundle stimulation but not directly to fimbrial stimulation.

To summarize the logic presented so far, it is conceivable that the reinforcing stimuli responsible for increases in the probability of a response that immediately precedes such stimuli elicit neural activity that ascends in the medial forebrain bundle. This ascending activity produces excitatory postsynaptic potentials in the medial septal area including the nucleus of the diagonal band. Cholinergic efferents from this area within the septum project through the lateral fimbria to terminate in CA3, CA4, fascia dentata and subiculum. Sensory stimuli (S^Ds) of neocortical origin converge in entorhinal cortex which also projects to the subiculum, CA3, CA4 and fascia dentata. Intrahippocampal processing is reflected back to the lateral septal nuclei, possibly through the dorsal fornix. The lateral septum, by virtue of interneuron connections with the medial septum, modulates the effects of ascending and descending activity of the medial forebrain bundle. Lesions restricted to the medial septal area change this complex system in such a way as to increase the effects that reinforcing stimuli have on operant behavior. It is hypothesized that fibers travelling ventrally and caudally from the ventral septal area and continuing caudally through the medial forebrain bundle affect brainstem motor systems in some unknown way. Figure 26 illustrates the foregoing scheme.

FACE PAGE FOR FIGURE 26

Hypothesized functional connections of the septum, hippocampus, entorhinal cortex and medial forebrain bundle and their modulatory action on caudal motor systems.

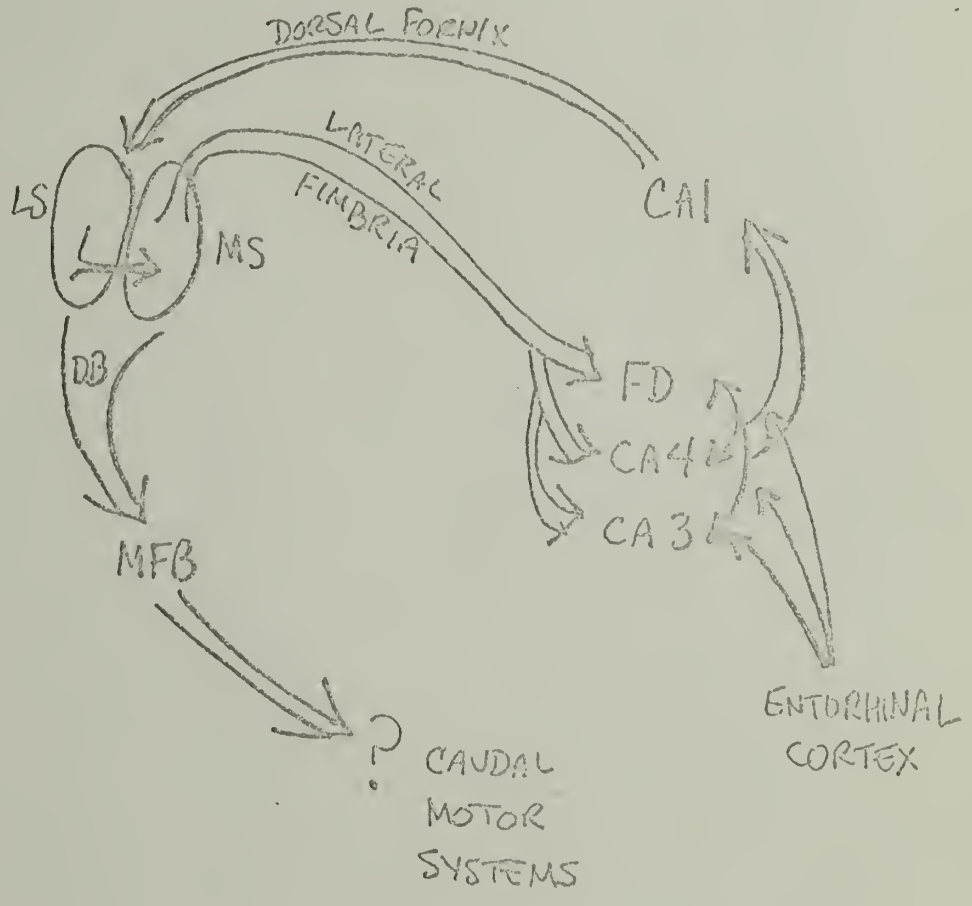

DORSAL FORNIX
LATERAL
FIMBRIA
LS
MS
CA1
DB
FD
CA4
CA3
MFB
ENTORHINAL
CORTEX
?
CAUDAL
MOTOR
SYSTEMS

FIGURE 26

Limbic System lesions and learning theory

Whatever the circuitry be, it is clear that medial septal lesions change the relations between discriminative stimuli, responses and reinforcing stimuli. In the discussion above, it has been assumed that the effects of reinforcers on responses are altered by septal lesions. Since changes in magnitude of reinforcement affect animals with septal lesions differentially than normal animals (Carlson et al, 1976) this assumption seems justified. Thus in the operant paradigm,

$$\text{if} \quad \overset{S^D}{\underset{DEP}{\text{or}}} \longrightarrow R \longrightarrow S^R \qquad \text{then} \qquad p \uparrow (S^D \longrightarrow R),$$

since the probability of response emission is greater following medial septal lesions, it is possible that the effects of reinforcing stimuli are somehow magnified in animals with damage to the medial septum or lateral fimbria.

Donahoe (1977) attempts to deal with the relations between reinforcing stimuli and responses by describing the effects of reinforcing stimuli in terms of the elicited behavior produced by them. Thus, a contingent eliciting stimulus such as food and designated as S_c elicits a contingent response such as eating and is designated by R_c. An operant contingency is instituted when the occurrence of S_c (food) and thus R_c (eating) is made contingent upon some noncontingent response such as a bar press (designated R_n) in

the presence of some noncontingent stimulus such as a cue light (designated S_n).

Donahoe summarizes the relational principle of reinforcement in the following way: the terminal or asymptotic probability of the noncontingent elicitation process ($p'R_n/S_n$) is a function of the baseline probability of the noncontingent process (pR_n/S_n) and the difference between pR_n/S_n and the baseline probability of the contingent elicitation process pR_c/S_c. The algebraic expression of these relations is:

$$\Delta pR_n/S_n = \Theta\ (pR_c/S_c - pR_n/S_n).$$

The change in the probability of an operant response in the presence of discriminative stimuli is a function of the difference between baseline probabilities of contingent elicitation processes (pR_c/S_c) and noncontingent elicitation processes (pR_n/S_n) weighted by some measure, Θ, of the sensitivity of the organism to that difference.

In the case of an organism with medial septal damage, terminal response probabilities ($\Delta pR_n/S_n$) are much higher than in normal animals. According to Donahoe's analysis, asymptotic response rates can be changed in one of three ways. First, a lower baseline operant level would serve to increase terminal rates. Second, increases in the probability of contingent elicitation processes (such as eating in the presence of food) would increase response probability. Third, increments in the value of Θ would increase response probability.

Considering the first possibility, the baseline probability of bar presses or head poke responses is quite low in the operant chamber environment in the absence of contingencies. Observations in our laboratory indicate that if there is any effect of septal lesions on operant level it is a slight enhancing effect. Inspection of the equation, $pR_n/S_n = \Theta\ (pR_c/S_c - pR_n/S_n)$, reveals that increases in baseline probabilities would serve only to decrease asymptotic response probabilities. Thus, given this view, it is possible to rule out changes in operant levels of the head poke response or lever press as responsible for the increases in response probabilities as a consequence of limbic lesions.

Continuing with this logic, it follows that the increased terminal response probabilities produced by limbic lesions change the values of either Θ, the sensitivity of the organism to the difference between contingent and noncontingent elicitation processes, or the probability of the contingent elicitation process (pR_c/S_c), or both.

Since Θ is the slope of the function describing the relation between the difference between contingent and noncontingent elicitation processes ($pR_c/S_c - pR_n/S_n$) and the response rate (pR_n/S_n) it cannot, a priori be measured. However, the probability of contingent elicitation processes can be measured. According to Premack (1965) a measure of pR_c/S_c can be determined by measuring the proportion of time that an organism engages in the process when given noncontingent access. The appropriate experiments have yet to examine

the effects of medial septal and lateral fimbrial lesions on the "preference" for contingent elicitation processes. However, the fact that rats and mice do not gain weight nor consume more than normal amounts of food (Ross, Grossman and Grossman, 1975) argues that eating, given food (pR_C/S_C), is not increased in probability. In fact, lesioned rats have been reported to lose weight and consume fewer calories than intact animals. If the probability of contingent elicitation processes were increased by medial septal lesions then we would expect animals with such lesions to eat more, given noncontingent access. There is no evidence that they do.

In light of Donahoe's interpretation of the relational principle of reinforcement and the effects of septal and lateral fimbrial lesions on operant response rates we would be forced to conclude that O, the sensitivity of the organisms to the differences in probabilities between contingent and noncontingent elicitation processes, is altered by limbic lesions. In such a view, the sensitivity of the organism to the weighted differences between contingent and noncontingent elicitation processes, Θ, is incremented in value by interruption of the fiber connections between the medial septal/diagonal band complex and the ventral hippocampus.

PART II

An Anatomical Study of the "Septal Rage" Syndrome

For many years it has been known that damage to the limbic forebrain region, the septum, results in dramatic changes in unconditioned behavior. Many species, mice (Standish, 1975), rats (Brady and Nauta, 1955) and cats (Moore, 1964), become hyper-reactive to a variety of unconditioned stimuli (visual, auditory, tactual and olfactory) following large lesions of the septal area and respond in an explosive fashion to even weak stimuli. Besides its involvement in conditioning (see Part I) the septal area seems to be part of a larger system which mediates a mammal's adaptive unconditioned response to its environment. The fact that large septal lesions result in a multitude of behavior changes argues that a unitary structural and functional conceptualization of the septum is an oversimplification.

When presented with a tactual stimulus, such as a puff of air, mice with septal lesions will vocalize, vigorously attempt to escape and jump about wildly. Mice with appropriately placed lesions have been observed to jump vertically 12 inches or more when struck by a stream of air. Rodents with such lesions have been variously described as aggressive, hyper-emotional, irritable, vicious or ragic; hence the term "septal rage".

While there have been several attempts to determine the anatomical and neurochemical bases of "septal rage" (see Fried, 1973

for a review), the neuroanatomical circuitry involved is yet unknown. Since 1955 when Brady and Nauta first reported the changes in affective behavior following septal lesions, the septal rage syndrome has become part of the lore of physiological psychology. Every elementary text includes a description and discussion of the syndrome, usually in the chapter labelled "emotion and motivation". The septal rage syndrome has been used in the analysis of anti-anxiety drugs such as librium and valium (Christmas and Maxell, 1970; Horowitz, Furgiuele, Brannick and Craver, 1963) as a method for studying the neurochemistry of emotion (Bernard, Berchek and Yutzey, 1975; Dominquez and Longo, 1970; Gage and Olton, 1976; Sofia, 1969), and even as an animal model of schizophrenia (Heath, 1976). While it is unclear whether the septal syndrome has any clinical or theoretical importance the existence of this lesion-induced syndrome has played a large role in the history of physiological psychology.

The cumulated results of experiments attempting to localize the critical area of the septum involved in the changes in affective behavior following lesions are contradictory and confusing. The usual method of these experiments has been to produce septal lesions in a number of rats, observe the animals for several days then determine the location of the smallest effective lesion. Thomas and Van Atta (1972) ascribe the hyper-reactivity following septal lesions to the percent damage of subseptal structures. Clody and Carlton (1969) reported that the medial septal nucleus is not part

of the "rage" circuitry, but that damage to the lateral septal nuclei is necessary for elicitation of hyper-reactivity. Turner (1970), on the other hand, holds damage to the bed nucleus of stria terminalis and the stria themselves responsible for the rage syndrome. Schnurr's attempts (1972) to discover the septal area responsible for affective changes led her to the conclusion that lesions restricted to the anterior dorsal area of the septum resulted in the typical hyper-reactivity. Harrison and Lyon (1957) asserted that there was no correlation between damaged structures and the emotional alterations observed. More recently, Standish (1975) reported that the effective lesion site may not even be in the septum itself, but just anterior in the region of the hippocampal rudiment. While there seems to be little agreement about the relevant structures involved in the lesion-induced hyper-reactivity, it appears that the posterior septal area is not involved.

Most of the attempts to discover the septal area involved in the elicited hyper-reactivity have focused on the septal nuclei themselves and employing a single lesion technique have largely ignored the larger system involved in the hyper-irritability of which the septum may only play a small part. A more promising approach in understanding the neural basis of this behavior change has been used by a few investigators. This approach studies the interrelations of the septum with the rest of the brain through the use of a multiple lesion technique. The logic of this method is

that if destruction of a structure outside the septal area changes the hyper-reactivity induced by septal damage, then that structure may be part of an efferent circuit mediating the rage syndrome.

Both septo-amygdalar and septo-hippocampal connections have been implicated in septal lesion-induced hyper-reactivity. Amygdala destruction has been reported to attenuate septal rage in rats (King and Meyer, 1958). The general conclusion of the literature on septal-amygdalar interactions is that the amygdala may be a structure directly involved in septal rage and that tissue damage in the septum leads to abnormal amygdalar activity which is directly or indirectly responsible for the expression of the hyper-reactivity.

Olton and Gage (1974) and Gage and Olton (1975) have concluded that it is septo-hippocampal interactions that are responsible for septal rage in rats. In 1974 they reported that fornix lesions 10 days prior to septal destruction eliminated the expected hyper-reactivity following the septal lesion. In a second experiment they reported that simultaneous septal and fornix/fimbria lesions also prevent the appearance of hyper-reactivity. These same authors in an experiment reported in 1975, placed selective lesions in the medial fornix, lateral fornix, precommissural fornix, anterior hippocampus, posterior hippocampus and entorhinal cortex. Only precommissural and postcommissural fornix lesions were effective in blocking the hyper-reactivity expected from subsequent septal lesions. These results indicated to the authors that terminations of the

fornix in the anterior hippocampus are directly involved in the appearance of septal rage. They concluded that the following septo-hippocampal-hypothalamic circuits mediate the dramatic change in affective behavior following septal lesions: 1) from the septum to the anterior hippocampus via the precommissural fornix and 2) from the anterior hippocampus to the hypothalamus via the post-commissural fornix.

These experiments are difficult to reconcile with other findings in the literature. Posterior septal lesions as well as fornix lesions have been generally reported to be ineffective in eliciting septal rage yet Olton and Gage have suggested that it is the posterior septal connections through the fornix that are responsible for the septal rage syndrome. Furthermore, medial septal lesions have proven to be ineffective in producing septal rage. It is the medial septal nucleus that sends fibers through the fornix to the anterior hippocampus (Raisman, 1966). The lateral septal nuclei have no hippocampal efferents. These data would indicate, contra to Olton and Gage's analysis, that the medial septal nucleus and its hippocampal connections are <u>not</u> involved in septal hyper-reactivity.

The study of the neural substrates of septal hyper-reactivity is complicated by the fact that, in rats, the irritability dissipates with time and handling. Mice, on the other hand, display the hyper-reactivity indefinitely and behavioral tests show no dimuition of the hyper-reactivity over weeks and months (Slotnick, McMullen and

Fleischer, 1973). The permanence of the effects of septal lesions on unconditioned behavior in the mouse has made it an ideal subject for multiple lesion research on the neural circuitry mediating septal hyper-reactivity.

Multiple lesion experiments in the mouse (Standish, 1975) cast further doubt on the conclusions drawn by Olton and Gage (1974) and Gage and Olton (1975). Irritability-inducing septal lesions in the mouse were followed in 3 days by a second lesion of major efferent structures of the septal nuclei; fimbria/fornix, amygdala, stria termninalis, diagonal band of Broca and olfactory bulbs. These experiments demonstrated that only bilateral amygdala lesions and olfactory bulb aspirations were effective in reducing septal rage in mice. Contrary to Olton and Gage, fimbria lesions had no effect on the changes in response to an unconditioned stimulus produced by septal lesions. Standish interpreted these results to suggest that septal lesions release the olfactory bulbs from tonic inhibition, thereby allowing the bulbs and other afferent cell groups to have a more powerful excitatory effect on the amygdala through the lateral olfactory tract. In this way, the amygdala's role in septal lesion-induced hyper-reactivity might involve septo-olfactory-amygdaloid connections rather than direct fiber terminations between septum and amygdala. Further support for these conclusions derives from the inability of lesions to tracts connecting the septum and amygdala, the stria terminalis and diagonal band, to reduce hyper-reactivity

in mice to an air puff stimulus.

The purpose of the present experiments was to determine, through silver degeneration analyses, which septal nuclei efferent projections are involved in the hyper-reactivity following restricted damage to parts of the septal area implicated in the septal rage syndrome. In pursuing this goal two further questions were able to be answered. 1) Is there an anatomical dissociation of the neural circuitry involved in septal rage and that is responsible for increments in operant response rate on a VI schedule and 2) Is denervation super-sensitivity responsible for the hyper-reactivity to tactual stimuli produced by damage to the septum?

Experiment 1

Anatomical Interdependence of Septal Lesion-induced Changes in Operant Behavior and Changes in Unconditioned Sensitivity to Tactual Stimuli

By concomitant observation of the effects of large septal lesions on conditioned operant behavior and unconditioned responsivity to tactual stimuli, the dependence of each behavior change on the other was determined. Comparison of axonal and termal degeneration patterns in brains of subjects showing changes in operant response rates and/or hyper-reactivity to an air puff stimulus permitted the determination of the anatomical dependence between the two measures of behavior change.

METHOD

Subjects

Eighteen adult male mice from Experiment 1, Part I, trained on a VI-40 sec. schedule and subjected to septal lesions served as subjects.

Apparatus

Operant chambers used in Experiment 1, Part I have previously been described. Response to unconditioned stimuli was determined using a 40 cc. ear syringe as the source of a stream of air. The testing apparatus consisted of a plastic cage (41 x 24 x 15 cm) which was covered by metal mesh screening (7 x 7 mm. mesh).

Procedure

Immediately prior to each animal's VI 40-sec. session mice were tested in a covered plastic cage for their response to a 40 cc. air puff stimulus directed at their dorsal surface. The air puff was applied by placing the nozzle of the syringe containing air against the screen cover and manually squeezing the bulb of the syringe. An animal received 1 point for displaying each of the following behaviors:

1) Vocalizing while being picked up by the tail
2) Escape running when the air stream struck the animal's back
3) Jumping with all four feet off the floor of the cage in response to the air stream

4) Repeated jumping and hitting the wire mesh ceiling of the testing apparatus.

Scores ranged from 0 to 4. Prototypical septal rage behavior received scores ranging from 3 to 4. Intact animals typically received a score of 0 or 1.

Following this reactivity test, animals were placed in operant chambers each day where food pellets were delivered on a VI-40 sec. schedule contingent upon a head poke response. When high stable responding maintained for seven consecutive days, each subject received a septal lesion under light ether anesthesia. During the following 7 days, operant responding and reactivity scores were obtained as usual. In this way, two classes of behavior, conditioned and unconditioned, were measured both before and after lesioning. Following the 14 VI session animals were perfused pericardially, the brains removed and axonal and terminal degeneration patterns subsequently analyzed using a modified Fink-Heimer silver stain.

RESULTS AND DISCUSSION

Only 2 mice of the 18 in Experiment 1 became hyper-reactive to sensory stimuli as a consequence of septal lesioning. Behavioral data, lesion location and efferent degeneration patterns from these animals, M54 and M89, are presented in figures 8 and 10 in Experiment 1. Mean baseline reactivity score for M54 was 1.0 and mean post lesion reactivity score was 3.5. The mean baseline reactivity

score for M89 was 1.0 and increased to 4.0 during the 7 post lesion days. The other 16 subjects' response to the air puff stimulus did not change in any detectable way. Hyper-reactivity to the air puff stimulus was readily apparent 24 hours after surgery in both M54 and M89 and remained undiminished until time of perfusion.

Lesions in these animals that resulted in septal "rage" also resulted in high rates of post lesion operant responding. Lesions in both cases were quite large and included a great deal of tissue anterior to the septum as well as the septum proper.

Fink-Heimer analyses revealed only one apparent difference in degeneration patterns between animals who became hyper-reactive and those who did not. The brains of both M54 and M89 contained moderate axonal and heavy terminal degeneration in the dorsomedial nuclei of the thalamus. No other subjects in Experiment 1 or 2 contained such distinctive degeneration. Silver degeneration analyses of the brain of M89 also revealed a distinct difference between that subject and others. The basolateral amygdala of one hemisphere contained light axonal degeneration and moderate terminal degeneration. The fact that the amygdaloid region of M54 contained no silver impregnation suggested that this unilateral degeneration in the basolateral amygdala in M89 was not a sufficient condition for the expression of septal lesion-induced hyper-reactivity. The presence of such degeneration in the amygdala does suggest, however, that areas anterior to the septum proper have connections with the amygdala

through the ventroamygdalofugal pathway. No degenerating fibers were observed in the stria terminalis.

The anatomical and behavioral independence of the effects of septal lesions on operant behavior and the effects on emotional reactivity to sensory stimuli is clear. All subjects in Experiment 1 receiving large septal lesions displayed obvious changes in conditioned behavior; response rates controlled by a variable interval schedule of food reinforcement increased unambiguouly. However, only two of the animals received lesions that resulted in changes in both operant behavior and unconditioned response to tactual stimulation. In these two animals heavy degeneration was found in the fascia dentata, CA3 and CA4 of the hippocampal formation and the dorsomedial nucleus of the thalamus. In no animals showing only changes in operant response rate was degeneration found in the dorsomedial nucleus. Thus, the anatomical changes responsible for increases in operant response rate (medial septal/diagonal band complex ——→ CA3, CA4, and fascia dentata) and those responsible for changes in unconditioned response to tactual stimuli (anterior septal area ——→ dorsomedial nucleus) appear to be quite distinct and independent.

Experiment 2

Time Course of Onset of Septal "Rage": Relevance to denervation supersensitivity

Increases in postsynaptic sensitivity to exogenous or endogenous

neurotransmitters following deafferentation is generally believed to occur in no less than 24 hours (Bird and Aghajanian, 1975). It is conceivable that the changes in behavioral response to unconditioned stimuli as a result of septal lesions follows the time course of the development of denervation supersensitivity on some involved efferent structure; possibly the dorsomedial nucleus (see Experiment 1, Part II). Were postsynaptic changes in sensitivity to presynaptic stimuli responsible for septal "rage" then hyper-reactivity to teactual stimuli would be expected to develop gradually over the 24 hours following surgery. If septal hyper-reactivity is dependent upon simple release of inhibition or excitation on some efferent structure following deafferentation by tissue damage within the septal area then hyper-reactivity would be expected to be manifest immediately after surgery.

METHOD

Subjects

Eight male B6D2F$_1$/J hybrid mice approximately 20 weeks of age served as subjects. Animals were housed in individual cages and maintained ad libitum on a 12 hour light-dark cycle. All experimentation occurred during the light cycle.

Apparatus

Response to unconditioned stimuli was determined using a 40 cc. ear syringe as a source of an air stream. The testing apparatus was

identical to that used in Experiment 1, Part I. Animals were tested and scored for their reaction to a stream of air directed at their dorsal surface in a plastic cage (41 x 24 x 15 cm.) that was covered by a metal mesh screen (7 x 7 mm. mesh).

Procedure

Each mouse was tested pre-operatively for its response to a stream of air directed at its back, and assigned a baseline reactivity score using the scoring procedure used in Experiment 1. Only animals receiving a baseline reactivity score of less than 2.0 were used as experimental subjects.

Variously placed lesions were produced in the septal area under brief and light ether anesthesia. Following surgery, animals were typically conscious and mobile within three minutes after removal from the stereotaxic apparatus. Ten minutes after tissue destruction the animal's response to the air puff stimulus was observed and rated. Each subject's response was tested every ten minutes for the following hour and every 24 hours for the next 4 days. One week following surgery animals were perfused and the brains removed. Axonal and terminal degeneration was subsequently analyzed using the Fink-Heimer procedure.

RESULTS AND DISCUSSION

The change in each animal's response to the air puff stimulus as a function of time is shown in figures 27-34. Prelesion reactivity

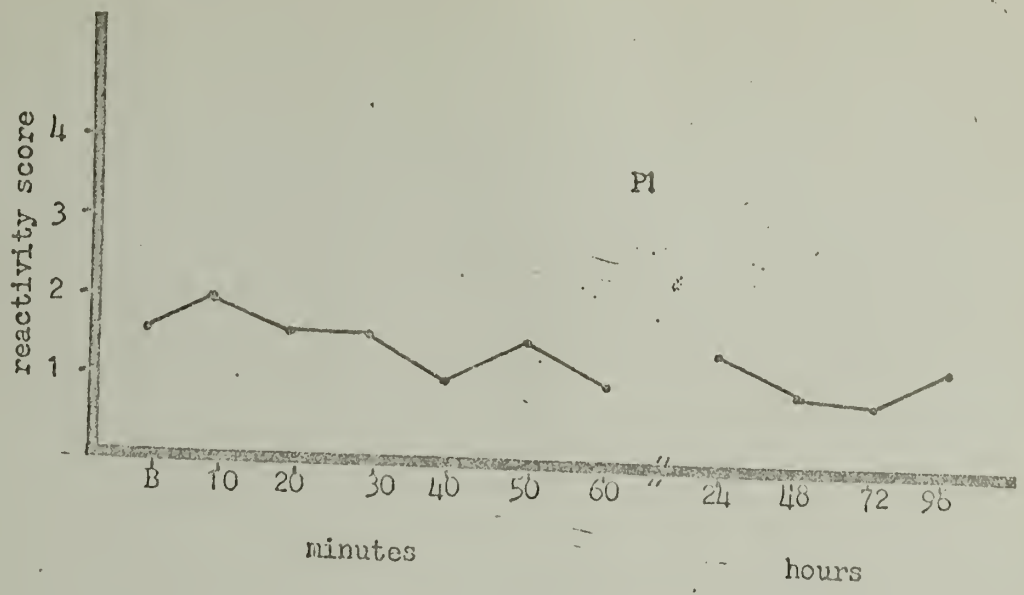
scores are indicated by "B". Only 2 animals (P6 and P10) of the 8 became hyper-reactive (post lesion scores of greater than 3.0) following surgery. In these two animals, hyper-reactive behavior was observed as quickly as 10 minutes following tissue destruction. Since the change in behavior occurred essentially immediately after surgery, denervation supersensitivity as a causal agent in this behavior change was ruled out. The two animals that became hyper-reactive (see figures 31 and 32) as a consequence of surgery became so within 20 minutes following thermocoagulations of the septal area, and remained so until perfusion a week later.

Fink-Heimer degeneration studies of only 2 of the 8 subjects revealed the presence of heavy bilateral degeneration within the dorsomedial nuclei of the thalamus. No trace of such degeneration in the dorsomedial thalamus was found in the other 6 animals who did not become hyper-reactive.

Other than the presence of degenerating axons and terminals within the dorsomedial nucleus, degeneration patterns in P6 and P10 were comparable to other animals with the exception of unilateral degeneration within the corticomedial amygdala in P6. Lesions associated with hyper-reactivity and degeneration in the dorsomedial nuclei were large and invaded tissue anterior to the septum proper. Results of this experiment suggested that the development of postsynaptic denervation supersensitivity as a result of deafferentation of septal efferents is not responsible for lesion induced hyper-reactivity.

FACE PAGE FOR FIGURES 27-34

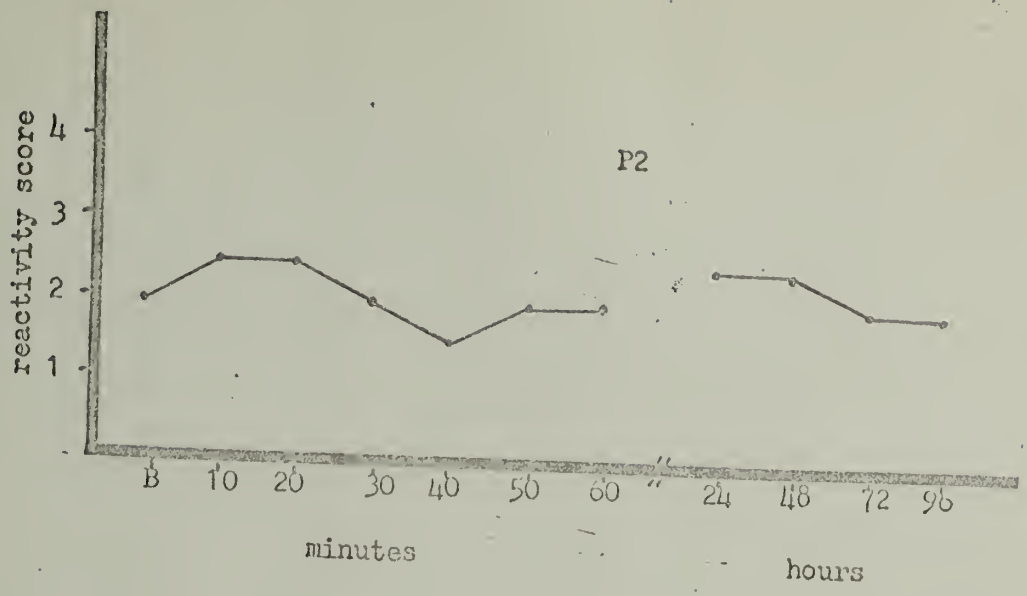
For each subject in Experiment 2 changes in reactivity to an air puff stimulus as a function of brain lesions aimed at the septum are shown for the 60 minutes immediately following surgery and the subsequent 96 hours. (B = prelesion baseline reactivity score.)



Degeneration Pattern

DT in n. accumbens septi
DF in vertical and horizontal diagonal band
DF in medial forebrain bundle
DT in lateral caudate n.
DF in precommissural fornix
DF in postcommissural fonix
DF in dorsal fornix
DF in medial fimbria
DF in lateral fimbria
DF in stria medullaris
DF and DT in medial and lateral habenular n.
DF and FT in mammillary bodies
DF and DT in anteroventral and anteromedial n. of thamamus
DF and DT in reuniens n. of thalamus
DF in anterior dorsal hippocampus (minimal)
DF in CA2 of dorsal hippocampus
DF in alveus
DF in CA3 and CA4 of ventral hippocampus
DF in fascia dentata (dorsal and ventral)
DF in fornix commissure
DF in subiculum

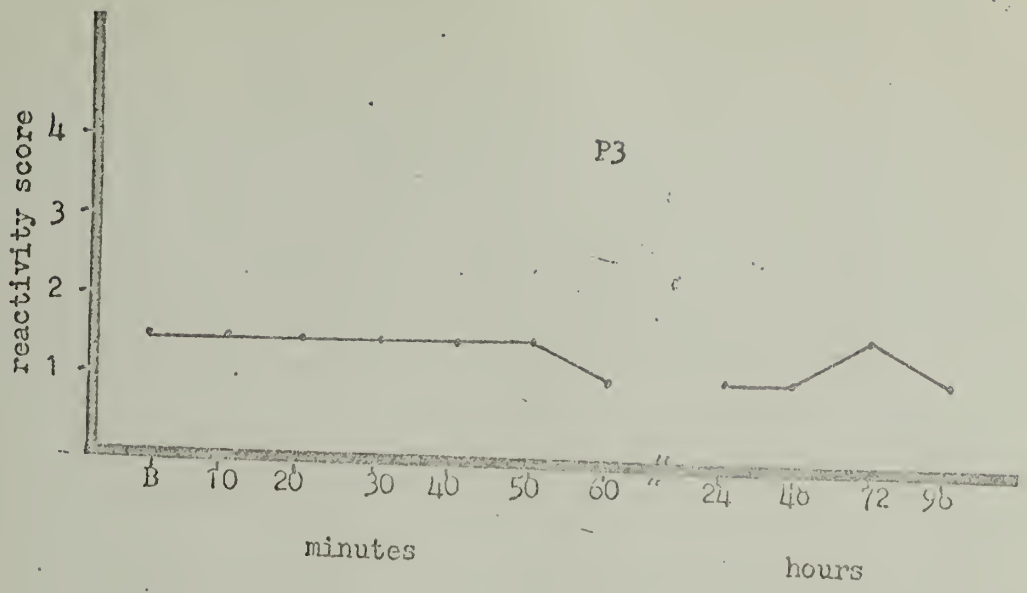
Figure 27



Degeneration Pattern

DT in n. accumbens septi
DF in vertical and horizontal diagonal band
DF in Medial forebrain bundle
DT in lateral caudate n.
DT in precommissural fornix
DF in postcommissural fornix
DF in dorsal fornix
DF in medial fimbria
DF in lateral fimbria
DF in stria medullaris
DF and DT in medial habenular n.
DF and DT in mammillary bodies
DF and DT in anteroventral and anteromedial n. of thalamus
DF and DT in anterodorsal n. of thalamus
DF and DT in reuniens n. of thalamus
DF and DT in ventromedial n. of hypothalamus
DF in anterior dorsal hippocampus
DF in alveus
DF in CA2 of dorsal hippocampus
DF in CA3 and CA4 of ventral hippocampus
DF in fornix commissure
DF in subiculum

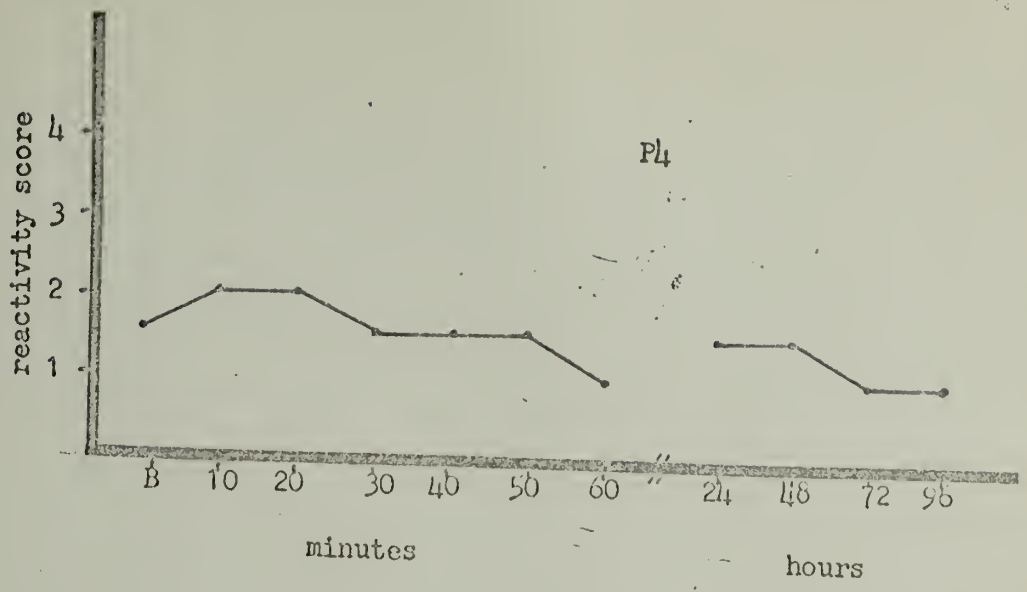
Figure 28



Degeneration Pattern

DF in anterior septum
DF in olfactory tubercle
DF in vertical and horizontal limb of diagonal band
DF in medial forebrain bundle (light)
DF in precommissural fornix
DF in postcommissural fornix
DF in dorsal fornix
DF in medial fimbria
DF in lateral fimbria
DF in stria medullaris (light)
DF in internal capsule
DF in anteroventral and anteromedial n. of thalamus
DF in reuniens n. of thalamus (light)

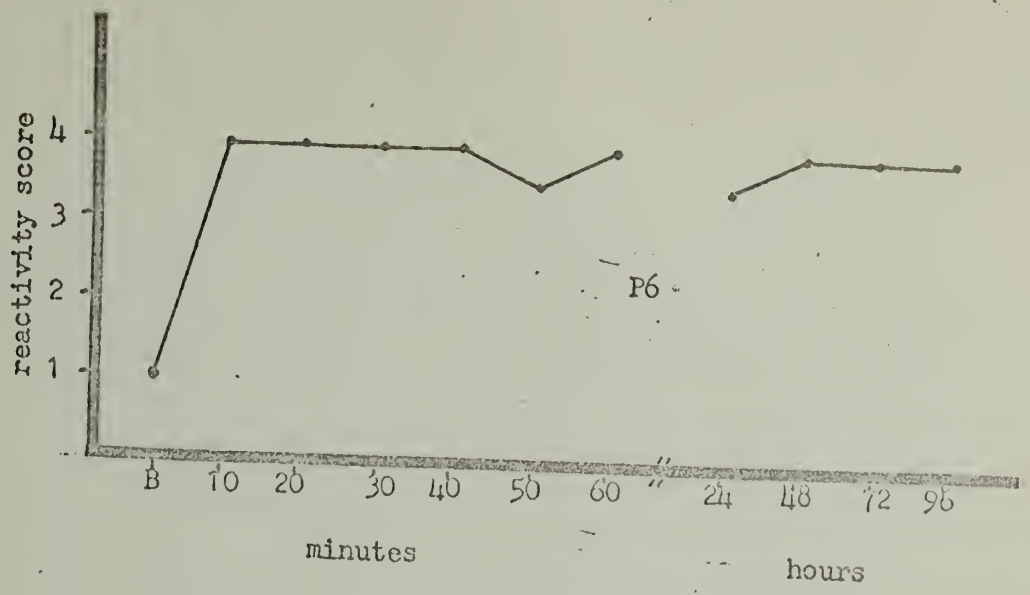
Figure 29



Degeneration Pattern

DF in vertical and horizontal diagonal band
DF in medial forebrain bundle
DT in lateral caudate n.
DF in precommissural fornix
DF in postcommissural fornix
DF in dorsal fornix
DF in lateral fimbria
DF in stria medullaris
DF in mammillary bodies
DF and DT in anteroventral and anteromedial n. of thalamus
DF and DT in reuniens n. of thalamus
DT in rhomboid n. of thalamus
DF in alveus
DF in CA2 of dorsal hippocampus
DF in CA3 and CA4 of ventral hippocampus
DF in dorsal fascia dentata
DF in ventral fascia dentata (light)
DF in fornix commissure
DF in subiculum

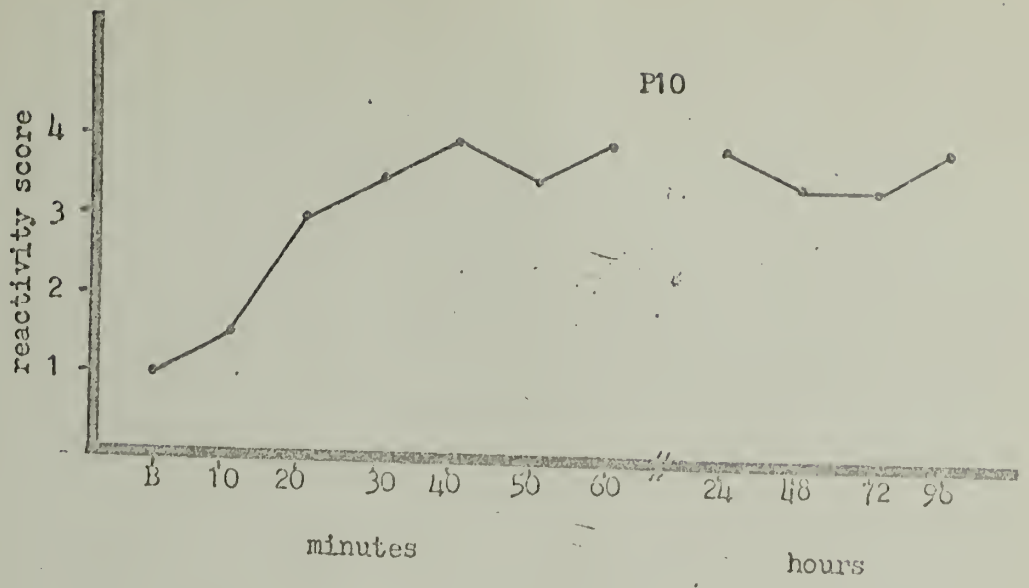
Figure 30



Degeneration Pattern

DT in n. accumbens septi
DF in vertical and horizontal diagonal band
DF in medial forebrain bundle
DF in anterior commissure
DF in olfactory tubercle
DT in lateral caudate n.
DF in precommissural fornix
DF in postcommissural fornix
DF in dorsal fornix
DF in lateral fimbria
DF in stria medullaris
DF and DT in medial and lateral habenular n.
DF in internal capsule
DF in dorsomedial n. of thalamus
DT in dorsomedial n. of thamalus
DF and DT in reuniens n. of thalamus
DF and DT in corticomedial n. of amygdala (light)
DF in anterior dorsal hippocampus
DF in alveus
DF in CA2 of dorsal hippocampus
DF in CA3 and CA4 of ventral hippocampus
DF in dorsal fascia dentata
DF in ventral fascia dentata (light)
DF in fornix commissure
DF in subiculum

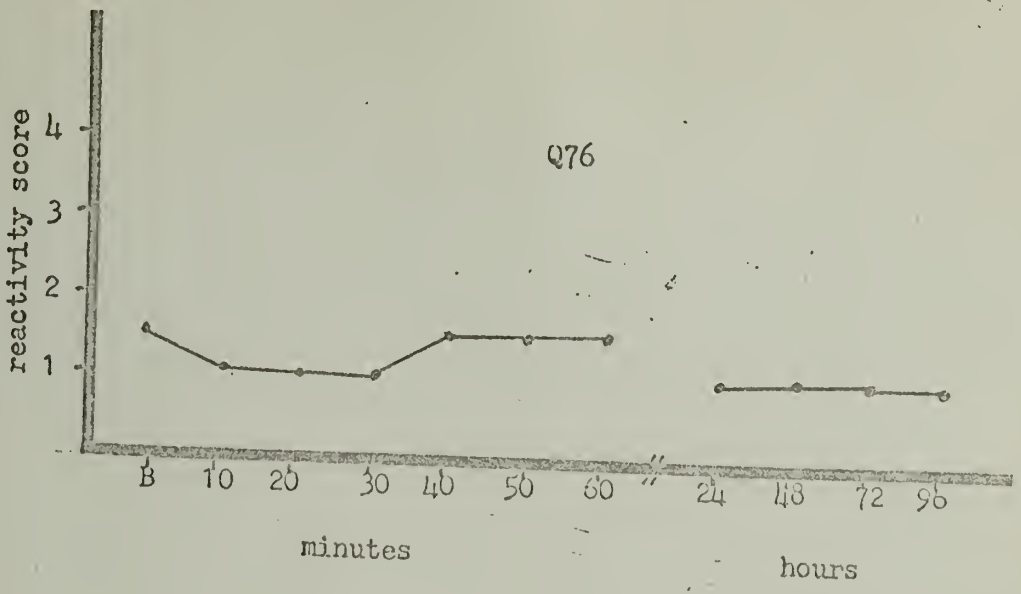
Figure 31



Degeneration Pattern

DF in lateral septal n.
DF in vertical and horizontal diagonal band
DF in medial forebrain bundle
DF in anterior commissure
DF in lateral caudate n.
DF in precommissural fornix
DF in postcommissural fornix
DF in dorsal fornix
DF in lateral fimbria
DF in stria medullaris
DF and DT in mammillary bodies
DF in internal capsule
DF and DT in anteroventral and anteromedial n. of thalamus
DF and DT in dorsomedial n. of thalamus
DF in anterior dorsal hippocampus
DF in alveus
DF in CA2 of dorsal hippocampus
DF in CA3 and CA4 of ventral hippocampus
DF in fascia dentata (dorsal and ventral)
DF in fornix commissure
DF in subiculum

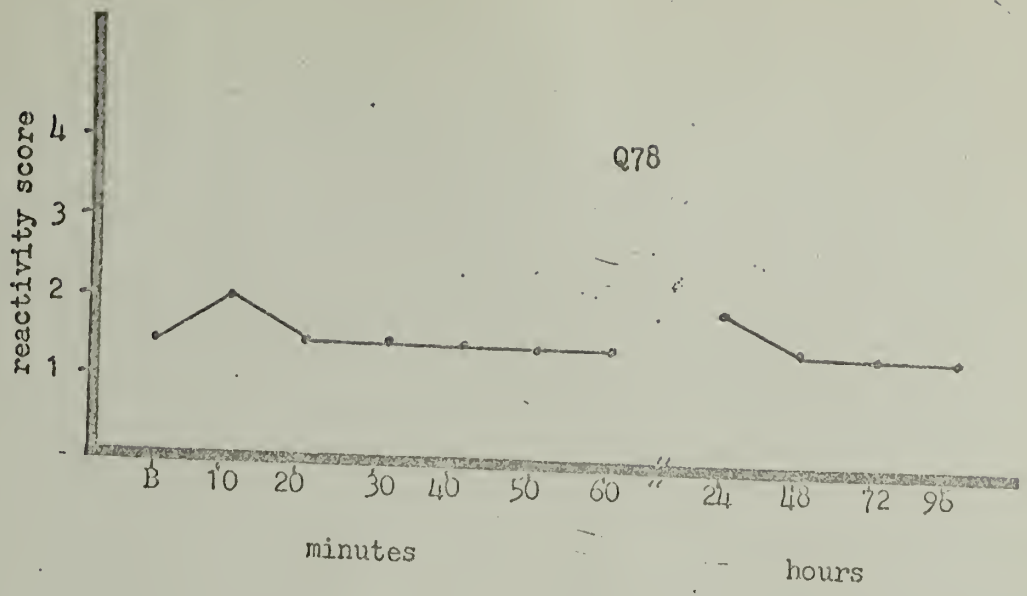
Figure 32



Degeneration Pattern

DF in vertical and horizontal diagonal band
DF in medial forebrain bundle
DF in anterior commissure
DF in precommissural fornix
DF in postcommissural fornix
DF in dorsal fornix
DF in lateral fimbria
DF in stria medullaris
DF and DT in medial and lateral habenular n.
DF and DT in mammillary bodies
DF and DT in anteroventral and anteromedial n. of thalamus
DF in anterior dorsal hippocampus (minimal)
DF in alveus
DF in CA2 of dorsal hippocampus
DF in CA3 and CA4 of ventral hippocampus
DF in fascia dentata (dorsal and ventral)
DF in fornix commissure
DF in subiculum

Figure 33



Degeneration Pattern

DF in anterior septum
DF in vertical and horizontal diagonal band
DF in medial forebrain bundle
DF in precommissural fornix
DF in postcommissural fornix
DF in dorsal fornix
DF in lateral fimbria
DF in stria medullaris
DF and DT in medial and lateral habenular n.
DF and DT in mammillary bodies
DF and DT in anteroventral and anteromedial n. of thalamus
DF in CA2 of dorsal hippocampus
DF in alveus
DF in CA3 and CA4 of ventral hippocampus
DF in fascia dentata (dorsal and ventral)
DF in commissure of fornix
DF in subiculum

Figure 34

GENERAL DISCUSSION

The results of experiments in Part II suggested that tissue damage just anterior to the septum proper results in hyper-reactivity to tactual stimuli characteristic of the so-called septal rage syndrome and heavy terminal degeneration within the dorsomedial nucleus of the thalamus. The effects of these lesions on unconditioned behavior and presumably on the dorsomedial nucleus is immediate and does not depend upon the development of postsynaptic membrane supersensitivity.

The dorsomedial nucleus is a midline thalamic nucleus that is not considered a strictly sensory or motor relay nucleus. The medial magnocellular division of the dorsomedial nucleus receives fibers from the amygdaloid complex and projects fibers, via the inferior thalamic peduncle, to the lateral preoptic and hypothalamic region, the rostral pole of the amygdaloid complex and basal olfactory structures. The lateral parvocellular portion of this nucleus is connected by a massive projection with nearly the entire frontal cortex. In primates, after extensive prefrontal cortical lesions or a prefrontal lobotomy, nearly all small cells within the dorsomedial nucleus degenerate (Carpenter, 1972).

According to Knook (1965) the dorsomedial nucleus receives afferent connections from a wide variety of structures lying within several levels of the neuraxis. Afferent connections include those from frontal cortex, the basal ganglia, the nucleus accumbens septi, the olfactory tubercle, pyriform cortex, amygdala, septum and nucleus

of the diagonal band, medial forebrain bundle, habenular nuclei, interpeduncular nuclei and several of the other thalamic nuclei.

In the brains of mice who became hyper-reactive following septal surgery, the pathway followed by septal area efferents to the dorsomedial nuclei was not clear. Degeneration was apparent in the inferior thalamic peduncle and an anatomical study by Krettek and Price (1977) reported that afferents to the dorsomedial nuclei travel in that fiber bundle.

Because of the report that amygdala lesions eliminate the hyper-reactivity produced by septal lesions (King and Meyer, 1958; Standish, 1975) it is possible that this finding and the evidence linking septal rage and the dorsomedial nuclei might be related. A reasonable interpretation of these data might be that afferent degeneration of the dorsomedial nuclei as a consequence of septal lesions results in abnormal neuronal activity within the basolateral amygdala. The change in functioning of the amygdala might be more or less directly involved in the changes in behavioral response to tactual stimuli. The evolution of the amygdala from the motor-related basal ganglia makes such a view tenable. Since basolateral amygdala lesions were more effective in reducing septal rage than corticomedial amygdala lesions (Standish, 1975), it is hypothesized that it is the basolateral amygdala that is more directly involved in septal rage.

Since the septum has no direct connections with the amygdala it is quite possible, in view of the results of the present experiments,

that abnormal activity within the basolateral amygdala following septal lesions is mediated through septal deafferentation of the dorsomedial nuclei. The dorsomedial nuclei and the basolateral amygdala are reciprocally interconnected via fibers that travel in the inferior thalamic peduncle. The ventroamygdalofugal pathway passes medially and forward to the lateral preoptic and hypothalamus, septum and nucleus of the diagonal band and olfactory tubercle. A prominant component bypasses the preoptic area and enters the thalamic peduncle to terminate in the medial region of the dorsomedial nucleus.

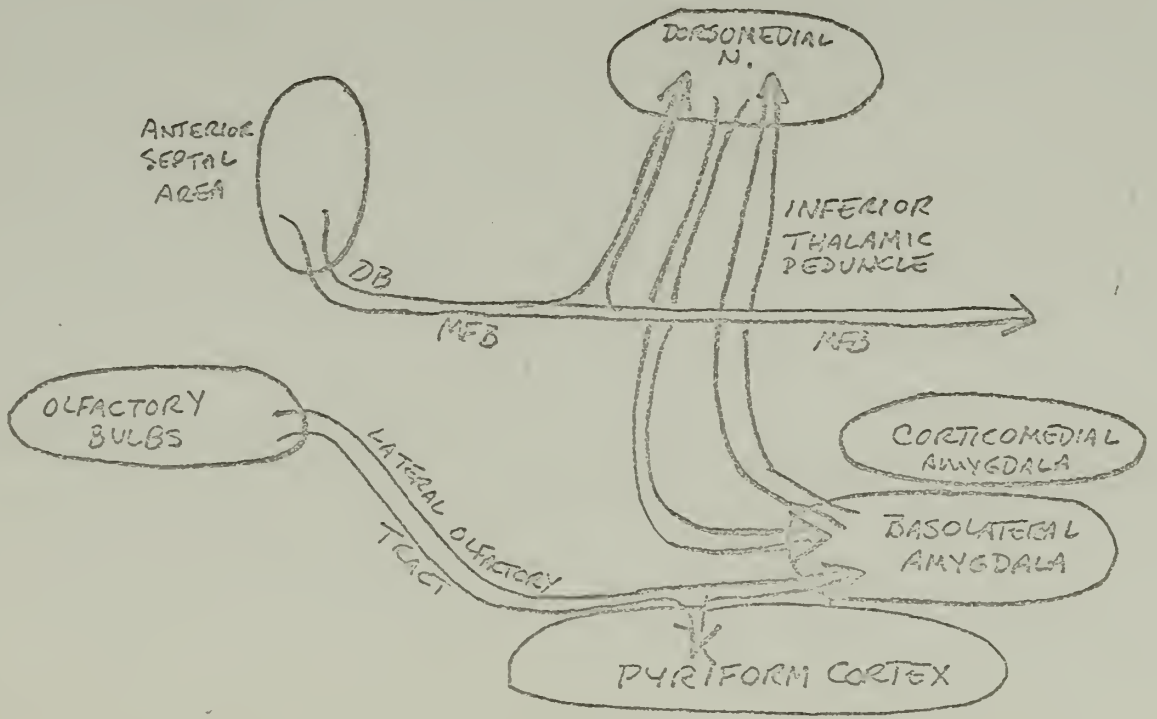
Of related interest is the finding that olfactory bulb aspirations, as well as amygdala damage, very effectively reduce the intensity of septal rage behavior. This is not surprising in light of the fact that the olfactory bulb has extensive connections with the basolateral amygdala through the lateral olfactory tract and pyriform cortex. In light of the evidence accumulating that relates the anterior septum, basolateral amygdala, dorsomedial nucleus and olfactory bulbs a plausible anatomical scheme of possible heuristic value is presented. See figure 35.

It is possible that large anterior septal lesions result in severe deafferentation of neurons within the dorsomedial nucleus that are efferent to the basolateral amygdala through the inferior thalamic peduncle. Deafferentation of the dorsomedial nuclei results in abnormal activity within the basolateral amygdala, and consequential effects upon some unknown efferent structure that is directly mediating the changes in behavior associated with the septal syndrome. These

FACE PAGE FOR FIGURE 35

Possible functional anatomical connections among the anterior septal area, dorsomedial nucleus of the thalamus, amygdaloid complex and olfactory bulbs involved in the septal rage syndrome.

FIGURE 35


DORSOMEDIAL N.
ANTERIOR SEPTAL AREA
DB
MFB
MFB
INFERIOR THALAMIC PEDUNCLE
OLFACTORY BULBS
LATERAL OLFACTORY TRACT
CORTICOMEDIAL AMYGDALA
BASOLATERAL AMYGDALA
PYRIFORM CORTEX

disrupting effects upon amygdala function and the effects upon amygdalar projection sites can be reduced by basolateral amygdala lesions or by olfactory bulb damage.

The septum is known to exert tonic inhibitory influence over olfactory bulb activity (Vom Saal, Hamilton, and Gandelman, 1975). Olfactory bulb neurons released from inhibition could, through the lateral olfactory tract, result in even more abnormal activity within the basolateral amygdala and its more response-relevant efferent structure. Olfactory bulb aspiration serves to reduce this disturbed afferent input into the amygdala. This scheme of the functional neuroanatomy involved in the septal rage syndrome is presented in figure 35.

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