



12-1972

The Effects of Frontal and Septal Ablation on Response Regulation in the Cat

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I am submitting herewith a dissertation written by Robert Numan entitled "The Effects of Frontal and Septal Ablation on Response Regulation in the Cat." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Psychology.

Joel F. Lubar, Major Professor

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Stephen J. Handel, William J. Davis, Jasper M. Brener

Accepted for the Council:

Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

September 6, 1972

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Joel F. Lutor

Major Professor

We have read this dissertation
and recommend its acceptance:

Stephen Gandel

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William James Davis

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Vice Chancellor for
Graduate Studies and Research

THE EFFECTS OF FRONTAL AND SEPTAL ABLATION
ON RESPONSE REGULATION IN THE CAT

A Dissertation
Presented to
the Graduate Council of
The University of Tennessee

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

by
Robert Numan
December 1972

DEDICATION

This dissertation is dedicated to those who have contributed and sacrificed the most:

C-2, C-7, C-37, C-55, C-68, C-77, C-82, S-6, S-20, S-69, S-70, S-71, S-74, S-75, S-95, P-10, P-22, P-40, P-41, P-56, P-79, P-80, P-81, O-50, and O-52.

ACKNOWLEDGEMENTS

I would like to thank the members of my dissertation committee, Drs. Joel F. Lubar, Jasper M. Brener, Stephen J. Handel and William J. Davis, for their assistance during the preparation of this dissertation. I am especially indebted to Dr. Joel F. Lubar, committee chairman, for sharing his thoughts, ideas, and knowledge with me throughout my graduate training.

Special thanks are extended to Sandy Inman for her friendship, and professional help throughout the preparation of this manuscript.

ABSTRACT

The literature dealing with the behavioral effects produced by ablation of the septum, frontal cortical areas and the hippocampus is reviewed. It is concluded that the medial septum, the dorsolateral frontal cortex (and its analogue in lower forms e.g., gyrus preceus in the cat and precollosal midline cortex in the rat) and the dorsal hippocampus form a nodal point within a larger neuronal system that is involved in response regulation.

A model, describing the response regulatory processes mediated by this fronto-cortical-limbic system is proposed. Motor programs are written in the frontal cortex and temporarily stored in hippocampal area CA₃. Feedback stimuli (both internal e.g., proprioceptive, and external e.g., reinforcement) consequent to response initiation are compared with the initial motor program in hippocampal area CA₁. If the feedback information matches with the expected outcomes dictated by the motor program, the response sequence is terminated. If comparator deviations arise, the frontal cortical areas are signalled of error via septo-hippocampal-entorhinal pathways and a new motor program is written. The role of proprioceptive feedback in response control is emphasized. Hippocampal theta activity is postulated to be a consequence of comparison.

An experiment was conducted in order to assess the effects of frontal (preceal) or septal damage on the ability of cats to acquire response control consistent with efficient performance on a DRL 40 second schedule of reinforcement. Available evidence (Laties, et al.,

1969; Kramer and Rilling, 1970) suggests that efficient DRL performance depends upon the organization and maintenance of collateral behaviors, which in turn facilitate timing behavior by pacing the temporal interval between responses. It is therefore proposed that frontal or septal ablation should impair DRL performance (when meaningful exteroceptive stimuli are lacking) by disrupting the neural mechanisms involved in the analysis of proprioceptive information derived from collateral responses. The experiment was conducted in three stages. During acquisition (30 days) no exteroceptive stimuli were available to signal the end of the required delay. Following acquisition fifteen days of DRL 40 with feedback (a red cue light indicates the termination of the required delay) was instituted. The feedback condition was followed by fifteen days of feedback withdrawal, during which the cue light was no longer used.

Damage to the anteromedial septum and diagonal band, or damage to gyrus preceus, which included its ventral sector, severely impaired the performance of cats during DRL acquisition. The deficit was ameliorated during the feedback period, but reasserted itself when the cue was no longer available. In addition, the shapes of the IRT histograms (indicative of patterns of responding) generated by the septal and preceal cats during the periods of acquisition and withdrawal were significantly correlated with each other, but not with the histograms generated by normal and operated controls. During the feedback period all histograms were related. Collateral behavior was evident in all animals during the period of acquisition and withdrawal, but was greatly reduced during the feedback period.

It is concluded that efficient DRL performance is dependent upon the utilization of response produced cues derived from collateral behavior, and that damage to the septum or the gyrus preceus impairs the utilization of such cues.

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CHAPTER I

CORTICO-LIMBIC MECHANISMS AND BEHAVIOR

A. INTRODUCTION

Throughout the past several decades great effort has been expended in order to attain a clearer understanding of brain-behavior relations. Physiologists, neurologists, and neuroanatomists have made progressive strides toward the elucidation of nervous system function; and the psychologist is now beginning to realize and understand some of the complexities of animal behavior. However, the processes involved in neuro-behavioral interactions are not nearly as well understood.

The purpose of this dissertation is, in part, to formulate my ideas on some of the mechanisms that may be involved in one class of neuro-behavioral interaction, specifically, those processes involved in response regulation. Major emphasis deals with the relationship between forebrain structures and response control. Telencephalic structures are among the most recently evolved brain areas, and a clear understanding of their structural and functional relations is likely to lead to a better comprehension of brain mechanisms in man.

The cerebral structures of prime interest in this review include the septum, hippocampus, and the frontal cortical areas. It is my belief that specific portions of these structures and their connections form a nodal point within a larger neuronal system involved in the programming and regulation of response patterns based on the assessment and integration of stimulus information from all sensory modalities.

This fronto-cortico-limbic system is conceived to accomplish the

following: (1) the programming of spatially and temporally integrated sequential movements, (2) the recalibration of motor programs based on afferent and reafferent feedback information, thus giving rise to movement control, and (3) differential stimulation of motor and sensory mechanisms (e.g., modified postural orientation and differential attentivity) for the efficient reception of anticipated meaningful stimulus input.

In the following section, the importance of sensory feedback for the programming and regulation of response patterns is discussed, with emphasis on the interaction of peripheral and central mechanisms. In the two succeeding sections, the anatomy of two neural regions, namely the septum and frontal lobes, is outlined. An understanding of these neural relations strongly suggests that these structures are part of the central mechanisms involved in response control and sensory motor integration. The conclusions formulated in these two neuroanatomical sections are supplemented by a review of the behavioral effects produced by destruction of these neural regions. I conclude with a discussion of the hippocampus, which appears to be an important structural and functional link between frontal and limbic mechanisms.

B. FEEDBACK AND RESPONSE CONTROL

Feedback may be defined as the stimulus consequences of behavior. Within the framework of this definition, one can distinguish at least two types of feedback information: (1) Feedback derived from the external environment, and (2) Feedback derived from the organism's own responses.

Early models of behavioral control through feedback mechanisms were developed by James (1890), and von Holst (1954). More recent endeavors (Adams, 1968; Anokhin, 1969; Greenwald, 1970; Kimble and Perlmutter, 1970) stress the same basic concepts, but have modified certain terminological and theoretical positions. For example, Anokhin's concept of "receptor of action" and von Holst's "efferent copy" are analogous. However, while some investigators emphasize the role of proprioception as an important feedback stimulus (e.g., Adams, 1968), others minimize its role (e.g., Merton, 1964). In addition, there still remain the questions of whether feedback mechanisms are controlled by peripheral-central loops, strictly central loops, or for that matter, whether feedback is necessary at all for response control. Before an attempt is made to resolve these problems, a brief description of the role played by feedback mechanisms in response control, general to most theories, is undertaken.

It is believed that motor programs are "written" in the cerebral cortices. The programming of motor acts is determined by the sensory information available to the organism (internal and external), the organism's emotional and motivational state of arousal, and previous experiential factors (memories). The sum total of these factors is analyzed in the cortex, and the initial stages of behavioral programming are set into motion. Motor programs are "written" in terms of expected outcomes which are based on the organism's intent (e.g., dig hole and burrow under ground in order to avoid predator, or press lever five times to avoid shock). The activation of a motor program leads to the formation of an efferent copy (image, acceptor of action) of that

program in the Central Nervous System (CNS). While the motor program is being carried out, feedback information (exteroceptive, proprioceptive, and interoceptive) is compared with the efferent copy, and deviations lead to response modifications until the expected outcomes are attained, matching feedback with the efferent copy. The response sequence is then terminated.

Throughout the past four decades, one type of feedback information, proprioceptive feedback, has received a great deal of attention and has led to many controversies. A selective survey of these efforts will be important to us for a variety of reasons. First, most of the findings have indicated that peripheral and central factors interact to form an integrative system for response control; and second, certain brain areas appear to be of particular importance for the utilization of this information for the formation and modification of motor programs.

The initial emphasis on the importance of proprioceptive feedback in motor control was derived from the work of Sherrington at the turn of the century. Sherrington found that unilateral limb deafferentation led to loss of "purposeful" use of the involved limb in monkeys (Taub et al., 1965).

Similar conclusions were derived from the early studies of Small (1900) and Watson (1907) in their discussion of maze learning in rats. These investigators concluded that since rats which sustained damage to sensory modalities such as vision and audition could still learn a maze task, this efficient performance was due to proprioceptive factors. Controversy soon developed, and more rigorous experimentation was

conducted. Finally, the results indicated that while proprioception may be utilized in maze learning, it is not a necessary form of feedback information, feedback from other modalities or even central mechanisms alone being sufficient (Adams, 1968).

The work of Taub and his associates (Taub and Berman, 1964; Taub et al., 1965; Taub and Berman, 1968) has helped to clarify this matter. These investigators performed both partial and complete, unilateral and bilateral rhizotomy in monkeys. In many cases the monkeys were blindfolded to omit the use of visual cues. After surgical preparation, free ranging activity and the retention and acquisition of conditioned avoidance tasks were studied. The surgical procedures did not seem to affect the final behavioral competence of the animals. Based on these findings Taub has proposed that:

. . . once a motor program has been written into the CNS (by whatever means), the specified behavior, having been initiated, can be performed without any guidance from extrinsic sources. (Taub et al., 1965, p. 12)

Merton (1964) and Keele (1968) have reached similar conclusions.

However, though Taub found that the final level of competence on these tasks is similar for normal and deafferented monkeys, he found that deafferentation severely retarded the acquisition of an avoidance response by a factor of three (Taub et al., 1966) and increased resistance to extinction of an avoidance response by a factor of four (Taub et al., 1965). In addition, "deafferents" showed an initial deficit in retention of an avoidance response (Taub and Berman, 1964). Finally, Taub (Taub et al., 1966) found that if additional feedback (experimenter produced) was afforded the deafferented monkeys during extinction

of an avoidance response, they then extinguish normally.

Such results would indicate that in the normal animal motor programs are "written" by the nervous system via feedback mechanisms similar to those described previously. These programs compare sensory information derived from movement with the movement command (efferent copy). When peripheral feedback into this neural system is disrupted, the CNS must rewrite its motor program, which is now dependent mainly upon central mechanisms. This delay for rewrite time may, in fact, be related to the initial performance decrements noted by Taub.

The investigations of Laszlo (Laszlo et al., 1969) lend further support for the interaction of central and peripheral factors in movement control. Laszlo found that while the presence of proprioceptive feedback is not essential to performance of skilled motor tasks in humans, her subjects, nonetheless, performed such tasks with reduced efficiency at the beginning of training. Laszlo found these effects in both discrete (indicative of developing motor skills) and continuous (indicative of well learned motor skills) tasks. However, a good portion of the skills literature maintains that proprioception plays a larger role in the development as contrasted with the maintenance of skilled movement (Keele, 1968; Clemens, 1972).

Research involving the effects of prismatic transformation of the visual field also supports the position that in normal organisms, movement feedback plays a strong role in the control and integration of motor activity. Since the investigations of Stratton in the late 1800's, there has developed a large body of literature dealing with the analysis of the mechanisms involved in adaptation to prismatic displacement.

Most of these studies (Epstein, 1967; Held, 1968) have indicated that active movement and its consequent proprioceptive feedback are the relevant variables in adaptation to prismatic displacement.

However, Hay and Pick (1966) found that proprioception is only important in the early stages of prismatic adaptation, lending further support for the position that proprioception is more important for the development, rather than the maintenance of motor skills. In addition, since active movement as contrasted to passive movement is a significant variable for adaptation, these studies also reinforce the contention for the interaction of peripheral and central factors in movement control.

At a more physiological level, a recent study by Vaughn, Gross, and Bossom (1970) is relevant to our present discussion. These investigators recorded electromyograms (EMGs) and corticomotor potentials in monkeys performing a well learned skilled movement before and after upper limb rhizotomy. Analysis of EMG indicates that deafferentation does indeed influence muscular contraction. The muscular contractions after rhizotomy were more variable and of increased duration. In addition, the shape of the cortical motor potential associated with movements did not differ from the preoperative recordings. This latter finding suggested to the authors that kinesthetic feedback is not registered in the motor cortex during the performance of well learned motor tasks.

The results of the Vaughn et al. (1970) study taken together indicate the following: (1) consistent with earlier findings, movement control can be executed in the absence of proprioceptive feedback,

(2) the form of muscular contraction, however, appears to be modified in the absence of proprioception, suggesting that the activities of a central motor program in the coordination of muscular activity is different from the normal peripheral-central mechanism, and (3) if kinesthetic information is not registered in the motor cortex during skilled movements, other brain areas may be involved in its analysis, or alternatively, this result may imply that in well learned automated movements, kinesthetic information is not utilized, central circuits processing the pertinent information.

In conclusion then, it appears that movement control is dependent upon the integrity of a neuronal servomechanism under normal conditions, and that a peripheral-central mechanism is functionally dominant. This assumption is supported by the finding of initial deficits in motor performance after application of drug, ischemic, or surgical deafferentation. The data which indicate a delay in the reorganization of the central programmer after prismatic transformation of the environment also supports this assumption since a period of active movement is necessary before accurate movements in the environment are possible. However, the plasticity of the CNS seems to allow for central control of movement in the absence of peripheral feedback. Thus, superimposed upon the peripheral-central feedback mechanism, there appears to be a functionally reliable central feedback loop for movement control. It is my contention that fronto-cortico-limbic mechanisms comprise part of the central pathways regulating sensory-motor integration, and the programming of motor acts.

C. THE NEUROANATOMY OF THE SEPTUM AND SEPTO-HIPPOCAMPAL RELATIONS

The septal area consists of a group of nuclei located within the general forebrain area commonly termed the limbic system. This nuclear group lies beneath the corpus collosum in the anteromedial wall of the hemisphere. It extends sagittally as far as the lateral ventricles, is bounded anterodorsally by the genu of the corpus collosum, and caudally by the descending columns of the fornix (Fox, 1940). The major nuclear groups of the septum include the medial and lateral septal nuclei, the posterior septal nucleus, the septo-fimbrial nucleus, the nucleus triangularis septi, and the nucleus of the diagonal band (Fox, 1940; Raisman, 1966; Andy and Stephen, 1968).

In the present discussion, I have outlined the most important septal connections, paying special attention to septo-hippocampal relations, especially as they are related to the control of the hippocampal theta rhythm. The efferents of the septum are discussed first, followed by a discussion of septal afferents. (See Figure I-1.)

Septal Efferents

Septal efferents can be subdivided into diencephalic and telencephalic components. The major projection sites of the diencephalic component include the hypothalamus, the medial habenula nucleus, and perhaps the dorsomedial nucleus of the thalamus and certain mesencephalic structures. The major projection sites of the telencephalic component are the hippocampus and olfactory tubercle.

Diencephalic Projections. Some of the fibers that leave the

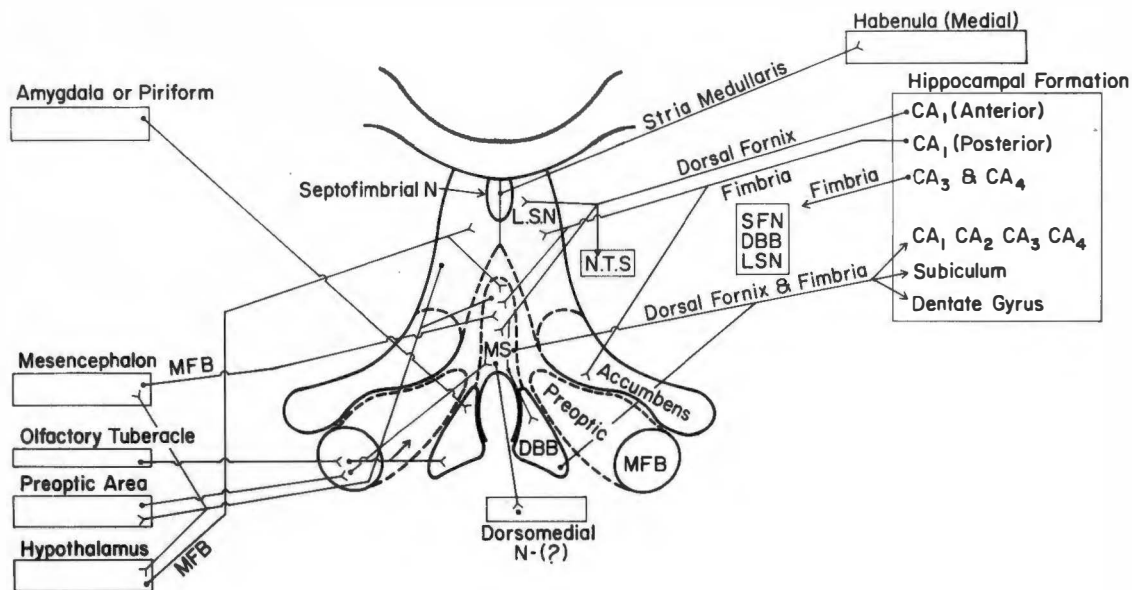


Figure I-1. Schematic representation of the main septal nuclear regions for the rat and their afferent and efferent connections.

CA₁, CA₂, CA₃, CA₄ = Cytoarchitectonic hippocampal fields

DBB = Diagonal band of Broca

LSN = Lateral septal nucleus

MFB = Medial forebrain bundle

MS = Medial septal nucleus

NTS = Nucleus triangularis septi

SFN = Septofimbrial nucleus

septum travel dorsalward in the stria medullaris to terminate in the medial habenula nucleus. Nauta (1960) has indicated that these fibers arise in the posterolateral septum, while Raisman (1966) presents anatomical support for a septo-fimbrial origin. This is an important pathway since it is a major link between forebrain structures and extrapyramidal structures of the midbrain. From the medial habenula nucleus fibers travel in the fasciculus retroflexus to the interpeduncular nucleus, and from there to the tegmental areas of the midbrain (Nauta, 1958). This circuit can be further extended back to forebrain structures via tegmental connections with the mammillary bodies (Krieckhaus, 1966).

A large group of fibers arise throughout the lateral and medial septal nuclei and travel ventralward in the medial forebrain bundle. These fibers terminate in various levels of the hypothalamus (Raisman, 1966), and Nauta (1958) has indicated that some of these fibers or their secondary projections travel as far as the subthalamus and even reach extrapyramidal and reticular structures of the midbrain. Guillery (1959) and Powell (1966) have indicated that the medial septal nucleus and the diagonal band nuclei project to the nucleus medialis dorsalis of the thalamus. This is an important connection since the dorsomedial nucleus of the thalamus is topographically connected with the prefrontal cortical areas (Akert, 1964).

Telencephalic Component. The most important component of the telencephalic septal projection is to the hippocampus. I discuss this projection in more detail shortly. For the present, it will suffice to note that these fibers arise in the medial septal nucleus and diagonal

band nucleus, and project via the fimbria and dorsal fornix to the posteroventral and anterodorsal portion of the hippocampus (Raisman et al., 1966; Lewis and Shute, 1967). The lateral septal nuclei do not project to the hippocampus (Raisman, 1966).

Septal Afferents

Septal afferents can also be discussed in terms of diencephalic and telencephalic components.

Diencephalic Component. The medial forebrain bundle is the major ascending pathway through which diencephalic and mesencephalic fibers reach the septum. Fibers arising in the hypothalamus travel to the lateral septal nucleus, while fibers arising in the mesencephalon travel to the medial septal nucleus. (Guillery, 1957; Nauta, 1958; Raisman, 1966).

Telencephalic Component. The major telencephalic projection to the septum arises in the hippocampus and travels in the dorsal fornix and fimbria to all areas of the septum (Raisman, 1966; Raisman et al., 1965, 1966). In addition the olfactory tubercle, pyriform cortex, and perhaps amygdala project to the septum (Raisman, 1966).

One anatomical system in the septum is of particular interest because it is probably responsible for the mediation of the hippocampal theta rhythm. Green and Arduini (1954) showed that the theta rhythm is evoked via pathways running from the septum to the hippocampus, and that blockage of the pathway via fornix section or specific septal

lesions results in a disruption of the theta rhythm. In addition, theta activity is also dependent upon an intact connection between the mesencephalic reticular formation and the septum (Petsche et al., 1965).

Neuroanatomically, rostrally projecting fibers arising in the mesencephalon enter the medial forebrain bundle, course through the lateral preoptic area and ascend to the nucleus of the diagonal band (Guillery, 1957; Nauta, 1958). From this point fibers enter the medial septal nucleus and are transmitted to the hippocampus (Raisman, 1966; Lewis and Shute, 1967). In addition, the latter authors have shown that this projection from the medial septum to the hippocampus is a cholinergic pathway. Evidence suggests that fibers from the diagonal band and extreme medial septum along the midline are responsible for the pacing of the hippocampal theta response (Petsche et al., 1962; Petsche et al., 1965; Macadar et al., 1970). These fibers (see Figure I-1, p. 10) travel in the dorsal fornix to hippocampal area CA₁ and perhaps CA₄ (Lewis and Shute, 1967; Carey, 1968). In addition, hippocampal area CA₁ projects back upon this extreme medial division of the septum via the dorsal fornix (Raisman et al., 1966). Thus, the possibility exists here for a feedback loop between the medial septum and hippocampal area CA₁ for septo-hippocampal modulation of the theta response. It should be mentioned, however, that Raisman (1966) denies the existence of fibers from the medial septum via the dorsal fornix to hippocampal field CA₁. Instead, he emphasizes a projection from the medial septal nucleus by way of the fimbria to fields CA₃ and CA₄ of the hippocampus. However, these fibers appear to arise in the more lateral portions of

the medial septum (Raisman et al., 1965), and may not be associated with the hippocampal theta response (Petsche et al., 1962).

Based on the neuroanatomical connections just discussed, it is proposed that the lateral portions of the septum, by way of its dense diencephalic projections to the hypothalamus, are related to the regulation of autonomic processes and emotional behavior in general. There is ample behavioral and neuroendocrinological data to support such a contention. The medial septum and diagonal band, on the other hand, seem to comprise an important linkage point between the mesencephalic reticular formation, mesencephalic motor centers, and fore-brain structures. It is this portion of the septum which I propose to be of importance for response control.

D. NEUROANATOMY OF FRONTAL CORTICAL AREAS

All cortex lying rostral to the central fissure (cruciate sulcus of carnivores) is considered frontal cortex. However, frontal cortex has been subdivided cytoarchitectonically into motor, premotor, and non-motor (association) areas (Akert, 1964). In non-human primates, the motor and association areas are separated by the arcuate fissure; the motor areas lying caudal to the arcuate fissure with its caudal boundary being the central fissure. Association cortex is designated as all cortex rostral to the arcuate sulcus. Within the arcuate sulcus itself is located the transitional area 8 of Brodmann or the frontal eye fields. Histologically, association frontal cortex in primates contains a well defined cortical layer IV which consists of granular cells (relatively absent in the motor area which has a rich pyramidal

layer V), and is topologically related to the dorsomedial nucleus of the thalamus. It is with the non-motor frontal association cortex that the research to be reviewed herein is concerned.

The frontal association cortex (FAC) of primates is further subdivided into dorsolateral and orbital (ventrolateral and ventromedial) sectors. In carnivores the FAC is divided into an orbital and a preoreal area. The preoreal area is inclusive to the gyrus preureus, and based on thalamo-cortical relations (Akert, 1964) is analogous to the dorsolateral division of primates. In rodents, the whole area of the frontal pole has, until quite recently, been considered FAC. However, Leonard (1969) has recently shown that this is not the case. She has shown that most of the area of the frontal pole, especially laterally, is motor type cortex. Only cortex lying on the midline and anterior to the corpus collosum is analogous to the dorsolateral sector of primates. Furthermore, in rodents, an area on the ventral surface of the brain in and around the rhinal sulcus is analogous to the orbital cortex of higher forms. Divac (1971), in a behavioral study, has recently supported Leonard's findings.

FAC Relations to the Dorsomedial Nucleus of the Thalamus

If one were to delineate FAC by cytoarchitectonics alone, it would be difficult to determine if carnivores, rodents and other sub-primate forms do indeed have frontal association cortex that is analogous to that of primates (Akert, 1964; Leonard, 1969). However, the dorsomedial nucleus of the thalamus does project topologically to differential frontal cortical zones in all mammals. Rose and Woolsey

(1948) suggested that this cortical projection field of the nucleus medialis dorsalis be considered homologous FAC, even though inter-specific differences in cytoarchitectonics may exist. Most anatomists have followed this suggestion, and the behavioral evidence to be reviewed shortly also supports this position.

The nucleus medialis dorsalis is subdivided into three regions: a medial magnocellular region; a lateral parvocellular region; and an extreme paralamellar region. The magnocellular region projects to the orbital surface, the parvocellular region to the dorsolateral sector, and the paralamellar portion to the transitional area 8 of Brodmann (Auer, 1956; Akert, 1964; Leonard, 1969).

Cortico-Cortical Connections of FAC

Recent neuroanatomical (Pandya and Kuypers, 1969; Pandya et al., 1969; Pandya and Vignolo, 1971; Jones, 1969) and neurophysiological (Encabo and Ruarte, 1967; Livanov, 1969; Rignall and Imbert, 1969; Beritashvili, 1971) investigations have strongly indicated that the FAC of primates and carnivores may be a prime site for the integration and analysis of varied sensory and motor inputs. In general, what has been shown is that the somatic, auditory, and visual areas first project to premotor cortex and their surrounding association cortex of origin. From these new secondary sites fibers are projected again to surrounding areas, and further anterior into the FAC. Furthermore, the new projection sites in the FAC are reciprocally interconnected with the original local projection areas of the primary sensory cortex and the supplementary motor areas.

Thus, what we have within the FAC is a complex neural system which would appear, neuroanatomically, to be of great import for sensory-motor integration. Further evidence indicating the importance of FAC in sensory-motor integration is discussed in the review of the behavioral literature below. However, I would like to point out at this time that damage to the cortical motor areas (4 and 6 of Brodmann) alone does not lead to obvious motor impairments in monkeys. However, when FAC is destroyed in addition to damage to the motor areas the ability of monkeys to maintain posture and carry out efficient sequential movements is lost (Peele, 1954), suggesting an important relationship between motor mechanisms and FAC in the programming of sequential motor acts.

Neuroanatomical Relations Between FAC and Subcortical Centers

Early interest in FAC centered around psychosurgical techniques. The effects of frontal lobotomy on emotional and social behavior were often attributed to disconnection of the FAC from the hypothalamus (Mettler, 1949; Freeman and Watts, 1950; Girgis, 1971). Connections from the hypothalamus to the FAC do, in fact, exist. Afferents to the frontal lobe arise in the posterior hypothalamus, ascend to the magnocellular division of the dorsomedial nucleus of the thalamus, and from there are transmitted to the orbital surface of the FAC (Le Gros Clark, 1948). Furthermore, the FAC (dorsolateral and orbital sectors) projects back upon the hypothalamus. The sites of termination are in the supra-optic and paraventricular nuclei, the lateral and posterior hypothalamic areas and the ~~mammillary~~ bodies (Le Gros Clark, 1948). More recent

studies (Devito and Smith, 1964; Johnson et al., 1968) have emphasized hypothalamic terminations in the lateral hypothalamic and lateral preoptic areas. Similar results based on degeneration have been found in the cat and rat after frontal ablation (Auer, 1956; Leonard, 1969). These findings are of importance since it is through the lateral preoptic and lateral hypothalamic areas that input from the mesencephalic reticular formation ascends to the medial septal nucleus for the modulation of the hippocampal theta response.

Besides its cortico-cortical relations with motor and premotor areas of the brain as outlined above, the FAC of primates, carnivores, and rodents has strong neural relations to extrapyramidal subcortical motor centers. Thus, there are efferents from the frontal cortical areas to the head of the caudate nucleus, putamen, claustrum, zona incerta, field H of Forel, nucleus subthalamicus, substantia nigra, and the nuclei of the midbrain tegmentum (Devito and Smith, 1964; Johnson et al., 1968; Leonard, 1969; Beritashvili, 1971; Girgis, 1971). Furthermore, the FAC may influence cerebellar mechanisms in primates, carnivores, and rodents via a projection to the pontine nuclei (Devito and Smith, 1964; Brodal, 1971a, 1971b; Leonard, 1969).

Limbic Relations of FAC

Nauta (1964) has indicated that the dorsolateral sector of the frontal cortical areas is closely related to the hippocampus, while the orbital surface of the frontal lobes is more closely related to the temporal lobe and amygdala. He points out that fibers leaving the dorsolateral sector diffusely distribute through the cingulum and

terminate in juxta-hippocampal regions. Secondary fibers arising from this point enter the hippocampus. On the other hand, the orbital surface is related to the temporal gyrus and amygdala via the fasciculus unciratus. More recent evidence does, in fact, show that the orbital gyrus projects to the amygdala, and the degeneration is greater in the basolateral nuclear group (Valverde, 1965; Girgis, 1971). Valverde (1965) made his observations on cat material. Leonard (1969) was unable to substantiate such long fiber connections in the rat.

Van Hoesen, Pandya, and Butters (1972) found that the frontal projection to entorhinal cortex in the macaque monkey terminates in area 28b. Area 28b of the entorhinal cortex in turn, projects diffusely to the apical dendritic zone of both hippocampal pyramidal and dentate granule cells. These investigators emphasize that, "...the entorhinal cortex is a final cortical link between the sensory systems of the neocortex and the hippocampus and dentate gyrus of the limbic system." (Van Hoesen et al., 1972, p. 1472)

Furthermore, the sensory-motor integrations that we have assumed to take place in the frontal cortical areas could modulate the channeling and processing of new sensory information in any one of three ways: (1) via reciprocal projections back to areas of primary sensory input (Jones, 1969), (2) via projections to the medial forebrain bundle, which carries reticular excitation to the limbic system (Mizuno et al., 1969; Valverde, 1965), and (3) via projections to the midline and intralaminar thalamic nuclear groups which constitute a major thalamic site for the telencephalic projection of the ascending reticular formation (Auer, 1956; Johnson et al., 1968).

Furthermore, which is of importance to us, it would appear that the FAC sends efferent fibers to the medial septum. However, the site of origin of these fibers within the FAC is not yet clear. Johnson et al. (1968) working with monkey material assert that the fibers originate in the orbital cortex. However, Devito and Smith (1964) found that fibers arising in the dorsolateral cortex reach the septum, and Beritashvili (1971) working with carnivores (cat and dog), places the origin in the preoreate gyrus, which is the analogue of dorsolateral FAC.

Nauta (1964) goes so far as to suggest that the FAC is a neocortical extension of limbic mechanisms, subserving the same basic functions. The neuroanatomical data reviewed in the previous two sections does indeed indicate strong anatomical relations between these two forebrain systems, and the behavioral literature to be reviewed below further substantiates such a point of view.

To recapitulate then, it would appear that the frontal cortical areas are an important nodal point in the brain involved in the processing and integration of multimodal sensory and motor input. Furthermore, this integrated input is transmitted to limbic structures via entorhinal-hippocampal pathways. In addition, based on the information received, the frontal cortical areas and limbic structures can regulate the channelling of new sensory information and the priming of motor mechanisms in a variety of ways: for example, via connections with extrapyramidal, motor, and premotor centers; via interactions with the reticular formation; and perhaps through a direct action on primary sensory mechanisms. More will be said on this last point shortly.

E. THE BEHAVIORAL PHYSIOLOGY OF THE SEPTUM

Two major hypotheses have evolved dealing with the role of the septal area in the regulation of behavioral processes. One hypothesis extends the view that the septal area is an important brain structure involved in the regulation of emotional states. The other hypothesis maintains that the septum is an integral part of a neuronal system which controls response processes in animals. The literature available suggests that both hypotheses have some merit, and in addition, there appears to be an anatomical specificity within the septum related to these functions.

In the following pages I review each of these major hypotheses, and in addition, survey the available literature dealing with the role of the septum in stimulus processing, since this topic has been quite crucial to our discussion so far.

The Septal Area and Emotionality

Behavioral Studies. Interest in the septal area can be traced back to early work by Spiegel, Miller, and Oppenheimer in 1940. They found that following septal lesions in cats there were extreme rage reactions. Brady and Nauta (1953, 1955) and King (1958) reported increases in the emotionality of rats following septal lesions. This early work taken together seemed to indicate that the septal area played an important role in emotionality.

In 1963 Lubar proposed that one effect of septal lesions might be to reduce "fear." This conclusion was based on the observation

that in a passive avoidance situation septal cats that had been punished, rapidly returned to the source of shock punishment. Normal animals after being shocked remained as far as possible from the electrified water dish and showed a strong conditioned emotional response (CER).

In rats there are also recent studies which show that septal animals are deficient in the formation of a CER (Harvey et al., 1965; Trafton, 1967). In addition, Kenyon (1962) and Kenyon and Kriekhaus (1965a, 1965b) found that septal ablations in rats lead to enhanced acquisition of a two-way shuttle avoidance response, and a deficit in the acquisition of a one-way active avoidance response. Furthermore, Kenyon and Kriekhaus (1965a, 1965b) explained the abnormal avoidance behavior of septal animals on the basis of decreased fearfulness and the attenuation of freezing behavior.

In trying to relate septal-produced changes in emotionality to performance on avoidance tasks it has been argued that the reason that the septal animals are superior in performance of a two-way avoidance response is that there is a reduction of approach-avoidance conflict due to an attenuated fear response (Lubar and Numan, 1972). The enhancement of two-way avoidance conditioning has been confirmed by many investigators (King, 1958; Kenyon and Kriekhaus, 1965a, 1965b; Green et al., 1967; Schwartzbaum et al., 1967). The implication of a diminished fear hypothesis for the septal animal may actually explain both the fact that there is an enhancement in two-way avoidance performance as well as a very striking deficit that has been reported for rats on the one-way task (Kenyon, 1962; Vanderwolf, 1964; McNew and Thompson, 1966; Deagle and Lubar, 1971). It is not unreasonable to

propose that the septal rat is generally deficient in avoidance learning. For example, septal ablation leads to deficits in passive avoidance and one-way active avoidance, as mentioned above. In addition, the septal rat is also deficient in a modification of the one-way task--the pole jump response (Grossman, 1968). These findings can also be explained in terms of an attenuated fear response based on CER formation to an aversive stimulus. That is, in these "simple" avoidance tasks, which do not involve a conflict component, the high CER of the normal animal facilitates rapid acquisition, and the low level of CER formation in the septal animal inhibits rapid acquisition of these tasks. However, when a conflict component is added to the avoidance situation the outcomes are reversed. Thus, the numerous findings of facilitation in the two-way shuttle avoidance can be explained via the same mechanism. Since inadequate CER formation would decrease the conflict normally inherent in the situation (returning to a box where shock was previously presented), this would result in decreased response suppression or freezing in septal animals and hence facilitation in this task.

In support of this interpretation, Garber and Simmons (1968) found that if they utilized a modified shuttle avoidance task in which one compartment delivered a high intensity shock, while the other delivered a relatively low intensity shock, that septal animals moved more quickly into the high shock compartment but had longer latencies for entrance into the low shock compartment when compared with controls.

Endocrinological Evidence for Septal Modulation of CER Mechanisms.

Since the work of Brady in the 1950's, it has been known that avoidance

conditioning procedures lead to activation of the adenohypophysis with concurrent release of ACTH, presumably due to the stress effects of shock and its anticipation. It would follow then that if one hypothesizes that septal ablation leads to decreased fear, one might also expect to find attenuated activity in the pituitary adreno-cortical system in response to stress. There are some data available which tend to support this point of view.

Usher, in a series of studies (Usher et al., 1967, 1969) found that septal ablation in rats led to enhancement in two-way shuttle avoidance along with a relative lack of stress-induced release of ACTH. The implication here is that septal ablation leads to a diminished stress response. Furthermore, Koranyi and Endroczi (1967) found that within thirty minutes following exogenous ACTH administration there was an inhibition of a conditioned avoidance response to which 100% performance had previously been established. In addition, Levine (1968) points out that low blood levels of ACTH are positively correlated with poor passive avoidance learning, while high levels are correlated with superior performance. These findings provide a possible secondary source of evidence for the point of view that septal ablation leads to an attenuation of the stress response, since as mentioned previously septal ablation leads to facilitation in the acquisition of a two-way shuttle avoidance and impairment in the acquisition of a passive avoidance response.

It should be pointed out, however, that both Endroczi and Lissak (1960) and Bohus (1961) found increased basal levels of ACTH after

septal ablation. Wertheim et al. (1969) found increased basal activity in the pituitary-adreno-cortical system to be highly correlated with superior performance on a Sidman avoidance schedule, a task in which septal ablation also leads to facilitation (Sodetz, 1970). However, these findings are congruent with each other, and do not emphasize changes in stress-induced release of ACTH but rather changes in the basal levels of the hormone. The fact that septal ablation may lead to increased basal levels of ACTH while blocking the release of ACTH in response to stress is supported by the work of Usher and Lamble (1969). They found that septal ablation in the rat led to an enhanced synthesis of ACTH but a relative inhibition of ACTH release in response to stress.

The possible mechanisms through which the septum might act to influence anterior hypophysial functions are at present obscure. However, Nauta (1958) has stressed that one "escape pathway" from his limbic system-midbrain circuit is to the medial hypothalamic region. This region, as Nauta points out, appears to be directly involved in the neuronal mechanisms which regulate anterior pituitary functions. The medial hypothalamus receives this input from limbic forebrain structures via the stria terminalis and medial fornix components (Nauta, 1958). A septal influence could possibly arise from the fornix projection, since fibers from the septum travel with precomissural fornix fibers to caudal structures via the medial forebrain bundle (Nauta, 1958; Raisman, 1966).

Specific Anatomical Loci Within the Septum Related to Emotionality.

In the neuroanatomical discussion of the septum, I emphasized that there is a marked difference between the connections of the lateral septum and its surrounds, and the medial septum. Specifically, the medial but not the lateral septum projects to the hippocampus, while the lateral septal nucleus has a strong projection to the hypothalamus. In addition, pharmacological evidence indicates that there are adrenergic terminals in the lateral septum (Fuxe, 1965), while the pathway from the diagonal band and medial septum to the hippocampus, which acts as the pacemaker for the hippocampal theta response, is cholinergic (Lewis and Shute, 1967; Macadar et al., 1970). Taking these findings into account, along with the obvious involvement of the hypothalamus in regulatory processes related to emotionality (Hess, 1957), one might expect that the more lateral portions of the septum, rather than the medial septal areas are part of a neural system which regulates emotional states.

The behavioral data which is available lends some support for such a conclusion. Van Hoesen et al. (1969), comparing the effects of a variety of lesions on avoidance learning, found that ablations involving the descending columns of the fornix (which sends fibers to the hypothalamus) produced the most profound effects on two-way shuttle avoidance acquisition, and that structures in the vicinity of the lateral septum (e.g., stria medullaris and habenula) produced large deficits in passive avoidance. Hamilton et al. (1970) found still a further differentiation within the septal area. These investigators found that ablation of the anteromedial septum did not disrupt passive avoidance behavior. Lesions localized in the lateral septal nuclei, however, led

to impairments in passive avoidance and facilitation in active avoidance. It should be emphasized, in addition, that large septal ablations which included the lateral and medial septal nuclei attenuated the effects seen after lateral ablation alone, thus indicating that the medial and lateral system may act in opposition to each other. Furthermore, Donovanick (1968) found no correlation between hippocampal theta activity, which is mediated by the medial septal nucleus, and avoidance performance. Finally, Kasper (1964) found that continuous stimulation of the lateral septum produced deficits in passive avoidance and a decrement in emotionality; medial septal stimulation did not have such an effect.

The interpretation of these data suggests that lesions placed in the lateral septal nuclei and surrounding neural tissue result in modified performance on avoidance tasks. Hence, the neural groups interrupted by these lesions might be involved in the formation of CER or other factors related to avoidance performance.

The Role of the Septum in the Regulation of Response Processes

Early Studies. Arising almost in parallel with models of septal function based upon emotionality were models based on response inhibition. In 1951 Kaada showed that electrical stimulation of the septal region and subcollosal cortex in cats and monkeys produces both autonomic and somatomotor response inhibition.

Incorporating Kaada's findings into a theory of septal function, McCleary (1961, 1966) postulated that since stimulation of the septal region produces an inhibition of somatomotor responses, that ablation

of this area should produce somatomotor disinhibition, or an inability to appropriately inhibit responses. McCleary (1966) felt that his findings showing impaired passive avoidance learning and enhanced two-way shuttle avoidance acquisition after septal ablation supplied strong support for this theory. However, the fact that septal animals are impaired in the acquisition of a one-way shuttle avoidance response is not congruent with this theory of septal function. As we have just seen, the effects of septal lesions on avoidance performance is perhaps best explained in terms of attenuation of CER formation to aversive stimuli. Nonetheless, there are a great many tasks which do require the inhibition of response tendencies without incorporating aversive stimuli into their paradigms, and it is on these tasks that septal animals do show very striking deficits. As we shall presently see, the theory as stated by McCleary is too simplistic, and in addition, there would also appear to exist within the septum an anatomical specificity for what has commonly come to be called septal perseveration.

Anatomical Specificity. Current research has indicated that the hippocampal theta response is highly correlated with voluntary movement (Vanderwolf, 1969, 1971). Since the medial septum appears to be the pacemaker for hippocampal theta, it may very well be the case that the medial portion of the septum plays a strong role in the regulation of response tendencies. For example, Donovan (1968) found that only ablations in the anteromedial septum disrupted hippocampal theta and performance on such tasks as spatial alternation and reversal. Lateral ablations do not disrupt hippocampal theta, nor do they impair reversal

learning. Similar effects appear after medial septal ablation in primates (Butters and Rosvold, 1968). Furthermore, the types of perseverative deficits that occur after septal ablation (e.g., over responding on operant schedules, lack of spontaneous alternation) appear to be due specifically to damage in the medial septum (including the diagonal band nuclei) (Carey, 1967, 1968; Clody and Carlton, 1969).

The Problem of Septal Perseveration. Earlier studies by Ellen and Powell (1962) showed that on a fixed interval (FI) schedule rats with septal lesions attained a higher terminal response rate at the end of the interval than controls. The work of Harvey and Hunt (1965) showed increased responding on both FI and continuous reinforcement (CRF) schedules; and Ellen, Wilson, and Powell (1964) found that septal rats were unable to withhold responding sufficiently long enough to obtain reinforcement on a DRL (differential reinforcement of low rates of response) schedule. These findings have been repeatedly replicated and have been extended to include increased resistance to operant extinction (Carey, 1967, 1968; Ellen and Butter, 1969; Hothersal et al., 1970; Schnelle, 1970).

Septal ablated animals also show perseverative behavior during the reversal and alternation of spatial discriminations. For example, septal rats are deficient when compared to normals on the reversal of a spatial discrimination (Schwartzbaum and Donovanick, 1968). Zucker and McCleary (1964) and Zucker (1965) found similar effects in cats, while Butters and Rosvold (1968) found the same in monkeys. Other investigators have found similar effects (Thompson and Langer, 1963; Hamilton

et al., 1970). In addition, Clody and Carlton (1969) found a decrease in spontaneous alternation in a T-maze following septal ablation in the rat, and Gittleston and Donovan (1968) found a septal produced deficit on reversal of a kinesthetic discrimination.

A great deal of interest regarding the effects of septal damage on response processes has been directed toward the DRL task. This is because DRL is a difficult schedule requiring the organism to pace its responses in order to receive reinforcement. The early findings of Ellen, Wilson and Powell (1964) indicating over responding by rats during DRL acquisition have been repeatedly confirmed (Burkett and Bunnell, 1966; Carey, 1967, 1968; Ellen and Butter, 1969; MacDougal et al., 1969; Ellen and Aitken, 1971; Agnew and Meyer, 1971).

When responding on a DRL schedule, the septal damaged animal over-responds; being unable to regulate its response rate to the demands of the schedule. It should be pointed out that these data do not indicate a complete lack of response regulation. For example, Carey (1967) has noted that normal and septal rats show the largest number of responses in the 0-2 second IRT interval of a DRL 22 second schedule early in training. As training progresses, the majority of these "response bursts" are eliminated by both septal and normal animals. The normal animal develops a bimodal distribution as training continues, with peaks at (1) relatively short IRTs, and (2) the minimal reinforcement interval. Septal animals, however, maintain a unimodal distribution with a peak in the range of relatively short IRTs.

Furthermore, the DRL deficit exhibited by septal rats has been found to be dependent upon the training procedures utilized. Caplan

and Stamm (1967) found no impairment in performance on DRL after septal ablation in rats if training proceeded slowly and the length of the DRL interval was gradually increased. Ellen and Butter (1969) found that septal animals could perform efficiently on a DRL schedule provided that the animals were given feedback signalling the availability of reinforcement. They interpreted the septal impairment in terms of a deficit in proprioceptive processing. That is, the septal animal cannot utilize the response feedback necessary for the formation of effective collateral behavior which in turn might be necessary for the development of an accurate temporal discrimination. Support for such a contention is supplied by the work of Laties et al. (1969) who have shown that collateral behavior (e.g., wood nibbling) developed by normal rats during DRL acquisition facilitated performance on this task. Ellen and Kelnhofer (1971) have added further support for this interpretation. They found that septal rats were impaired on a counting schedule where the animal was required to respond five times on one lever before switching to another to obtain reinforcement, again indicating inefficient use of response produced cues.

Besides the "proprioceptive hypothesis" presented by Ellen and his associates, there have been many other attempts to explain the perseverative tendencies of septal damaged animals. One line of research has stemmed from the fact that septal damaged animals are over-reactive to both positive and negative taste properties of nutrients and thus perhaps are more highly motivated than are normal animals (Harvey and Hunt, 1965; Beatty and Schwartzbaum, 1967). More specifically,

in the case of studies using water as a reinforcer, it has been emphasized that septal damaged rats may have an enhanced drive for water consumption, since under normal ad-libitum conditions their water intake is significantly greater than that of normal animals (Harvey and Hunt, 1965; Wolfe et al., 1967; Lubar et al., 1968). However, Zucker (1965), working with cats, has indicated that food intake in these animals after septal ablation did not differ from that of normal animals, and Wolfe et al. (1967) have reported increased water consumption in septal ablated rats without a concurrent increase in runway speeds for a water reward. Carey (1967) has controlled for the possible enhancement of thirst in septal rats deprived of water for 23 hours by depriving a normal group for 72 hours. Nevertheless, his septal rats still over-responded on a DRL 22 second schedule. Furthermore, the investigations of Lubar et al. (1969) and Carey (1968, 1969) have shown that increased ingestion of water is due to lesions placed posterior and ventral in the septum, while a large number of studies (Burkett and Bunnell, 1966; Carey, 1968, 1969; Donovan, 1968) have shown that lesions of the antero-medial septum and diagonal band lead to perseverative tendencies. In addition, Clody and Carlton (1969) have shown that lesions of the medial septum which produce perseverative tendencies in rats on a variety of tasks do not lead to increased ingestion of sucrose ad-libitum. Thus, there is both behavioral and anatomical evidence which tends to indicate that septal produced perseveration is not due to an enhanced motivational state:

Many investigators have attempted to explain septal produced

perseveration in terms of response disinhibition. For example, Carey (1968) believes that overresponding in rats following anteromedial septal ablation is due to the interruption of a neuronal circuit arising in the midbrain reticular formation, passing through the medial septum, and terminating in the hippocampus. Thus, according to Carey, septal ablation leads to a severe deafferentation of the hippocampus from reticular inputs, "eliminating the inhibitory function of the hippocampus." I concur with Carey's neuroanatomical description, however, an explanation of the behavioral data simply in terms of disinhibition is not justified. For example, a simple form of the response disinhibition model will not suffice, since presentation of an external cue acting as a discriminative stimulus for responding leads to normal inhibition (response pacing) in septal rats (Ellen and Butter, 1969; Kelsey and Grossman, 1971). More complex statements of the response disinhibition model of septal function emphasize the point that perseveration will not occur unless a response is dominant. Hence, septal lesions lead to an inability to modify dominant response tendencies as is the case with deficits in reversal learning. Overresponding on DRL is explained, then, as an inability to modify responses developed during CRF training to the DRL requirements. Both of these suggestions receive negative support based on current findings. Thus, Kelsey and Grossman (1971), using a modified DRL procedure in which CRF pretraining was not necessary, still found a deficit after septal ablation in rats. In addition, septal ablation does not lead to response perseveration during the reversal of a brightness discrimination, but does lead to

impaired performance when a spatial discrimination is reversed (Schwartzbaum and Donovanick, 1968). Thus it is quite clear that most forms of the response inhibition model of septal function cannot adequately explain the findings. What is clear, however, is that septal ablations, specifically those localized in the anteromedial septum, generally impair the organism's ability to regulate its response output, based on the consequences of action, when exteroceptive stimuli are absent or largely lacking.

The Septum and the Regulation of Sensory Information

There has been a large number of studies which have shown that after septal ablation, animals are more sensitive and/or more reactive to stimuli from various sensory modalities. These results have been found for tactile stimuli (Brady and Nauta, 1953; King, 1958; Lints and Harvey, 1969; Lubar, Brener, Deagle, Numan, and Clemens, 1970), visual stimuli (Schwartzbaum et al., 1967), and auditory stimuli (Brady and Nauta, 1953; Schwartzbaum and Gay, 1966; Gotsick, 1969). These results, taken together, indicate that the septum may play a role in the processing of sensory information.

This conclusion is supported by recent neurophysiological investigations. Lorens and Brown (1967) found that stimulation of the septum attenuated photically evoked potentials in the visual cortex of the cat. Golden and Lubar (1971) replicated this finding and extended the results to include auditory evoked potentials. Furthermore, the latter investigators found that septal ablation increased photic and auditory cortically evoked potentials. These results supply physiological

evidence upon which to refer the commonly observed behavioral finding that septal animals are hyperreactive to auditory and visual stimuli.

The recent work of Powell and his collaborators (Powell and Hoelle, 1967; Powell et al., 1970) add neuroanatomical and additional neurophysiological support for a septal role in sensory processing. Powell and Hoelle (1967) found septal efferents to the inferior colliculus and medial geniculate body (MGB) of the cat. In a follow-up study (Powell et al., 1970) septal stimulation was found to give rise to inhibitory as well as excitatory effects on MGB unit firing in the cat. It appears that this effect on MGB units can be induced through the septum alone, or through a septal-inferior collicular interaction. Furthermore, septal activation of MGB units was found to survive section of the posterior mesencephalic reticular formation. However, as Powell points out, these results do not exclude the possibility of a septal effect via more rostral portions of the reticular formation. Nauta (1958) has indicated that the septum receives and sends secondary and perhaps primary fibers to the mesencephalic reticular formation, thus, a septal effect on sensory mechanisms via a reticular interaction cannot be excluded. What can be concluded based on the behavioral, physiological, and neuroanatomical findings discussed above is that the septum does play a regulatory role in the processing of sensory information. This role is probably expressed through septal connections with: (1) other limbic-forebrain structures; (2) the reticular system; and (3) primary sensory, probably subcortical, centers.

The various experiments just discussed (see Table I-1 for a review) clearly support the conclusion derived from our neuroanatomical survey

TABLE I-1

BEHAVIORAL AND PHYSIOLOGICAL CHANGES FOLLOWING SEPTAL MANIPULATION

Type of Septal Manipulation	Behavioral or Physiological Change	Anatomical Specificity	Species in Which Effect Has Been Found
Ablation	Enhancement of two-way shuttle avoidance acquisition	Lateral septum, descending columns of the fornix	Rat Cat
Ablation	Retardation of one-way shuttle avoidance acquisition	Not investigated	Rat
Ablation	Deficit in passive avoidance	Stria medullaris, habenula	Rat
Stimulation	Deficit in passive avoidance and attenuated emotionality as indicated by urination and defecation in an aversive situation	Lateral septum	Rat
Ablation	Attenuation of CER formation and conditioned suppression	Not investigated	Rat
Ablation	Increased basal blood levels of ACTH, decreased stress induced release of ACTH	Not investigated	Rat Cat Dog

TABLE I-1 (continued)

Type of Septal Manipulation	Behavioral or Physiological Change	Anatomical Specificity	Species in Which Effect Has Been Found
Ablation	Increased reactivity to stimuli from various modalities	Not investigated	Rat
Stimulation	Somato-motor and autonomic inhibition	Not investigated	Rat, Cat, Dog, Monkey
Ablation	Abolition of hippocampal theta response	Medial septal nucleus and dorsal diagonal band nucleus	Rat Rabbit
Ablation	Deficit on the reversal of a position discrimination	Medial septal nucleus, and strongly correlated with abolition of hippocampal theta response (in rat)	Rat Cat Monkey
Ablation	No impairment on the reversal of an object discrimination	Not investigated	Rat
Ablation	Lack of response pacing on DRL schedules of reinforcement (cue eliminates deficit)	Medial septum	Rat
Ablation	Increased rates of response on CRF, FR, and FI schedules of reinforcement and increases in resistance to extinction	Medial septum	Rat Monkey

TABLE I-1 (continued)

Type of Septal Manipulation	Behavioral or Physiological Change	Anatomical Specificity	Species in Which Effect Has Been Found
Ablation	Decrease in spontaneous alternation and stimulus perseveration	Medial septum	Rat
Ablation	Poor response control on counting schedules	Medial septum	Rat
Ablation	Increased water intake	Posteroventral septum	Rat
Stimulation	Decrement of auditory and photic cortically evoked potentials	Not investigated	Cat
Stimulation	Excitation or inhibition of MGB unit firing	Not investigated	Cat

of the septum. The lateral septal area, with its strong hypothalamic relations, appears to play a strong role in the modulation of CER formation. The medial septal nucleus, which is closely related to the ascending reticular formation and theta activation in the hippocampus, and extrapyramidal motor centers plays a strong role in response regulatory processes. Destruction of the medial septum seems to particularly disrupt the formation or modification of motor programs especially when external cue stimulation is lacking. These results suggest that the medial septum plays some role in utilization of proprioceptive, spatio-vestibular, and perhaps interoceptive information for response regulation. Furthermore, the septum may function in some way for the processing of sensory information.

F. THE BEHAVIORAL PHYSIOLOGY OF FRONTAL ASSOCIATION CORTEX

One of the first experimental studies dealing with frontal lobe function from which much of the current research has stemmed was carried out by Jacobsen in 1936. He observed that monkeys with frontal damage were impaired in delayed response and delayed alternation problems as well as in problems involving sequential acts. His brain-damaged monkeys showed stereotyped and hyperdistractible behavior along with increased activity and appetite. However, his monkeys performed normally on simple problem box tasks and visual discriminations. Based on these results, especially the deficits on delayed response, Jacobsen theorized that frontal lobe injury disturbs the mechanisms of immediate memory.

Stanley and Jaynes (1949) cite extensive evidence which indicates that bilateral removal of the frontal cortical areas in monkeys leads

to hypermotility and poor performance on the following tasks: habit reversal problems, seriatum problems (In this latter task a sequential and ordered pattern of responding is required.), conditional reactions, and delayed response. Simple discriminations were not affected by frontal ablation. Based on these findings, these experimenters proposed a theory of "cortical act-inhibition" as an explanation for frontal lobe function. Basically this theory proposes that deficits found after frontal ablation are not due to an impairment in learning ability, but rather an impairment in performance; the brain damaged animal being unable to inhibit previously learned response sequences.

Furthermore, early behavioral studies in primates have shown that the amount of sensory input is an important factor for the etiology of some of the deficits observed after frontal ablation. Thus, enucleation, darkness, and barbiturate administration have been found to ameliorate some of the abnormalities (e.g., hyperactivity, delayed response deficit) found after frontal ablation (Kennard et al., 1941; Malmö, 1942; Mishkin, Rosvold, and Pribram, 1953).

Most of the early physiological work dealing with frontal lobe function indicated that the orbital surface of the frontal lobes plays a prominent role in autonomic regulation. Thus, stimulation of the orbital gyrus arrests respiratory movements, may elevate or depress blood pressure depending on locus, and leads to rapid rises in the temperature of the extremities (Stanley and Jaynes, 1949). These early findings were supported by neuroanatomical and neuronographic studies (Le Gros Clark, 1948) indicating the close relationship between the orbital

surface and the hypothalamus. More recent physiological and anatomical studies have continued to support these conclusions (Kaada, 1960; Girgis, 1971).

Thus, even in the early investigations of frontal lobe function some segregation of function was envisioned within the frontal cortex; the orbital area appeared to be related to autonomic control, while the dorsolateral cortex was related to memory processes and response modulatory functions. In addition, there is some evidence in these early studies for a possible sensory-motor integrative function of FAC.

Contemporary research, with a few exceptions (Gross and Weiskrantz, 1964; Tubbs, 1969; Beritashvili, 1971) no longer maintains that the FAC is directly involved with memory processes. In some cases, however, certain portions of the FAC have been attributed a role in specific types of memory, for example, proprioceptive memory (Goldman and Rosvold, 1970). The reason that the memory hypothesis of frontal lobe function has become untenable is partly due to the findings noted above, indicating that barbiturates, enucleation, and darkness can alleviate some of the deficits found after frontal ablation. In addition, the findings indicating a lack of impairment on simple discrimination problems after frontal ablation does not lend support for a fronto-cortical involvement in memory functions. Furthermore, learning set performance is not disturbed after frontal ablation (Miles, 1964).

Most of the current research has attempted to explain frontal lobe function in terms of response modulatory processes of one kind or another. These views have been advanced for both convexity cortex and orbital cortex, and include various species ranging from rodents to primates,

including man (Mishkin, 1964; Goldman and Rosvold, 1970; Wegener and Stamm, 1966; Stamm, 1970; Wagman, 1968; Konorski, 1967; Divac, 1971; Luria, 1966).

In the following sections a systematic study of some of these findings is presented. Simian data will be analyzed first, followed by data from carnivores, rodents, and man. I will conclude with a discussion of the frontal lobes regulatory role on sensory mechanisms.

Simians

Damage to the dorsolateral (dl) surface of the primate frontal lobe (most noted in macaques, squirrel monkeys, and baboons; chimpanzees appear to be an exception) has repeatedly been found to lead to poor performance on spatial delayed response, spatial reversal and spatial delayed alternation. The focus for these deficits appears to lie within the principal sulcus (ps) and to be highly dependent on the spatial factors inherent in these situations (Mishkin, 1964; Gross and Weiskrantz, 1964; Butter, 1969; Goldman et al., 1971; Goldman and Rosvold, 1970; Butters et al., 1971). Performance on most simple discrimination tasks presented simultaneously, successively, or differentially usually is not disturbed (Warren and Akert, 1964). Furthermore, lesions in other portions of association cortex never lead to such a severe pattern of deficits coupled with normal visual discrimination performance (Rosvold and Szwachbart, 1964). In addition, these ablations, except for a transitional area which lies between the orbital surface and dl, do not produce deficits on similar tasks which do not involve spatial factors (e.g., object reversal), or where the importance

of spatial factors has been diminished (Butter, 1969; Mishkin et al., 1969; Stamm, 1970).

Based on these findings, Goldman and Rosvold (1970) proposed that the role of dl cortex in primates may involve some form of proprioceptive memory. They conclude that since in the delayed response and delayed alternation tasks there are no salient external cues to guide behavior, monkeys may learn by remembering their own spatially directed responses on the preceding trial (in the case of delayed alternation), or during the baiting phase (for delayed response). In support of this hypothesis, Cianci et al. (1967) found that monkeys with dorsolateral ablations were not impaired when tested on an indirect delayed response task (a cue indicates the position of the baited foodwell previous to delay). These results also indicate that a general memory impairment is not involved in the frontal deficit. Buddington et al. (1969), using a similar procedure, indicates that dorsolateral damage in the squirrel monkey results in an increased dependence upon external cues for the guidance of behavior during response formation. Furthermore Stamm (1970), testing macaques on three different delayed alternation tasks requiring differential use of kinesthetic information, found that the tasks which relied most strongly on kinesthetic information gave rise to the largest deficits. Finally, on the basis of a series of experimental conditions involving an alternation of stimulus and response requirements, Wegener and Stamm (1966) conclude that the dorsolateral surface plays an important role in proprioceptive integration, especially as related to spatial orientation.

Performance on certain operant tasks after frontal ablation also indicates an inability to regulate response patterns. Thus, over responding on DRL and FI schedules of reinforcement have been reported (Glickstein et al., 1964; Pribram, 1959). However, as was the case with septal animals, deficits on DRL, and in addition on delayed response, can be mitigated if the delay requirements are progressively, rather than abruptly increased (Stamm, 1964; Divac and Warren, 1971).

Based on the totality of these findings, I would like to rephrase Goldman and Rosvold's hypothesis. It appears that dl cortex, primarily in the region of the principal sulcus is, in fact, involved in the utilization of proprioceptive information. However, I do not believe the mechanism to be specifically mnemonic in nature, since poor response regulation occurs on the operant schedules noted above, and also on spatial reversal tasks. These tasks would not appear to be directly dependent on memory mechanisms. Rather, I would like to propose that after dl ablation primates have difficulty in regulating response patterns when pertinent exteroceptive stimuli are lacking. Thus, these surgical preparations cannot centrally integrate feedback from previous responses in order to regulate the formation of new response patterns.

Damage to the orbital surface of the frontal lobes leads to poor performance during the reversal of an object discrimination, increases in resistance to extinction, and poor differentiation (different responses are related to different stimuli) learning (Mishkin, 1964; Butters and Rosvold, 1968; Butter, 1969; Mishkin et al., 1969). These deficits are considered to be primarily perseverative in nature, and

due to an inability to suppress strong response tendencies both for preferences and aversions (Mishkin, 1964; Mishkin et al., 1969; McEnany and Butter, 1969).

However, due to the close anatomical relationship between the dorsolateral and orbital cortex, it is not surprising that there is some overlap in the pattern of deficits observed between the two. In addition, there would appear to be a zone of transition between the two areas (Mishkin et al., 1969). Thus, Divac (1967) has pointed out that although orbital ablations produce severe deficits in object discrimination reversal, they may also produce impairments on delayed alternation. In addition, Butter (1969) has shown that ablation of the posteromedial sector of the orbital frontal cortex increases resistance to extinction and leads to deficits during the reversal of an object discrimination, while ablation of the lateral orbital surface produces deficient performance on the reversal of a spatial discrimination.

Thus, the two major sectors of the primate FAC appear to play a strong role in response regulatory processes. In addition, the overall spectrum of deficits produced by these two sectors is quite similar to those that occur after septal ablation, and in addition, are related to behavioral patterns seen after hippocampal injury (Douglas, 1967; Kimble, 1968).

Carnivores

We should recall that gyrus preceus is the carnivore analogue to dl cortex in primates. The orbital gyri in the two species are analogous. Most of the work dealing with frontal lobe function in carnivores

has stressed the role of the preoreal gyrus, however, some studies have investigated the orbital gyrus.

Cats and dogs have repeatedly been found to be deficient on delayed response tests after frontal ablation, specifically after those ablations involving gyrus preoreus. However, this deficit is transient, and less severe than that found in primates after dl damage. Furthermore, dogs appear to learn the response by properly orienting themselves in space during the delay period, while cats have been shown to perform successfully, at least for short delays, without utilizing this solution (Konorski and Lawicka, 1964; Brutowski, 1965; Warren, 1964; Divac and Warren, 1971; Divac, 1971).

Warren (1964) found that large frontal ablations in cats permanently impaired performance on object and spatial reversal problems. The effect is more severe for spatial reversal. Warren et al. (1969) found similar results in the cat when lesions were restricted to gyrus preoreus. In addition, the extent of the deficit was positively correlated with the degree of degeneration in nucleus medialis dorsalis of the thalamus. Furthermore, ablation of the pericruciate area, which lies in the vicinity of gyrus preoreus, did not lead to such impairments. In addition, Warren et al. (1969) found that cats with preoreal ablation were not significantly impaired on a go, no-go object discrimination, and Warren (1964) found the same results for a successive object discrimination. Together these findings indicate, at least for the cat, that after preoreal ablation animals have difficulty in modifying response patterns; the impairments being greater on spatial tasks, and not simply due to a loss in inhibitory control.

Further evidence indicating that carnivores with proreal ablation have difficulty in regulating response patterns, especially when exteroceptive stimuli are lacking, is supplied by a study conducted by Wagman (1968). She found that proreal damaged cats were deficient when tested on the retention of a 6:1 counting schedule learned preoperatively. Furthermore, the presentation of a cue light indicating when the designated count had been reached alleviated the impairment.

Teitelbaum (1964) found that both proreal and hippocampal ablations impaired the reversal of a tactile discrimination in cats. Teitelbaum suggests that these structures are part of one system, since the effects produced by either lesion alone were remarkably similar, and both structures ablated together did not lead to an additive effect.

In previous sections it was indicated that the orbital gyrus of the prefrontal lobes is related to the neural mechanisms regulating emotional states. This conclusion was reached primarily on the basis of physiological and anatomical studies indicating a close relation between the orbital surface, and amygdaloid hypothalamic mechanisms. Our discussion of the orbital gyrus in primates, however, indicated a strong role played by this area in response regulation. Recent studies in both cats and dogs have indicated that the orbital gyrus is involved in response modulation, especially when related to motivational and emotional factors.

Brutowski (1964, 1965) utilizing both classical and instrumental procedures in a variety of differentiation tasks, and reinforcing responses with both positive and negative reinforcement, found that

previously inhibitory CR's became disinhibited after frontal ablation. Furthermore, he found increased autonomic and motor reactivity to emotional and sensory stimuli. In addition, there was a general increase in defensive-aggressive behavior in situations which utilized noxious stimulation. Brutowski postulates that these alterations in inhibitory processes are due to emotional hyperexcitation. These general disinhibitory effects have since been replicated (Wolf, 1967; Mayers et al., 1971) and the focus for the deficit appears to be within the orbital gyrus (Brutowski, 1964, 1965; Mayers et al., 1971).

Brutowski (1965) points out that frontal damaged monkeys and dogs are impaired on various instrumental avoidance tasks, and that the posteromedial orbital cortex may be involved in these deficits. In support of these findings Cornwell (1966) has shown that cats with orbitofrontal ablations are impaired in the acquisition of a one-way active avoidance task.

Rodents

Early anatomical studies indicated that the frontal poles of the rat brain were analogous to the FAC in higher forms (Krieg, 1946). However, frontopolar ablations in rats generally do not lead to the pattern of deficits seen after FAC ablation in higher forms (Divac, 1971; Srebro and Divac, 1972).

Recent anatomical work by Leonard (1969) has shown that precollosal midline cortex, rather than frontopolar cortex, is the projection site of nucleus medialis dorsalis of the thalamus of the rat. Her results strongly suggest that this cortex is the analogue of FAC.

Damage to this area in the rat does lead to impairments that are similar, though perhaps less severe than those produced by FAC ablation in cats and monkeys. Thompson and Langer (1963) and Barker and Thomas (1966) found that ablation of the anterior midline cortex in the rat leads to deficits in spatial reversal and alternation respectively. Furthermore, Divac (1971) found that whereas ablation of the precollosal midline cortex in the rat impaired retention of a spatial reversal, ablation of the frontal poles did not.

Some Comments on Frontal Lobe Function in Man

Early studies stressed personality changes after frontal lobotomy in man. These modifications included increased or decreased activity, restlessness and irritability, more vigorous reactions to external stimuli, less depth of feeling, and increases in egocentrism and extroversion (Mettler, 1949; Freeman and Watts, 1950). However, as far as performance on general tests of intelligence was concerned, there did not appear to be any drastic changes after frontal lobe damage or disconnection (Mettler, 1949; Freeman and Watts, 1950). Nevertheless, utilization of past experience or information gained from consequences of action for the planning of future behavior appeared to be disturbed (Freeman and Watts, 1950). Freeman and Watts concluded that damage to FAC in man impairs initiation of constructive acts due to an inability to visualize what effect one's actions will have upon himself and the environment. On the other hand, Hutton (1943) emphasizes that while normal humans behave on the basis of stimuli which are derived both externally and internally, the frontal damaged patient, while capable

of responding to stimulation from without, cannot utilize stimuli derived from within. Thus, even in these early studies emphasis was already developing that indicated that frontal damage in man leads to poor behavioral planning due mainly to a lack of utilization of feedback information relative to the consequences of action.

More recently, Teuber (1959, 1964) has shown that damage to the frontal area in man does not produce significant losses on standard intelligence tests, and that performance on the hidden figure test showed them neither better nor worse than subjects with lesions elsewhere in the brain. He found similar results on certain problem solving tasks, including concept formation.

One deficit Teuber does find to be associated with frontal lobe damage concerns the perception of the upright. Frontal ablations in man impair the ability to set a tilted luminous rod in its upright position when the patient is seated in a darkened room. However, for the effect to occur, the subject's body must also be tilted. These results indicate impaired utilization of proprioceptive or vestibular cues, especially as they are related to feedback necessary to localize oneself properly in space.

Furthermore, some evidence has developed to indicate that pre-frontal ablation in man leads to an inability to program motor acts based on verbal, visual, and signalled instructions. Thus, Luria (1964, 1965, 1966) found that frontal patients could not perform sequential tapping tasks to specific rhythms, nor copy sequences of objects. The subject appears to persevere with response patterns developed early

in the sequence. In most cases these patients understand the instructions and objectives of the task. These results indicate that frontal damage in humans can lead to a disruption of the mechanisms involved in the programming of motor acts. Luria (1965, 1966) emphasizes that these disturbances are due to impairments of regulatory mechanisms which enable the outcome of action to be compared with the initial intention.

In agreement with the above results, Milner (1964) found that frontal damage in human subjects caused severe impairments on the Wisconsin Card Sorting Test. This effect did not appear to be due to a general intellectual impairment, since subjects with parietal and temporal damage showed greater losses on IQ tests but performed efficiently on this task. Rather, the impairment appears to be due to an inability to modify response patterns when feedback contingencies relative to the correct response are changed. Furthermore, the subjects are able to verbalize the requirements of the task but, nevertheless, are unable to use this verbalization as a guide to action.

Human subjects with frontal damage also show a similar loss of response flexibility on certain maze tasks (Konorski, 1967; Milner, 1964; Ackerly, 1964). In most cases noted above, the largest behavioral changes occur after destruction of dorsolateral cortex (Milner, 1964; Luria, 1966; Konorski, 1967).

Girgis (1971) presents a wealth of provocative evidence which indicates that damage to the orbital surface of the frontal lobe in humans leads to changes in emotionality, without greatly impairing the response modulatory characteristics so often seen after dorsolateral

damage. Indeed, recent psychosurgical techniques (Girgis, 1971) have shown that restricted lesions limited to orbital cortex greatly improves many depressive states, when other methods (e.g., drugs, shock treatments, psychotherapy) have failed. Furthermore, Girgis emphasizes the importance of two neuronal circuits; one extends from the posteromedial orbital area to the mammillary bodies and the anterior thalamic nuclear groups via the descending columns of the fornix, the other extends from the more lateral portions of orbital cortex to the amygdala.

Regulatory Role of Frontal Cortex on Sensory Processes

The intimate anatomical relations between the FAC and sensory systems via cortical projections, and FAC connections with the reticular formation by way of the medial forebrain bundle and the intralaminar and midline nuclei of the thalamus indicate that the frontal lobes may play an important role in sensory integration and regulation. Indeed, there is some behavioral evidence in support of this view.

Early work by Malmö (1942) showed that delayed response impairments in monkeys could be reduced if during the delay period, the experimental chamber was darkened. This finding (though probably contributing to the delayed response deficit, is not the main cause of this impairment (Divac, 1969; Warren and Akert, 1964)), indicated that frontally ablated animals may be more reactive to novel sensory stimuli, and thus more easily distracted. This assumption has been consistently supported (Warren and Akert, 1964; Brutowski, 1965; Grueninger and Pribram, 1969).

In addition, though frontally ablated animals are not impaired on

simple discrimination tasks, more complex sensory discriminations, especially when they are related to differential response patterns, are often difficult to solve by the frontal animal. For example, monkeys with prefrontal ablations are inferior when compared to controls on a multiple choice test (Pribram, 1959; Pribram et al., 1964). In this task, the number of objects the animal must discriminate at a given time increases over trials. Similarly, Wegener and Stamm (1966) found that macaques have difficulty in learning a successive discrimination when this task is interspersed with other tasks which require response modification. Furthermore, Butler and Eayrs (1969) found that macaques with lateral frontal ablations were impaired on a conditional reaction. In this task the animal must shift its response between two stimuli conditional on the occurrence of yet a third stimulus. Butler and Eayrs hypothesize that frontal animals are unable to regulate response patterns when more than one channel of sensory information must be utilized. This finding is supported by work with humans which has shown an impairment by frontal patients on the category test of the Halstead Battery. In this task objects must be grouped into categories based on multiple stimulus attributes (Halstead, 1947; Rylander, 1939; Reitan, 1964).

These results indicate, on the whole, that while simple discriminations do not appear to be disturbed after frontal ablation, integrative sensory functions, especially as they are related to response regulatory processes are often disturbed after frontal ablation. (See Tables I-2, I-3, and I-4 for a summary of the behavioral impairments after frontal ablation.)

TABLE I-2

BEHAVIORAL CHANGES FOLLOWING DAMAGE TO THE FRONTOCORTICAL
AREAS IN HUMANS AND SIMIANS

Dorsolateral CortexOrbital CortexHumans

IQ and general intelligence
normal

IQ and general intelligence
normal

Inability to perceive the "up-
right" when body is tilted and
external cues are eliminated

Improvement in patients with
severe depressive states

Perseverate motor patterns that
develop early on such tasks as
drawing a series of patterns and
tapping to specific rhythms

Various emotionality changes

Poor performance on card sorting
test

Poor performance on category test
of the Halstead Battery and Form-
board Test

Poor differentiation learning

Simians

Hyperdistractability

Increased resistance to operant
extinction

Deficient performance on
delayed response (direct)

Deficient performance on the
reversal of object and spatial
discriminations

Deficient performance on the
reversal of a spatial discrimin-
ation

Poor differentiation learning

Poor performance on seriatum
problems

Normal performance on delayed
response

TABLE I-2 (continued)

Dorsolateral Cortex	Orbital Cortex
<u>Simians</u>	
Increasingly poor performance on tasks which increasingly depend on kinesthetic cues for their solution	Normal discrimination learning
Overrespond on DRL and FI schedules of reinforcement	
Impairment of the formation of conditional reactions	
Normal performance on indirect (cued) delayed response	
Learning set performance normal	
Normal discrimination learning (simultaneous and successive)	

TABLE I-3

BEHAVIORAL CHANGES FOLLOWING DAMAGE TO THE
FRONTOCORTICAL AREAS IN CARNIVORES

<u>Proneal Gyrus</u>	<u>Orbital Gyrus</u>
Transient deficits on delayed response	Disinhibition of previously inhibitory conditioned responses
Deficient performance on the reversal of a spatial or object discrimination, deficiency is greater for the spatial task	Increased autonomic and motoric responses to aversive stimuli
Poor performance on counting schedule (cue eliminates deficit)	Deficit in the acquisition of a one-way avoidance response
Normal performance on go, no-go, successive, and simultaneous object discriminations	

TABLE I-4

BEHAVIORAL CHANGES FOLLOWING DAMAGE TO THE
FRONTOCORTICAL AREAS IN RODENTS

Precollosal Midline Cortex

Poor performance on the reversal of a spatial discrimination

Poor performance on spatial alternation

G. A LINK BETWEEN FRONTO-CORTICAL AND LIMBIC

MECHANISMS: THE HIPPOCAMPUS

The hippocampus is a comparatively simple paleo-cortical structure composed of three main cellular layers. The most prominent cells of the hippocampus are the pyramidal cells, the axons of which form the hippocampal efferent system (Raisman et al., 1965). Based on the cytoarchitectonic variation in different parts of the hippocampus, especially the pyramidal layer, Lorente de No has subdivided the hippocampus into four fields denoted CA₁, CA₂, CA₃ and CA₄. A great deal of the cortical sensory input integrated in the FAC travels via the entorhinal area and the perforant pathway to area CA₁ of the hippocampus and to the peripheral dendrites of the granule cells in the stratum moleculare of the dentate gyrus (Raisman et al., 1965; Van Hoesen, Pandya, and Butters, 1972). The dentate granule cells give rise to "mossy fibers" which synapse on the giant pyramids of hippocampal areas CA₃ and CA₄. "Shaeffer collaterals" arise from the pyramids of CA₃ and CA₄ to act upon area CA₁, closing the circuit (Raisman et al., 1965, 1966).

Olds (1969) has analyzed this system by indicating that cortical sensory input enters the hippocampus through the dentate gyrus, is stored and/or transformed into appropriate motor patterns based on this input in hippocampal areas CA₃ and CA₄, and the activity in CA₁ transforms these sensory motor patterns into "output codes" for appropriate motor behavior. However, since the cortical sensory input also enters hippocampal area CA₁ (Raisman et al., 1965, 1966), we have here a feedback mechanism in area CA₁ whereby the motor command stored in CA₃ and

CA₄ can be matched against fluctuating input signals in a manner similar to the servomechanisms discussed in previous sections, thus allowing the consequences of motor program activation to be evaluated.

To digress for a moment, we should recall that the extreme medial septum and dorsal diagonal band nucleus pace the hippocampal theta rhythm (highly correlated with voluntary movement and orientation which will be discussed in more detail shortly) via afferents through the dorsal fornix to hippocampal area CA₁. Hippocampal area CA₁ in turn projects back onto this portion of the septum. Furthermore, the more lateral portions of the medial septal nucleus have reciprocal connections with hippocampal area CA₃ and CA₄ by way of the fimbria.

In addition, both the septum and the hippocampus are related to the reticular formation and the extrapyramidal motor centers of the brainstem by way of the limbic-midbrain circuit of Nauta (Nauta, 1958). By way of the reticular system additional integrated sensory information becomes available to these forebrain structures. These forebrain regions in addition, can act back upon the reticular system so as to rechannel sensory input. In addition, this forebrain system may prime brainstem motor mechanisms either through the reticulo-spinal system or by direct action on extrapyramidal motor centers.

Furthermore, Votaw (1959, 1960) has supplied evidence for the existence of a septal-hippocampal-entorhinal path of conduction. It would be of interest to speculate if this pathway could not perhaps provide a channel through which septo-hippocampal integrations could be returned to the frontal cortical areas so as to complete the feedback loop. Figure I-2 summarizes schematically what I have said to this point.

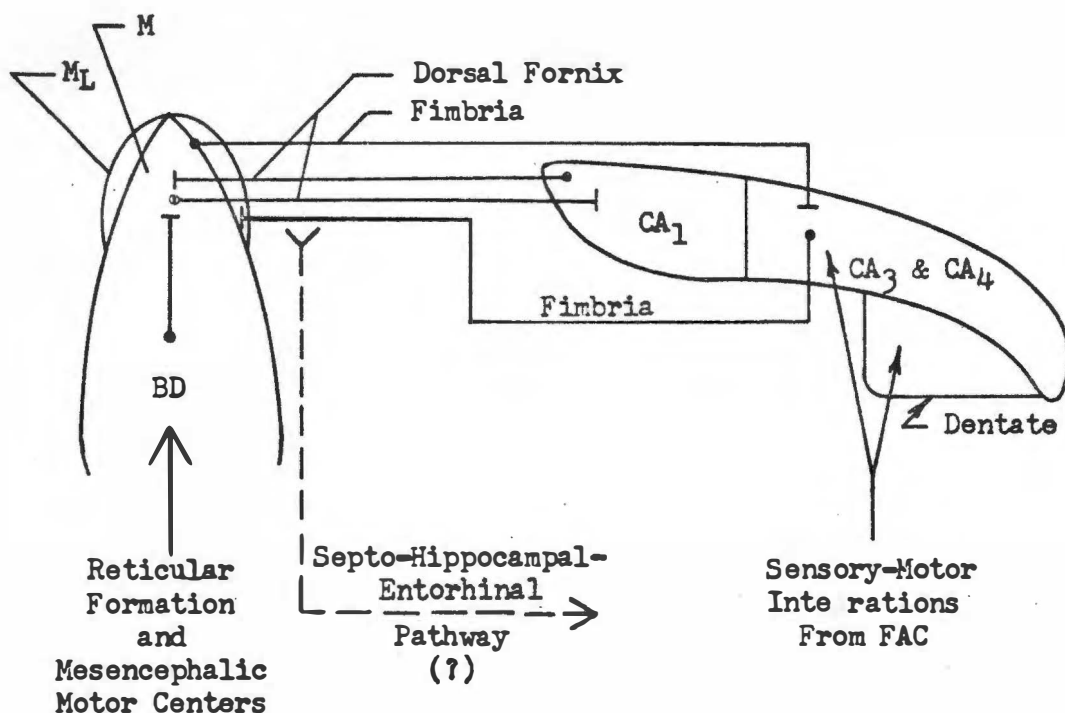


Figure I-2. Schematic representation of the neural relations between the septum, hippocampus, and FAC.

CA₁, CA₂, CA₃, CA₄ = Cytoarchitectonic hippocampal fields
 BD = Diagonal band of Broca
 M = Medial septum along the midline
 M_L = Lateral portion of medial septal nucleus
 Dentate = Dentate gyrus of hippocampus
 FAC = Frontal association cortex

Damage to the hippocampus in a variety of species leads to deficits that are similar to those found after frontal cortical damage and damage to the septum. Thus, damage to the hippocampus increases resistance to extinction, decreases spontaneous alternation and leads to poor performance on the reversal of both object and spatial discrimination. There are no impairments on simple discriminations of various types (Kimble, 1968; Douglas, 1967; Dalland, 1970). Furthermore, deficits on delayed response and delayed alternation have frequently been found after hippocampal ablation (Brutowski, 1965; Douglas, 1967). Whether or not hippocampal ablation gives rise to poor performance on a DRL schedule of reinforcement has not yet been clearly determined (Douglas, 1967; Ellen and Aitken, 1970). Within the hippocampus proper, Rosvold and Szwarcbart (1964) present data which indicate that damage to cytoarchitectonic fields CA₁ and CA₄ is more highly correlated with poor performance on delayed alternation in monkeys than damage to other areas. These various deficits found after hippocampal ablation do not appear to be due simply to a disruption of inhibitory mechanisms, since hippocampal animals inhibit responses on no-go trials of a go, no-go single alternation equally well, if not better than normal animals (Means et al., 1970).

Recent studies have indicated that normal animals use extra-maze cues (when available) in solving various spatial discriminations, and only switch to response cues during over-training (Means and Douglas, 1970). However, hippocampal animals use response cues rather than extra-maze cues throughout training (Means and Douglas, 1970; Ellen and Bate, 1970). Furthermore, Dalland (1970), studying spontaneous

alternation behavior in rats, found that hippocampal animals persevere responses rather than places (response perseveration as contrasted with stimulus perseveration), and Silveria and Kimble (1968) have shown that on the reversal of a brightness discrimination, a task where response cues are irrelevant, hippocampally ablated animals persevere responses rather than choices to the acquired stimulus. Since hippocampal animals have no difficulty in the acquisition of most motor responses, and may not show perseveration on tasks that do not require the modification of a prepotent response (Winocur and Mills, 1969) it would appear that the formation of motor programs is not disturbed after hippocampal ablation. Rather, what appears to be the case is that once a motor program is formed, it is not modified; thus the animal becomes "stuck" on a particular mode of response, and thus shows response perseveration.

Most of the experiments discussed above compared the effects of septal and hippocampal ablation. It is now important to contrast the effects of the two. As was mentioned earlier in our discussion, septal ablation also leads to strong perseverative tendencies. However, in the case of the septal animal, perseveration is not always dependent upon the modification of prepotent response tendencies (Winocur and Mills, 1969; Kelsey and Grossman, 1971). In addition, perseveration after septal ablation would appear to be of the stimulus type (place perseveration) rather than the response type found after hippocampal ablation, and septal animals are more prone to utilize extra-maze cues in a Dashiell maze rather than response cues (Clody and Carlton, 1969; Dalland, 1970; Ellen and Bate, 1970). These findings add further support for the proposal of Ellen and Butter (1969) that septal ablation leads to impaired utilization of response generated cues.

The Hippocampal Theta Rhythm

The theta rhythm is a slow synchronized electrical signal (4-7 Hz) which can be recorded from the hippocampus during various organismic states. The integrity of the hippocampal theta response depends on afferents derived from the medial septum and diagonal band, presumably originating in the reticular formation of the mesencephalon. Theta activity arises in the pyramidal cells of the dorsal hippocampus and is most prominent in fields CA₁ and CA₄ of the hippocampus (Petsche et al., 1965; Vanderwolf, 1969; Bennett, 1971). The dentate gyrus is typically dominated by fast activity (Vanderwolf, 1971).

Bennett (1971) after reviewing the literature dealing with the behavioral correlates of hippocampal theta concludes that the occurrence of theta is probably most indicative of organismic orientation towards meaningful environmental stimuli. He suggests that the theta response is indicative of situations in which a comparison between incoming and formerly stored information takes place. However, Vanderwolf (1969, 1971) has shown that theta activity preceeds and accompanies voluntary types of movement. Vanderwolf also found that stimulation of the dentate gyrus suppressed theta activity and caused cessation of ongoing voluntary movement. It is my belief that both of the processes (orientation and voluntary movement) are strongly indicative of the roles the hippocampus might play in behavior. Finally, hippocampal theta does not appear to be correlated with the mere acquisition of reinforcement (Vanderwolf, 1971; Ball and Gray, 1971).

More recently (Gray, 1972) it has been found that septal driving of the hippocampal theta response during acquisition of a locomotor

task subsequently increased resistance to extinction. However, if theta-driving was applied during extinction, extinction was facilitated. In addition, the higher the mean theta frequencies elicited, the greater the effects of the driving. Moreover, blockage of hippocampal theta during acquisition subsequently reduced resistance to extinction (Gray et al., 1972). Gray explains these effects in terms of frustrative non-reward. However, if we take into account the data discussed above, an alternative and perhaps better explanation is available. I believe that the occurrence of hippocampal theta may be related to the modification of motor programs, based on the consequences of action. If this were the case, enhancement of theta during acquisition would be indicative of the development of a "strong" motor program which would be greatly resistant to the effects of extinction. On the other hand, enhancement of theta during extinction could be interpreted as facilitating the extinction effect via the rapid formation of a new motor program based on the consequences of action (e.g., absence of reward). In addition, blockage of hippocampal theta during acquisition would lead to the formation of a "weak" motor program, which would be easily disrupted by the effects of extinction.

CHAPTER II

A MODEL OF RESPONSE CONTROL

To recapitulate, the dorsolateral frontal cortex, the medial septum, and the hippocampus are reciprocally related neuroanatomically, and have similar afferent and efferent connections with various cortical and subcortical centers. In addition, the behavioral deficits observed after destruction of these areas are highly similar and would appear to be related to response regulatory processes. Based on the information discussed in previous sections, it would not seem unreasonable to assume that these three regions are part of a single neural system involved with the formulation and modification of motor programs based on feedback information derived from the consequences of action.

Since the frontal cortical areas integrate sensory information from all modalities with motor information derived from the primary and secondary motor areas, I would like to suggest that motor programs are formulated in the prefrontal cortical areas. The formulation of these motor programs is based on the available sensory information, the motivational and emotional state of the organism (integrated in orbital cortex), and previous experiential factors which dictate the organism's expectations. The area lying in the region of the principal sulcus of the dorsolateral frontal cortex would appear to be of particular importance for the assessment of proprioceptive information for the motor program. Once a motor program is formulated, it is transmitted via the perforant pathway to the hippocampus and is temporarily stored in hippocampal area CA₃. Hippocampal area CA₃ can thus be considered

the memory mechanism of the system since it stores the trace of the original motor program. Initiation of the motor program occurs when the FAC activates motor mechanisms in the precentral gyrus which in turn emits an efferent signal. The efferent signal causes an efferent copy of the trace stored in CA_3 to be transferred to area CA_1 of the hippocampus. The efferent signal also leads to response initiation and its concurrent reafferent feedback. This reafferent feedback is transmitted through spiral mechanisms to mesencephalic motor centers. From these midbrain centers the information is carried to (1) the motor cortex, and (2) the median forebrain bundle (MFB). From these points the reafferent information is transmitted to either the frontal cortical areas or the medial septal nucleus respectively. The medial septal nucleus transmits reafference to CA_1 of the hippocampus where it is compared with the efferent copy derived from the CA_3 trace. If the consequences of responding are congruent with the anticipated expectations and therefore the initial motor program, the reafferent and efferent copies will match and the response sequence will be terminated. However, if the anticipated consequences of response are not attained, reafference and efferent copy will not match, and the mechanisms involved in formulating a new motor program are set into motion. Under this condition, the fronto-cortical areas are signalled as to the inappropriateness of the previous response pattern via septo-hippocampal-entorhinal pathways, and based on the stimulus information available, and especially the reafference which was just transmitted to the frontal cortical areas, a new motor program is written, transmitted to CA_3 of the hippocampus and the process begins anew, and continues until efferent

copy and reafference information match thus terminating the response sequence. Figure II-1 is a schematic representation of this model.

I have stressed the importance of reafferent information in this analysis for the sake of simplicity, it should be made clear, however, that other sources of stimulus feedback information are utilized for response control, especially by the hippocampus and FAC. However, it appears from the research that is currently available that the prime role of the medial portion of the septum is to transmit reafferent information to hippocampal area CA₁.

From this analysis it can be seen that destruction of the medial septum should produce perseveration mainly in situations that are largely lacking in exteroceptive stimuli. In this situation, motor programs are reformulated mainly on the basis of proprioceptive feedback, and since the septum, as indicated by the model, is one of the prime transmitters of this information to CA₁ of the hippocampus, response regulation under these conditions should be inferior to that of normals. As we have seen, this is in fact the case; septal perseveration occurs when the animal must rely on response feedback for response regulation, but does not occur in cases where exteroceptive stimuli are present (e.g., object reversal, cued DRL). In addition, the model would also predict stimulus perseveration in septal animals mainly due to an overreliance on stimulus cues, and an inability to utilize response cues.

Destruction of the hippocampus has been shown to lead to perseveration both in the presence and absence of exteroceptive cues. However,

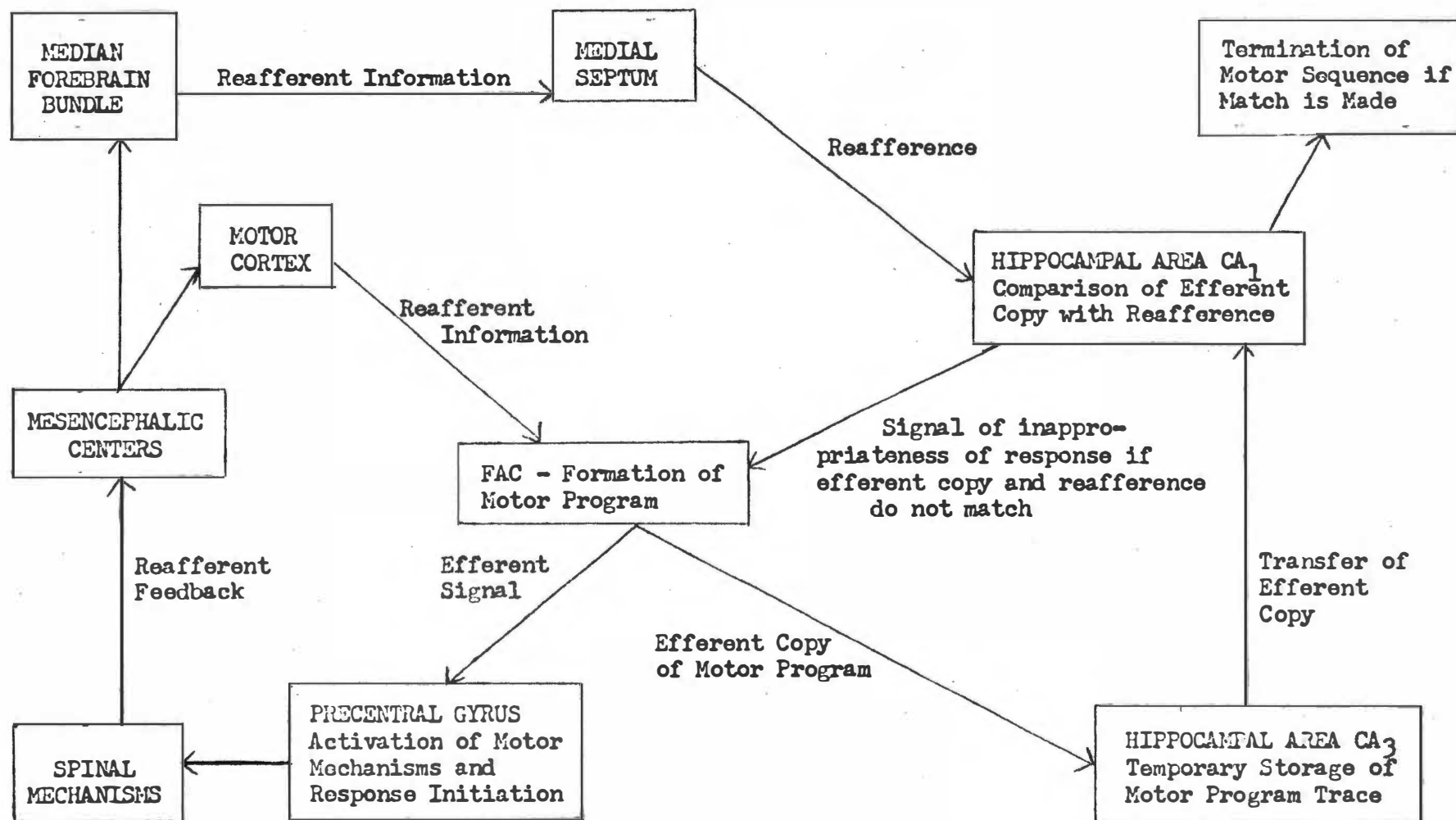


Figure II-1. Schematic representation of model of response control presented in text.

perseveration in hippocampally ablated animals is of the response type rather than the stimulus type found after septal ablation. This is the case since in the absence of the hippocampus, motor programs can be written by the frontal cortex, but their modification is impaired since the hippocampus, as depicted by our model, is the region where the multisensory consequences of action are compared with the initial intentions, deviations from expectations informing the frontal cortical areas of error and leading to the reformulation of response patterns. Destruction of the hippocampus impairs these reformulation processes, and the organism tends to persevere initial response patterns.

Damage to the dorsolateral surface of the FAC in and around the principal sulcus, gives rise to a loss of response regulation mainly in tasks that depend on proprioceptive information. Our model has stressed the importance of this region for the utilization of proprioceptive feedback in the formulation of motor programs. Larger frontal lesions lead to more severe response deficits on spatial and non-spatial problems due to the elimination of appropriate sensory motor integrative processes in the formulation of response patterns.

This model, of course, is not complete. Overlap of function must exist between these structures, and other brain regions probably subserve somewhat similar functions, since a total loss of response regulation never occurs after destruction to any of these areas. In many cases these surgical preparations can reacquire appropriate response control given extended periods of training.

This fronto-cortical-limbic model may also be involved in the differential biasing and/or priming of sensory and motor mechanisms.

The transmission of reafferent information via the medial septum to hippocampal area CA₁, in addition to its role described above, is also conceived to activate neural mechanisms in the hippocampus which in turn transmits information back through CA₁ circuitry to the medial septum. From this point subcortical sensory mechanisms may be differentially inhibited or excited either directly, or via MFB connections with the reticular formation. Similarly, extrapyramidal structures of the mesencephalon and even spinal motor mechanisms can be tuned by information passed from the septum through MFB pathways to the mesencephalon. In this way the organism can orient itself to anticipated meaningful stimulus input.

In previous sections I have indicated that the hippocampal theta rhythm is highly correlated with both the orienting response and voluntary movement. In addition, the hippocampal theta response is dependent on pathways running from the medial septum to hippocampal area CA₁. One can now see why this is the case. Reafferent information traveling from the medial septum to hippocampal area CA₁ is compared with the efferent copy of the motor program. It is the neural mechanisms involved in this comparison process that I believe are correlated with hippocampal theta. The correlation with voluntary movement is seen to be a secondary consequence of reafference transmission (reafference being dependent on movement). Secondly, this same pathway activates neural circuits in the hippocampus which send commands back to the septum for differential priming of sensory and motor centers, leading to the orienting response.

The model does not account for all the data available in the field, and is not intended to. Other neural regions should have been included, since it is clear both neuroanatomically and functionally, that they play a significant role in this system (e.g., caudate nucleus (Divac, 1971); amygdala (Douglas, 1967)). However, I do believe that many of the ideas expressed above are testable, and should lead to many years of fruitful investigation.

CHAPTER III

THE EXPERIMENT

The behavioral effects observed in a variety of species after frontal or septal ablation were shown to be strikingly similar. It has even been contended that the septum and the frontal cortical areas are members of a specific neuronal system involved in response regulatory processes (e.g., Butters and Rosvold, 1968). However, there have been few studies which have compared the effects of these lesions within the same experimental paradigm and under identical laboratory conditions. The present experiment was conducted, in part, in order to make such a comparison. The performance of cats with septal and frontal ablation was compared on the acquisition and maintenance of appropriate response control on a differential reinforcement of low rates of response 40 second schedule (DRL 40).

The specific task (DRL) and species (cat) were chosen for a variety of reasons. First, there is very little information available dealing with the performance of cats on DRL schedules of reinforcement, whether they be normal or brain damaged. In fact, this investigator was able to uncover only two such studies (Isaacson et al., 1968; Bennett and Gottfried, 1970). In both of these studies only the most superficial analysis of the data was attempted. Thus, it appeared important to determine the ability of brain damaged cats, and cats in general to acquire a behavioral repertoire consistent with efficient DRL performance. Second, DRL performance severely deteriorates after septal

ablation in rats (Ellen and Butter, 1969; MacDougal et al., 1969a; Agnew and Meyer, 1971) and after frontal ablation in primates (Glickstein et al., 1964). However, there is no data available pertaining to the behavior of cats with frontal or septal ablation on this schedule.

Stamm (1964) found that monkeys with frontal ablation were able to acquire response control on a DRL schedule if the delay interval was gradually, rather than abruptly increased. Caplan and Stamm (1967) found similar effects in septal ablated rats. In addition, Ellen and Butter (1969) found that DRL deficits are mitigated in septal rats, if an exteroceptive cue is presented at the end of the delay interval (informing the animal of the availability of reinforcement). These results have led some investigators to postulate that deficits on DRL are due to an inefficient utilization of feedback from response produced cues (Ellen and Butter, 1969; Van Hoesen et al., 1972b; Wagman, 1968). The reasoning of these investigators rests upon the assumption that efficient DRL performance depends upon the organization and maintenance of collateral behavior, which in turn facilitates timing behavior by pacing the temporal interval between responses.

However, whether or not collateral behavior is necessary for efficient performance on DRL has not yet been clearly determined. For example, Wilson and Keller (1953) emphasized that changes in response rate during DRL acquisition results from the partial extinction of bar pressing, and the strengthening of behavior that is incompatible with it (i.e., collateral behavior). Wilson and Keller maintain that:

The strength of this collateral behavior is maintained through conditioned reinforcers provided by the stimulation attending the responses which make up a crude chain of behavior. (Wilson and Keller, 1953, pp. 192-193)

These investigators did find that their animals developed easily recognizable and predictable forms of collateral behavior. In contrast, some investigators stress that the formation of a temporal discrimination is not dependent on the formation of collateral behavior, but is due rather to the recalibration of an internal clock. Thus, Anger (1956) and Kelleher et al. (1959) found that rats could accurately time intervals of 20 seconds or more in the absence of the development of chains of overt behavior.

The most recent investigations have indicated, that while collateral behavior is utilized and facilitates performance on DRL, it is not the only mechanism utilized for accurate timing. Thus, Laties et al. (1969) found high correlations (.63-.89) between amount of collateral behavior and number of reinforcements obtained on a DRL schedule. Furthermore, these investigators found that if they blocked collateral behavior, efficiency on DRL was markedly reduced. However, Laties et al. stress that these correlations are not unity, thus suggesting that when collateral behavior is present, it is not the only factor controlling lever pressing behavior. Other investigators have also found that the presence of collateral behavior is highly correlated with efficient DRL performance (Hodos et al., 1962; Kramer and Rilling, 1970).

It would further follow then, that if septal and preoreal ablated cats have difficulty in utilizing feedback information derived from responses, and if efficient DRL performance in cats is dependent on

the utilization of such cues, then the response distributions generated by our operated animals should be similar, and their performance should be inferior to controls. In addition, during the presentation of an exteroceptive cue indicating the end of the interval, performance should be enhanced. However, if any of these conditions are not met, then it could be concluded that, either DRL acquisition in cats is not dependent on the utilization of response produced cues, but on other factors which may or may not be selectively impaired by specific surgical intervention; or that septal or preorel animals, but not both, have difficulty in utilizing response generated cues. It is expected that the form of the response distributions generated by these animals will enable us to narrow the possibilities.

A. METHOD

Subjects

The subjects were 25 adult cats (11 male, 14 female) ranging in weight between 1.8 - 3.8 kg. (mean 2.8 kg.). All animals were housed in individual cages and maintained on a standard diet of commercial cat food. They were assigned to one of four groups, the sexes being equally distributed in each. Seven animals served as normal controls, two animals sustained damage to the cortical areas around gyrus preoreus (coronal and sigmoid gyri) and served as operated controls, eight underwent bilateral ablation of gyrus preoreus, and eight received septal lesions. One control (C-55) and one septal (S-20) subject had prior experience in active avoidance, the remainder were experimentally naive.

Surgery and Histology

All surgery was performed aseptically 1 - 14 months (mean 6.3 months) prior to the experiment. The animals were anesthetized with sodium pentobarbital (60 mg./kg.), placed in a stereotaxic head holder, and one stage bilateral removals of the designated area were performed. Two of the septal ablations were produced by aspiration (S-20, S-71); the remaining six were produced electrolytically. All proreal damage was achieved through subpial aspiration.

In the case of the septal lesions, a large craniotomy extending 2 mm. bilaterally beginning at the posterior border of the frontal sinus and extending back 2 mm. caudal to bregma was performed. For the aspirated septal lesions, the dura was incised and folded back, the hemispheres were retracted and the genu of the corpus collosum was visualized. A glass pipette was extended through the genu and suction was applied bilaterally. For the electrolytic septal lesions, a stainless steel 22 guage needle electrode, insulated except for 1 mm. at the tip was inserted into the brain at 6 points bilaterally 1 mm. from the midline. The three A-P coordinates were 14.5, 16, and 18. At plane A-P 14.5 the D-V placements were +2 and +4, at planes A-P 16 and 18 the D-V placements were +1 and +3. Placements were based on the Snider and Niemer Stereotaxic Atlas of the Cat Brain (1961). Electrolysis was produced by 3.5 ma anodal current applied for 45 seconds.

In the case of the proreal ablations, a large craniotomy was performed similar to the one used for the septal ablations, except that the wound extended more anteriorly into the frontal sinus, and

laterally to the edge of the skull. The dura was incised and folded back, the brain was gently retracted and lifted from an anteroventral point; the gyrus proreus was visualized and removed bilaterally by subpial aspiration. Cortical control ablations were performed in a similar manner, with destruction aimed at the coronal and anterior sigmoid gyri, the gyrus proreus was spared in both cases.

After completion of surgery, the bone wound was covered with gel-foam and sulfathiozale was applied; the skin wound was then sutured. For three days postoperatively all animals received 300,000 IU procaine penicillin intramuscularly.

Following the completion of the experiment, the operated animals were administered a lethal dose of sodium pentobarbital, perfused intracardially with normal saline followed by ten percent formalin in saline solution and the brains were removed.

The extent of bilateral damage to gyrus proreus was measured, under a jewelers loop, with a millimeter rule and drawn directly on standard diagrams of the medial, lateral, and frontal aspects of the cat brain. In addition, photographs of all brains sustaining cortical damage (proreal and operated control) were taken, and are available from the author upon request.

The brains which sustained septal damage were frozen, and sections were cut at 30 microns through the extent of the lesion. Every tenth section was mounted, and stained with cresyl-violet. Brain sections .5 mm. apart in the A-P plane were viewed through a microprojector. The microprojections were superimposed upon identical sections of the

cat septum as presented by Andy and Stephan (1964). The percent damage to individual nuclear groups was then calculated from bilateral measurements made with a millimeter rule.

Apparatus

The apparatus used was an operant chamber designed especially for cats. The chamber was constructed of wood, and sound attenuated internally with fiberglass and platerboard. The inside diameters measured 111.8 X 67.3 X 111.8 cm. The floor and front door (except for a centrally located one-way viewing mirror measuring 35.6 X 20.3 cm.) were covered internally with brown peg-board, the side walls were also covered with peg-board, but only to a level of 50.3 cm. above the floor of the apparatus. The remainder of the chamber was painted flat white. A centrally located brass rod (diameter .63 cm.) extended through the height of the chamber. A standard tennis ball was impaled by the brass rod, being secured to the rod at a level of 33 cm. above the chamber floor. Deflection of the rod 1 cm. in any lateral direction (at the level of the tennis ball) closed a contact with a brass ring located in the ceiling of the chamber, and through which the rod extended. Closure of this contact activated electromechanical and solid state circuitry causing a response to be recorded and reinforcement to be delivered if the schedule contingencies were met. Reinforcement consisted of 1 cc. evaporated milk (5:1 dilution) delivered through a Skinner solenoid valve (Skinner Corp., V5 series). The feeder was a metal cup (12.7 cm. diameter, 5.1 cm. deep), centrally located on the rear wall 91 cm. above the floor, and identical in all respects to the

food cups that the animals ate from in their home cages. A 7.5 watt red cue light was mounted 12.7 cm. above the center of the metal feeder. The chamber was illuminated by a 25 watt blue light bulb located centrally on the rear wall 91.8 cm above the floor. Ventilation was introduced through two fans, which also generated a constant 65 db white noise.

The schedule contingencies were carried out by electromechanical circuitry, and the total number of responses and reinforcements were recorded on electromechanical counters and a cumulative recorder. In addition, interresponse times were measured by an Ortec Digital Rate-meter (Model 434) and printed out on teletype. The teletype, Digital Ratemeter, and all control equipment that could possibly supply the animal with auditory or visual cues relative to the schedule contingencies were located in another room.

Procedure

The experiment was carried out in two stages, the second stage essentially being a replication of the first. Fifteen cats (Controls 7, 68, 77, 55; Operated Controls 50 and 52; Proreals 40, 41, 10, 22, and 56; and Septals 6, 69, 71, and 20) served as subjects in the first stage, and ten cats (Controls 37, 2 and 82; Proreals 80, 81 and 79; and Septals 70, 74, 75 and 95) served as subjects in the replication. The numbers in parenthesis refer to colony cage numbers. Both stages were carried out during the same time of year, and under identical laboratory conditions.

For three weeks prior to the experiment, all subjects were adapted to a 22.75 hour food and water deprivation schedule. During feeding animals were allowed 1 hour and 15 minutes food and water ad libitum.

The subjects were maintained on this deprivation schedule throughout the experiment. During training, the feeding periods were initiated approximately 1 hour after each daily session. Adaptation to deprivation was followed by three days of habituation to the operant chamber. Animals were transported in a carrying cage from the colony room and placed in the operant chamber for 30 minutes. During this time, fresh milk was always available in the metal feeder. At the completion of the three day habituation period the animals were shaped to press the brass rod for a 1 cc. milk reward. Shaping was terminated when the animal self-initiated at least 30 presses in a 30 minute period on a schedule of continuous reinforcement (CRF). After reaching this criterion the animals were run for an additional 6 days on CRF.

On the day following the completion of CRF training animals were placed on a differential reinforcement of low rates of response 40 second schedule (DRL 40). On this schedule a response is reinforced only if it occurs 40 seconds after a previous response. This specified time between responses is called the interresponse time (IRT). If an IRT is less than 40 seconds, reinforcement is not provided, the DRL timer is recycled, and the animal must withhold responding for an additional 40 seconds before a response will lead to reinforcement. In this way, the animal is reinforced for pressing at a low rate (i.e., one response every forty seconds) and punished (withheld reinforcement) for pressing at high rates. DRL 40 training was run in three successive stages as follows: (1) acquisition, (2) feedback, and (3) feedback withdrawal. Acquisition training was carried out for thirty days. During this stage, there were no exteroceptive stimuli available to signal the end

of the required delay. At the completion of the 30 day acquisition period, fifteen days of DRL 40 with feedback was instituted. Under this condition the 7.5 watt red light bulb located above the feeder was activated at the end of the 40 second DRL interval. Any response occurring while the red light was on led to reinforcement, turned off the light, and recycled the DRL timer.

The feedback condition was followed by 15 days of feedback withdrawal, during which the cue light was no longer utilized. Throughout the entire experiment (shaping, CRF, and all stages of DRL) animals were run for 30 minutes per day and 6 days per week (range 5-7). The following events were recorded and represent the main experimental variables: total number of reinforcements, total number of responses, and interresponse times (subsequently grouped into 2 second class intervals). In addition, a measure of efficiency was derived as follows: Total Reinforcements/Total Responses.

B. RESULTS AND DISCUSSION

Three cats (Septal 20, and Controls 77 and 82) did not develop stable response rates during testing. These cats showed erratic performance throughout training and did not respond at all on many testing days. The data from these cats is therefore not included in the present analysis. The remaining animals all developed stable response rates and showed no obvious differences due to sex or age of lesion.

Tables III-1, III-2, and III-3 show the mean efficiency ratios (number of reinforcements/number of responses), mean reinforcements, and mean responses respectively for each cat during the different stages

TABLE III-1

MEAN EFFICIENCY RATIOS DURING DIFFERENT STAGES OF DRL TRAINING

Animal	Days 1 - 30 of Acquisition		Days 1 - 15 Cue		Days 1 - 15 Cue Withdrawal	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
C-7	.336	.167	.502	.109	.576	.161
C-68	.151	.089	.528	.242	.478	.094
C-55	.258	.070	.660	.228	.356	.083
C-2	.180	.094	.658	.170	.578	.141
C-37	.090	.054	.256	.173	.188	.089
S _a -6	.029	.017	.638	.157	.160	.077
S _a -69	.037	.014	.252	.224	.158	.030
S _a -95	.073	.056	.228	.162	.134	.020
S _b -75	.230	.073	.582	.325	.362	.071
S _b -74	.276	.171	.650	.126	.540	.200
S _b -70	.382	.167	.738	.114	.632	.102
S _c -71	.207	.159	.638	.077	.564	.177
P _a -41	.076	.019	.282	.200	.188	.089
P _a -40	.081	.023	.634	.213	.174	.070
P _a -22	.099	.049	.480	.126	.212	.064
P _b -10	.127	.046	.260	.048	.218	.058
P _b -56	.162	.056	.590	.190	.292	.084
P _b -81	.231	.147	.712	.151	.574	.084
P _b -80	.243	.127	.742	.157	.432	.065
P _c -79	.241	.067	.648	.129	.466	.079
O-50	.339	.223	.658	.056	.656	.057
O-52	.140	.091	.350	.172	.306	.065

TABLE III-1 (Continued)

C = Control
S = Septal
P = Proreal
O = Operated Control

S_a = High percentage of damage to antero-medial septum and diagonal band nuclei; with minimal damage to anterior limbic cortex.

S_b = Small percentage of damage to antero-medial septum and diagonal band nuclei and/or extensive damage to anterior limbic cortex.

S_c = Damage only to anterior limbic cortex, subsequently included in operated control group.

P_a = High percentage damage to gyrus preoreus, including its ventral sector.

P_b = Small percentage of damage to gyrus preoreus, or absence of damage to its ventral sector.

P_c = Partial unilateral ablation of gyrus preoreus; subsequently included in operated control group.

TABLE III-2

MEAN REINFORCEMENTS DURING DIFFERENT STAGES OF DRL TRAINING

Animal	Days 1 - 30 of Acquisition		Days 1 - 15 Cue		Days 1 - 15 Cue Withdrawal	
	<u>Mean</u>	<u>S.D.</u>	<u>Mean</u>	<u>S.D.</u>	<u>Mean</u>	<u>S.D.</u>
C-7	14.9	6.45	16.6	3.91	11.8	3.03
C-68	14.2	4.16	26.2	9.20	22.2	1.79
C-55	12.0	4.27	29.0	9.03	17.0	3.00
C-2	13.5	3.47	24.6	3.84	24.8	3.42
C-37	7.9	2.52	14.4	7.09	12.2	3.90
S _a -6	3.5	1.27	24.6	3.32	8.6	2.07
S _a -69	4.8	2.20	14.8	8.90	9.4	2.19
S _a -95	7.8	2.15	14.0	6.36	10.0	1.22
S _b -75	13.4	2.41	25.6	9.91	18.8	2.68
S _b -74	12.1	6.24	26.6	4.04	24.4	6.66
S _b -70	17.4	4.03	28.0	1.94	26.4	3.85
S _c -71	11.4	5.54	24.4	1.82	21.6	3.21
P _a -41	3.9	1.37	11.8	6.18	14.0	1.22
P _a -40	8.2	1.81	27.0	7.84	9.8	2.77
P _a -22	8.7	2.21	16.2	2.75	11.4	2.07
P _b -10	10.7	1.25	16.0	2.00	13.2	2.49
P _b -56	10.2	2.70	24.0	6.44	14.0	2.91
P _b -81	11.3	4.47	23.4	4.72	22.0	3.32
P _b -80	15.5	4.14	29.6	4.22	22.0	3.16
P _c -79	13.8	2.91	27.0	4.30	20.8	3.03
O-50	16.1	7.36	28.6	3.05	27.0	2.00
O-32	12.2	3.29	19.2	5.80	21.6	3.21

For subscript designations see Table III-1 on page 83.

TABLE III-3

MEAN NUMBER OF RESPONSES DURING CRF TRAINING AND DIFFERENT STAGES OF DRL

Animal	6 Days CRF		Days 1 - 30 DRL Acquisition		Days 1 - 15 Cue		Days 1 - 15 Cue Withdrawal	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
C-7	56.0	16.97	49.5	18.29	35.0	3.24	22.4	3.65
C-68	115.0	33.94	117.1	38.41	61.0	26.40	49.6	7.64
C-55	76.5	17.67	48.8	12.16	44.6	4.27	48.8	4.15
C-2	70.0	11.31	89.4	25.98	39.2	8.93	44.4	6.07
C-37	66.0	1.41	102.1	25.02	67.4	17.90	71.4	6.27
S _a -6	103.0	16.97	131.0	33.28	44.0	9.46	64.2	9.68
S _a -69	105.0	2.83	133.0	10.45	75.0	22.45	61.0	4.85
S _a -95	83.5	2.02	134.8	33.27	73.6	17.98	79.4	6.35
S _b -75	58.0	9.90	66.0	13.08	50.6	12.84	54.2	6.83
S _b -74	36.5	3.53	51.4	14.32	42.4	4.93	49.0	8.15
S _b -70	41.5	3.53	52.8	12.50	38.4	1.95	41.2	2.28
S _c -71	96.5	16.26	66.3	25.37	39.6	3.05	41.8	10.26
P _a -41	100.0	21.21	54.1	10.40	52.6	25.05	89.8	33.36
P _a -40	76.5	6.36	103.8	19.94	45.0	5.70	63.4	5.68
P _a -22	83.5	10.61	100.4	16.69	39.7	12.87	61.0	12.59
P _b -10	118.0	31.11	93.0	31.73	65.6	6.58	62.2	6.76
P _b -56	73.0	2.83	64.5	12.89	43.4	4.51	50.2	5.89
P _b -81	35.0	1.41	61.3	21.99	33.2	2.77	38.8	2.68
P _b -80	104.5	14.85	80.0	31.85	41.0	4.95	51.2	2.17
P _c -79	63.0	1.41	58.0	6.12	42.2	2.28	45.2	1.48
O-50	116.0	21.21	56.1	16.81	42.4	2.61	42.4	2.07
O-52	94.0	1.41	104.1	33.88	63.8	17.33	65.4	4.28

For subscript designations see Table III-1 on page 83.

of DRL training. In addition, Table III-3 (p. 85) shows the mean number of responses for each cat during the six days of CRF training. All means and standard deviations were calculated from daily observations blocked into three day periods. These latter data are presented in Tables A-1 through A-6 of Appendix A.

These data clearly show that both the septal and prereal groups consist of two subgroups. Three animals in the septal group (S-6, S-69, and S-95) and three animals in the prereal group (P-41, P-40, and P-22) showed extremely poor performance during the 30 day acquisition period and during the 15 days of cue withdrawal. These animals obtained fewer reinforcements and emitted more responses (thus leading to lower efficiency ratios) than any of the other animals during these periods. In addition, the small standard deviations associated with the means for efficiency and reinforcements during the 30 day acquisition period suggest that these animals did not modify their performance during acquisition. The remaining cats in the septal group perform as well, if not better, than the normal controls, while the performance of the remaining cats in the prereal group is comparable to that of the normal controls.

A more complete analysis of these data is presented below, however, it is first necessary to explain the differential within group performances of the septal and prereal cats.

Histological Findings and Their Relationship to DRL Performance

The lesion reconstructions for the prereal and operated control groups are presented in Appendix B. These reconstructions are drawn

on standard diagrams of the medial, lateral, and frontal aspects of the cat brain. Table III-4 of the text shows, for the septal group, the percentage of damage to specific nuclei in and around the septum. The specific nuclei and subdivisions of the cat septum noted in this table are based on the findings of Andy and Stephan (1964).

In the following presentation of the histological findings all performance comparisons, unless otherwise indicated have been derived from the results presented in Tables III-1 through III-3 (pp. 82-85) of the text and A-1 through A-6 of Appendix A. Two of the three septal animals noted above to perform poorly during DRL training (S-6 and S-95) had the largest septal ablations, and sustained the most extensive damage to the anteromedial septum and diagonal band nuclei. Furthermore, S-95 did not sustain any damage to anterior limbic cortex, and S-6 had only 10% of this brain region destroyed. The third septal cat which performed poorly on DRL (S-69) showed only a moderate amount of septal damage. However, the lesion in this animal was medially placed, destroying 55% of the anteromedial nucleus and only about 30% of the lateral nuclear groups. The anterior limbic cortex was not damaged. S-75 performed as well as the normal animals on DRL. In this cat the anterior portion of the septum (A-18.5 to A-17.5) was completely spared. More posteriorly, the lateral septal nuclear groups were extensively damaged, while only the more lateral portions of the medial septal groups and diagonal band nuclei were effected. Only at the level of the fornix did the ablation extend toward the midline. S-70, performing somewhat better on DRL in comparison to the control cats, sustained only minimal damage to the septum, but extensive damage to

TABLE III-4

PERCENT DAMAGE TO STRUCTURES IN AND AROUND THE SEPTUM

Animal	Structures in and Around the Septum																	A	C	IC	ST	TA
	DA	DE	DI	DM	MA	MP	BD	LI	LE	AL	H	CC	NC	F	FI	FX						
S _a -6	95	65	35	45	80	75	75	75	40	10	80	5	0	55	25	25	0	5	0	5	5	
S _a -69	65	55	65	30	55	40	35	35	30	0	70	10	0	0	0	0	0	0	0	0	0	
S _a -95	95	70	70	80	95	70	50	40	65	0	40	15	5	70	30	35	65	5	5	5	5	
S _b -75	15	55	40	45	40	55	35	85	85	0	0	5	0	55	25	40	50	5	5	0	0	
S _b -74	95	10	20	25	70	40	40	20	5	50	75	5	5	10	10	10	0	0	0	0	0	
S _b -70	80	15	0	30	20	0	0	20	20	60	30	0	10	0	0	0	0	0	0	0	0	
S _c -71	0	0	0	0	0	0	0	0	0	80	20	15	0	0	0	0	0	0	0	0	0	

A-Nucleus septalis triangularis

AL-Anterior limbic cortex

BD-Nucleus of the diagonal band of Broca
pars dorsalis

C-Bed nucleus of the anterior commissure

CC-Corpus Callosum

DA-Nucleus septalis dorsalis pars anterior

DE-Nucleus septalis dorsalis pars externa

DI-Nucleus septalis dorsalis pars interna

DM-Nucleus septalis dorsalis pars intermidius

F-Nucleus septalis fimbrialis

FI-Fimbria

FX-Fornix

H-Anterior continuation of the hippocampus

IC-Islands of Calleja

LE-Nucleus septalis lateralis pars externa

LI-Nucleus septalis lateralis pars interna

MA-Nucleus septalis medialis pars anterior

MP-Nucleus septalis medialis pars posterior

NC-Nucleus caudatus

ST-Stria terminalis

TA-Bed nucleus of the stria terminalis
pars anterior

anterior limbic cortex (60%). S-71 did not receive any damage to the septum proper, while its lesion destroyed 80% of the anterior limbic cortex. This cat also performed somewhat better on DRL in comparison to the normal controls. S-74 had a moderately sized septal lesion located medially within the septum. However, this lesion also destroyed 50% of the anterior limbic cortex. The performance of this cat was somewhat facilitated in comparison to controls.

These findings indicate that large septal lesions, especially those damaging the anteromedial septum and diagonal band nuclei disrupt performance on DRL, while anterior limbic damage has a facilitatory effect.

There are similar relations within the proreal group. The three proreal cats (P-41, P-40, P-22) which were deficient on DRL incurred the greatest amount of proreal damage, especially to its ventral sector. (See Figure B-1 in Appendix B.) P-79, performing within the normal range, sustained only unilateral damage which was confined to the middle third of gyrus proreus. On the side opposite the proreal injury there was damage to the anterior sigmoid gyrus. The remainder of the proreal cats, all performed within the normal range and sustained bilateral damage which spared the ventral sector of gyrus proreus.

Here again, the findings indicate that large ablations, and in the case of gyrus proreus, especially those invading its ventral sector, are responsible for poor performance on DRL.

The operated control animals (O-50, O-52), performing in the normal range, received bilateral damage to the anterior sigmoid and coronal gyri. Gyrus proreus was not damaged in either case.

In an attempt to support these interpretations objectively, a measure of extent of damage was obtained for correlation with performance for the septal and preoreal groups. The Spearman rank correlation statistic was utilized in all cases. In addition, for all correlations, the mean efficiency ratio over the last six days of DRL acquisition was used as an index of performance (derived from Table A-1, Appendix A). This measure is the optimal index of performance since it takes into account response rate and reinforcements obtained. Furthermore, this index emphasizes terminal performance during acquisition, and is not contaminated by the effects of feedback (as an index derived from the 15 day withdrawal period would have been).

For the septal group two separate rank order correlations were computed. In one case, the mean percentage damage to the anteromedial septum and diagonal band nuclei was ranked against poor performance on DRL. In the other case, the percentage of damage to anterior limbic cortex was ranked against superior performance on DRL. Tables III-5 and III-6 show the derived brain damage percentages (calculated from Table III-4, p. 88) and the mean efficiency ratios for the last six days of acquisition with their respective rank orderings. Table III-7 presents the results of the Spearman rank correlation. The extent of damage to the anteromedial septum and diagonal band was found to be significantly correlated with poor performance on DRL ($r_s = .72$, $P < .05$). In addition, the extent of damage to anterior limbic cortex is highly correlated with superior performance on DRL. This result is marginally significant ($r_s = .67$, $.05 < P < .1$).

TABLE III-5

RANK ORDERS FOR THE PERCENTAGE DAMAGE TO THE ANTEROMEDIAL
SEPTUM AND DIAGONAL BAND AND FOR THE MEAN EFFICIENCY
RATIO DURING THE LAST 6 DAYS OF DRL ACQUISITION

Animal	Damage to Antero- medial Septum and Diagonal Band	Rank	Mean Efficiency Last 6 Days of DRL Acquisition	Rank
S _a -6	77.5	7	.02	7
S _a -69	45.0	4	.03	6
S _a -95	72.5	6	.14	5
S _b -75	37.5	3	.20	4
S _b -74	55.0	5	.47	2.5
S _b -70	10.0	2	.55	1
S _c -71	0.0	1	.47	2.5

For subscript designations see Table III-1 on page 83.

TABLE III-6

RANK ORDERS FOR THE PERCENTAGE DAMAGE TO THE ANTERIOR
 LIMBIC CORTEX AND FOR THE MEAN EFFICIENCY RATIO
 DURING THE LAST 6 DAYS OF DRL ACQUISITION

Animal	Damage to Anterior Limbic Cortex	Rank	Mean Efficiency Last 6 Days of DRL Acquisition	Rank
S _a -6	10	4	.02	1
S _a -69	0	2	.03	2
S _a -95	0	2	.14	3
S _b -75	0	2	.20	4
S _b -74	50	5	.47	5.5
S _b -70	60	6	.55	7
S _c -71	80	7	.47	5.5

For subscript designations see Table III-1 on page 83.

TABLE III-7

RANK ORDER CORRELATION COEFFICIENTS AND THEIR PROBABILITIES FOR
THE RELATIONSHIP BETWEEN EXTENT OF DAMAGE IN THE
ANTEROMEDIAL SEPTUM-DIAGONAL BAND OR THE
ANTERIOR LIMBIC CORTEX AND PERFORMANCE
DURING THE LAST 6 DAYS OF
DRL ACQUISITION

Relationship	Correlation Coefficient	Probabilities
Between Anteromedial Septum-Diagonal Band Damage and Poor Performance	.72	$P < .05$
Between Anterior Limbic Cortex Damage and Superior Performance	.67	$.05 < P < .10$

In addition to these relationships, analysis of Table III-4 (p. 88) also shows that damage to the dorsal nuclear groups of the septum is related to poor performance on DRL. Septals 6, 69, and 95 all performed less efficiently on DRL than the other septal subjects and they also sustained more damage to the dorsal nuclear groups.

For the proreal group, two correlations were also computed. In one case, the overall extent of damage to gyrus proraus was ranked against poor performance on DRL. The ablations were rated on a scale of 0 - 3; maximal damage indicated by a score of 3. The scores were computed by allowing a maximum of 1 point (indicating total damage) for damage on each of the aspects of the cat brain (medial, lateral, and frontal). For the second correlation, the percentage of damage to the ventral sector of gyrus proraus (computed from frontal plane sections only) was also ranked against poor DRL performance. Tables III-8 and III-9 show the derived brain damage ratings and the mean efficiency ratios for the last six days of acquisition with their respective rank orderings. Table III-10 presents the results of the Spearman rank correlation. Both overall damage and extent of ventral damage were found to be significantly correlated with poor performance on DRL as indicated by mean efficiency during the last six days of acquisition ($r_s = .72$, $P < .05$; $r_s = .76$, $P < .05$ respectively).

Regrouping

Based on the above findings, an objective regrouping of the subjects was undertaken in order to allow a clearer presentation of the behavioral findings. The septal group was divided as follows: those

TABLE III-8

RANK ORDERS FOR TOTAL DAMAGE RATINGS TO GYRUS PROREUS
AND FOR THE MEAN EFFICIENCY RATIO DURING THE
LAST 6 DAYS OF DRL ACQUISITION

Animal	Rating of Damage to Gyrus Proreus	Rank	Mean Efficiency Last 6 Days of DRL Acquisition	Rank
P _a -41	2.70	6	.09	8
P _a -40	2.70	6	.10	7
P _a -22	2.70	6	.13	5
P _b -10	1.40	2	.18	4
P _b -56	2.30	5	.12	6
P _b -81	1.80	3	.42	1
P _b -80	1.95	4	.41	2
P _c -79	1.20	1	.20	3

For subscript designations see Table III-1 on page 83.

TABLE III-9

RANK ORDERS FOR PERCENTAGE DAMAGE TO THE VENTRAL SECTOR OF
GYRUS PROREUS AND FOR THE MEAN EFFICIENCY RATIO DURING
THE LAST 6 DAYS OF DRL ACQUISITION

Animal	Damage to Ventral Sector of Gyrus Proreus	Rank	Mean Efficiency Last 6 Days of DRL Acquisition	Rank
P _a -41	75	7	.09	8
P _a -40	90	8	.10	7
P _a -22	70	6	.13	5
P _b -10	15	3	.18	4
P _b -56	20	4	.12	6
P _b -81	10	1.5	.42	1
P _b -80	30	5	.41	2
P _c -79	10	1.5	.20	3

For subscript designations see Table III-1 on page 83.

TABLE III-10

RANK ORDER CORRELATION COEFFICIENTS AND THEIR PROBABILITIES
 FOR THE RELATIONSHIP BETWEEN EXTENT OF DAMAGE
 TO THE GYRUS PROREUS OR ITS VENTRAL SECTOR
 AND PERFORMANCE DURING THE LAST
 6 DAYS OF DRL ACQUISITION

Relationship	Correlation Coefficient	Probabilities
Between Total Proreal Damage and Poor Performance	.72	$P < .05$
Between Damage to the Ventral Sector of Gyrus Proreus and Poor Performance	.76	$P < .05$

animals which showed maximal damage to the anteromedial septum and diagonal band nuclei, along with minimal damage to anterior limbic cortex, comprised one septal subgroup. Henceforth this group will be designated as septal subgroup A (Group S_a). Those septal cats which showed minimal damage to the anteromedial septum and diagonal band, and/or extensive damage to anterior limbic cortex, formed a second septal subgroup, henceforth designated as septal subgroup B (Group S_b). Cat S-71 was added to the operated control group, since this animal incurred no damage to any of the septal nuclei. In a similar manner, those prereal animals which sustained maximal damage to gyrus preceus, and especially to its ventral sector, formed prereal subgroup A (Group P_a), while those animals with the smallest prereal ablations, sparing the ventral sector, comprised prereal subgroup B (Group P_b). Cat P-79 was added to the operated control group (Group OC) since this animal only incurred minor unilateral damage to gyrus preceus, along with some damage to the anterior sigmoid gyrus on the side opposite the prereal injury. The normal control group (Group NC) remained the same. Table III-11 shows the results of this regrouping procedure.

The results based on this regrouping are presented in four sections. CRF data is presented first, followed by data for the 30 days of DRL acquisition. The third section presents data for DRL performance during the 15 day feedback period and the 15 day feedback withdrawal period. In the last section some observations on collateral behavior are presented.

Unless otherwise specified, the following statistical tests were used to assess main effects:

TABLE III-11

REGROUPING ASSIGNMENTS BASED UPON ANATOMICAL DAMAGE

Normal Controls	Operated Controls	Septal Subgroup A	Septal Subgroup B	Proreal Subgroup A	Proreal Subgroup B
C-7	O-50	S-6	S-75	P-41	P-10
C-68	O-52	S-69	S-74	P-40	P-56
C-55	S-71	S-95	S-70	P-22	P-81
C-2	P-79				P-80
C-37					

1. One-tailed t-tests were computed for paired comparisons of group means.
2. All correlations (to assess days effect and to compare the shapes of IRT histograms) that involved only two sets of rankings were measured by the Spearman rank correlation coefficient (r_s).
3. All correlations that involved more than two sets of rankings were measured by the Kendall coefficient of concordance (W).

CRF Training

Figure III-1 shows the mean number of responses emitted by each group during the 6 days of CRF training. All groups responded at about the same rate with the exception of Group S_b . This group emitted fewer responses than any other group. This effect is significant for all paired comparisons ($P < .05$) except for the comparison between Groups S_b and P_b . Of particular interest is the comparison between Groups S_a and S_b . Group S_a emitted more than twice as many responses across the six days of CRF testing than did Group S_b ($t = 5.487$, $df = 4$, $P < .01$).

DRL Acquisition

Figure III-2 shows the mean efficiency ratios for each group during the 30 days of DRL acquisition. The performance of Group NC is superior to that of Groups S_a and P_a , and about equal to that of Groups OC and P_b . Group S_b was facilitated in comparison to the other groups during the early stages of DRL acquisition. Figures III-3 and III-4 show, however, that this transient facilitation was due to a reduction in response rate, rather than an increase in the number of

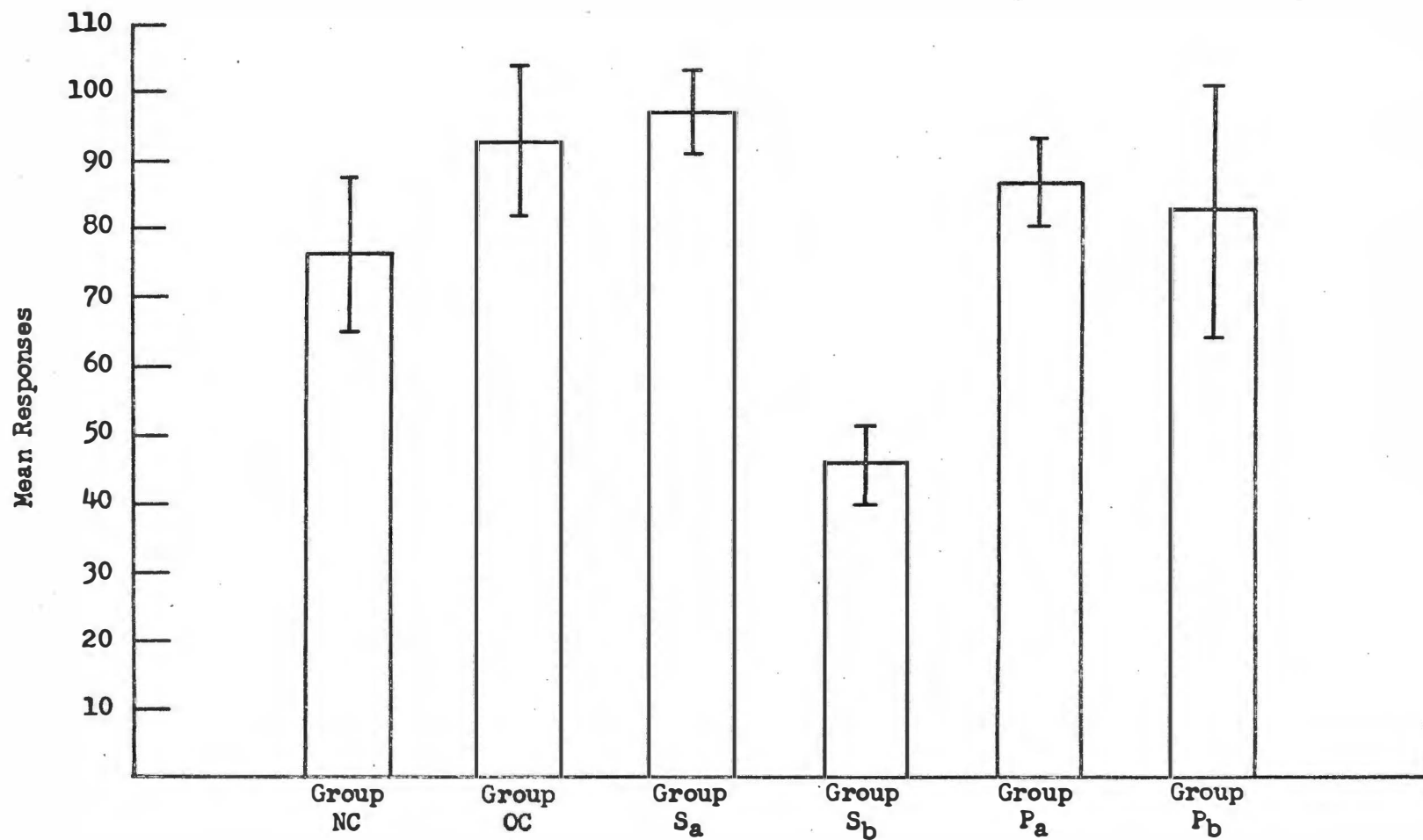


Figure III-1. Mean number of responses during 6 days CRF training.

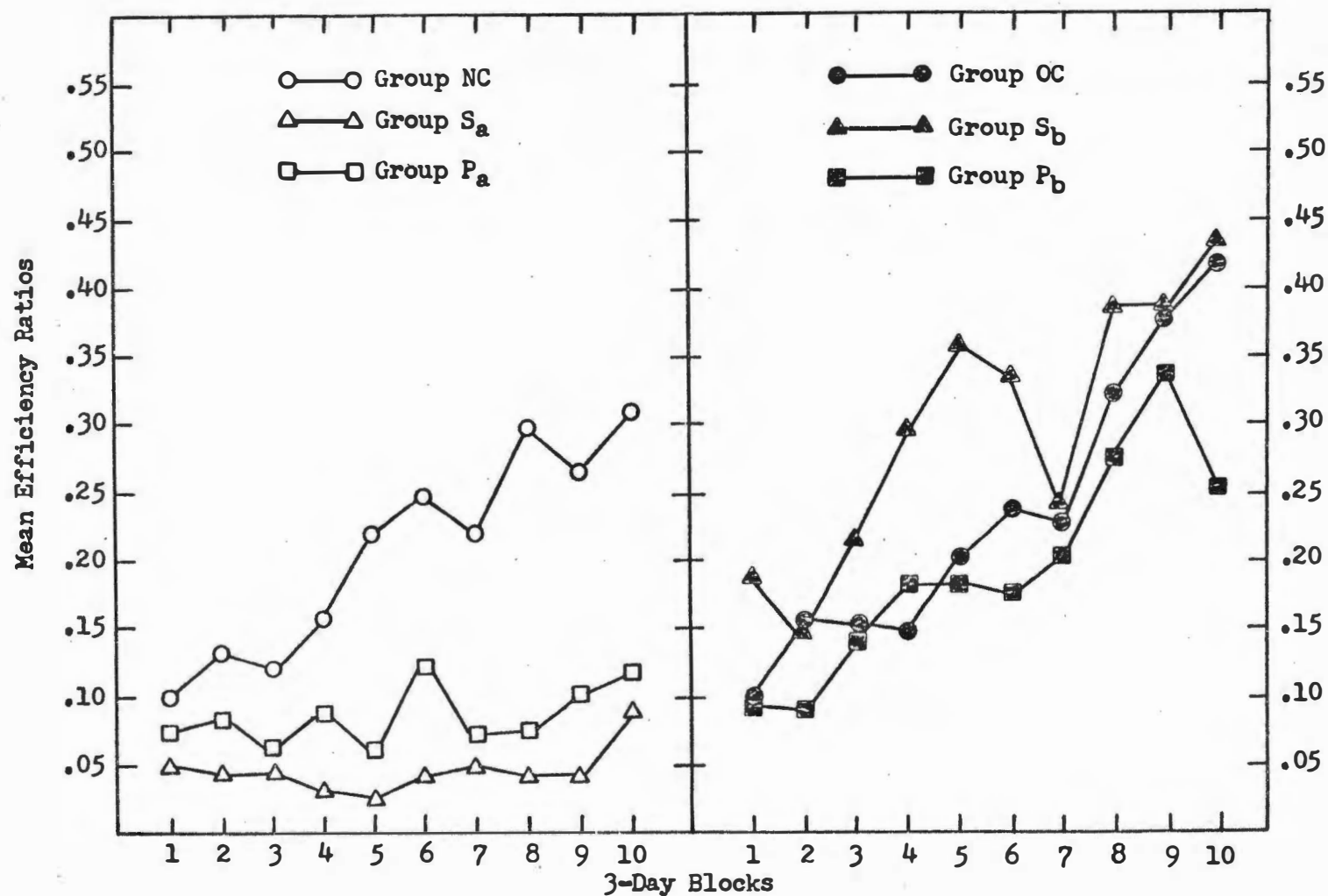


Figure III-2. Mean efficiency ratios during DRL acquisition.

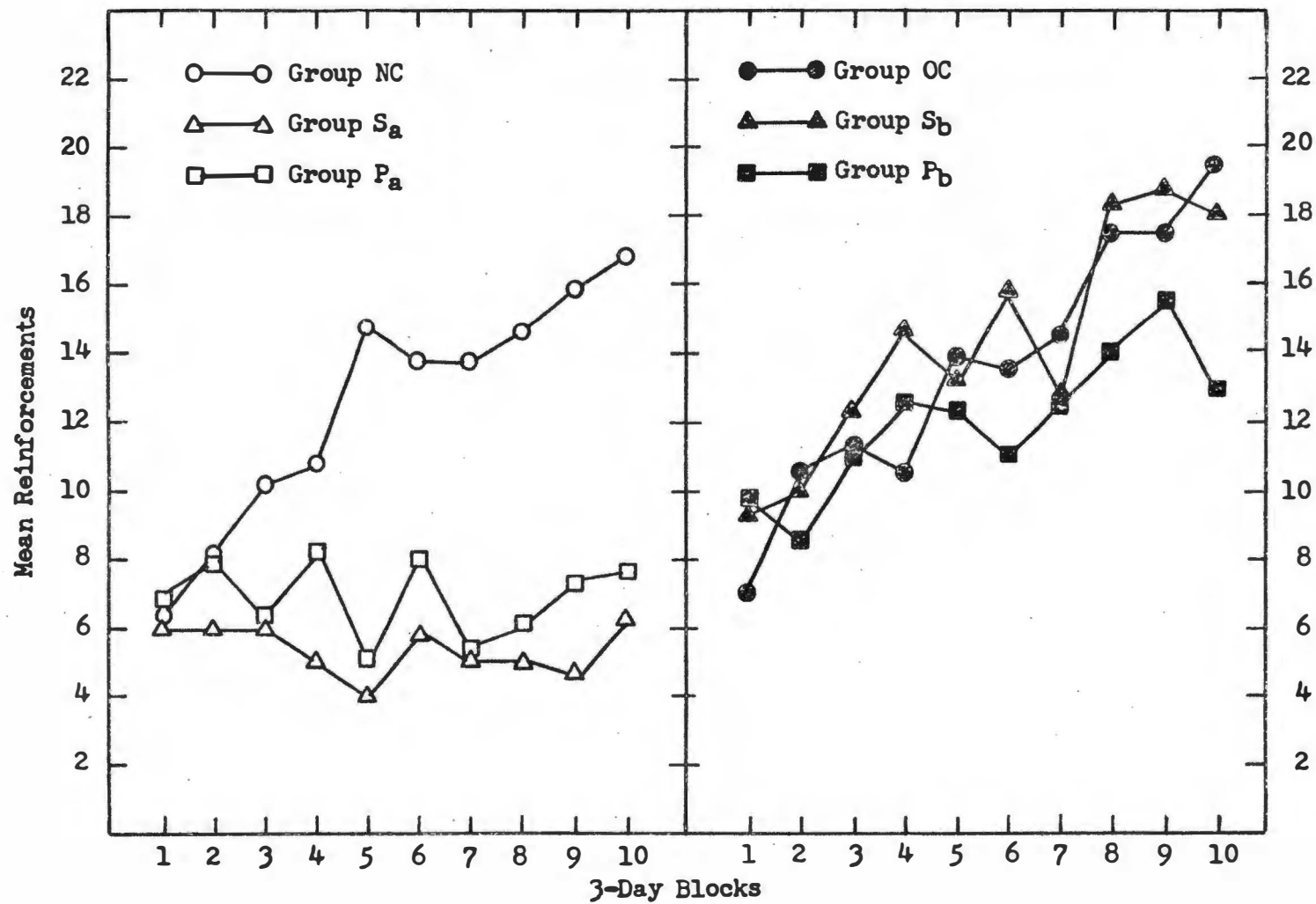


Figure III-3. Mean reinforcements during DRL acquisition.

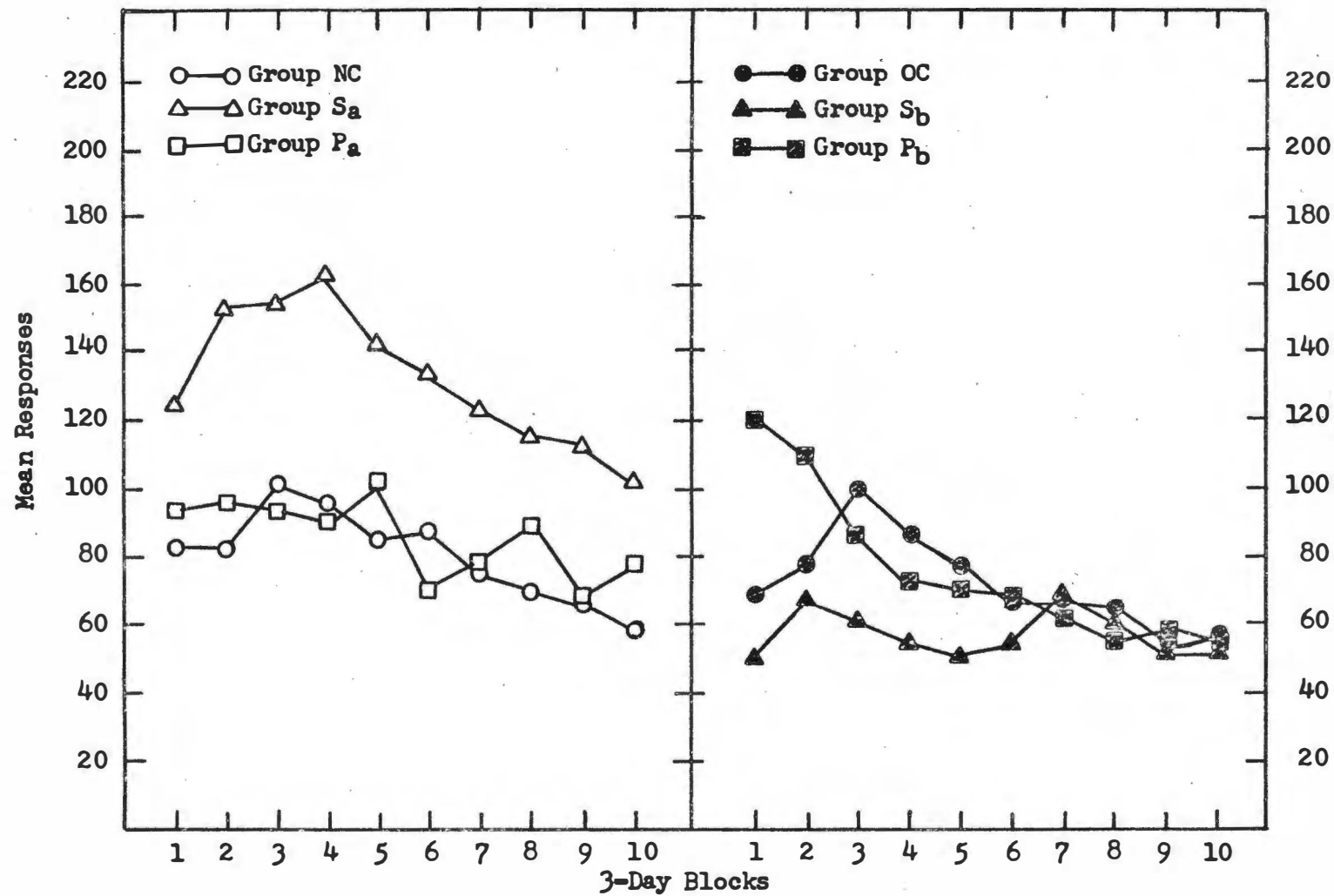


Figure III-4. Mean responses during DRL acquisition.

reinforcements obtained. The strength of the relationship between degree of efficiency and days of training was calculated for each group. Increased efficiency for Group NC is significantly correlated with days of training ($r_s = .954$, $P < .01$). There was no relationship between days of training and efficiency for Groups S_a or P_a ($r_s = .367$, $P > .05$; $r_s = .391$, $P > .05$ respectively). The efficiency ratios of the three remaining groups were compared over days. The relationship between degree of efficiency and days of training was found to be highly significant ($W = .923$, $r_{sav} = .897$, $\chi^2 = 33.2$, $df = 9$, $P < .01$). Table III-12 presents the rank orderings used in these calculations.

Figure III-3 (p. 103) shows the mean number of reinforced responses for each group during the 30 days of DRL acquisition. The results are virtually identical to those discussed above. The relationship between days of training during acquisition and performance as indicated by number of reinforcements is significant for Group NC ($r_s = .924$, $P < .01$), not significant for Groups S_a and P_a ($r_s = -.212$, $P > .05$; $r_s = -.182$, $P > .05$ respectively) and significant for the remaining three groups ($W = .887$, $r_{sav} = .849$, $\chi^2 = 31.9$, $P < .01$). The ranked scores are shown in Table III-13.

It is therefore evident that those cats which sustained damage to the medial septum and diagonal band nuclei, and those sustaining severe preorel damage including its ventral sector did not show an increase in number of reinforced responses or efficiency during the course of DRL acquisition. In contrast, all other groups show a marked improvement in performance during the course of training.

TABLE III-12

RANK ORDERS FOR DAYS AND EFFICIENCY RATIOS UTILIZED TO CALCULATE
SPEARMAN RANK CORRELATION COEFFICIENTS AND THE KENDALL
COEFFICIENT OF CONCORDANCE DURING ACQUISITION

3 Day Blocks	Normal Control	Operated Control	Septal Subgroup A	Septal Subgroup B	Proreal Subgroup A	Proreal Subgroup B
1	1	1	8.5	2	4.5	2
2	3	4	3	1	6	1
3	2	2	5.5	3	2	3
4	4	3	2	5	7	4.5
5	5.5	5	1	7	1	4.5
6	7	7	5.5	6	10	6
7	5.5	6	8.5	4	3	7
8	9	8	5.5	8.5	4.5	9
9	8	9	5.5	8.5	8	10
10	10	10	10	10	9	8

TABLE III-13

RANK ORDERS FOR DAYS AND REINFORCEMENTS UTILIZED TO CALCULATE
SPEARMAN RANK CORRELATION COEFFICIENTS AND THE KENDALL
COEFFICIENT OF CONCORDANCE DURING ACQUISITION

3 Day Blocks	Normal Control	Operated Control	Septal Subgroup A	Septal Subgroup B	Proreal Subgroup A	Proreal Subgroup B
1	1	1	8	1	5	2
2	2	2.5	8	2	10	1
3	3	4	8	3	3.5	3.5
4	4	2.5	4	6	9	6.5
5	8	6	1	5	1.5	5
6	5.5	5	6	7	9	3.5
7	5.5	7	4	4	1.5	6.5
8	7	8.5	4	9	3.5	9
9	9	8.5	2	10	6	10
10	10	10	10	8	7	8

The various groups were compared for the mean number of reinforced responses during the first six days of acquisition, and for the last six days of acquisition. There were no significant differences during the first six days of acquisition. By the last six days of DRL acquisition the separation between groups was quite clear (Figure III-3, p. 103). Groups NC, OC, S_b and P_b did not differ from each other and each obtained significantly more reinforcements than did Group S_a ($P < .01$, $df = 6$, $t = 3.6$; $P < .05$, $df = 5$, $t = 3.3$; $P < .01$, $df = 4$, $t = 3.85$; $P < .05$, $df = 5$, $t = 2.78$ respectively). Similarly Groups NC, OC, and S_b all obtained significantly more reinforcements than did Group P_a ($P < .01$, $df = 6$, $t = 3.53$; $P < .05$, $df = 5$, $t = 3.20$; $P < .01$, $df = 4$, $t = 4.47$ respectively). Group P_b obtained a greater mean number of reinforcements than Group P_a during the last six days of acquisition, but the effect was only marginally significant ($.05 < P < .10$, $df = 5$, $t = 1.93$). Groups S_a and P_a did not differ.

Figure III-4 (p. 104) shows the mean number of responses emitted by each group over the 30 days of DRL acquisition. The relationship between days of training during acquisition and reduction in response rate was significant for Groups NC ($r_s = .697$, $P < .05$), S_a ($r_s = .77$, $P < .01$) and P_a ($r_s = .718$, $P < .05$). The remaining groups showed the same trend ($W = .62$, $r_{sav} = .50$, $\chi^2 = 22.2$, $df = 9$, $P < .01$).*

Though all groups reduced their response rates to the demands of the DRL schedule, Group S_a emitted more responses than any of the other groups throughout DRL acquisition. During the last six days of DRL acquisition Groups NC, OC, S_b , P_a , and P_b did not differ in their

*Though reduction in response rate was significantly related to days of training for all groups, this effect was minimal and variable for groups P_a and S_b (Figure III-4, p. 104).

response rates, and all emitted significantly fewer responses than did Group S_a ($P < .01$, $df = 6$, $t = 4.94$; $P < .01$, $df = 5$, $t = 4.91$; $P < .01$, $df = 4$, $t = 4.05$; $P < .05$, $df = 4$, $t = 2.77$; $P < .01$, $df = 5$, $t = 4.99$ respectively).

Figure III-5 shows the interresponse time histograms for each group during DRL acquisition. The numbers on the abscissa indicate the lower boundary point of successive two second class intervals. During days 1 - 6 of acquisition (solid line in Figure III-5) all groups show predominantly short interresponse times indicative of the transition from CRF training. By the last six days of DRL acquisition (dotted line in Figure III-5) all groups show a reduction in short latency responses and a shift in the IRT histogram towards the right. However, while the peaks of these shifts occur around the 40 second class interval for Groups NC, OC, S_b , and P_b , they occur over much shorter class intervals for Groups S_a and P_a . It is therefore quite clear that Groups S_a and P_a have not developed a temporal discrimination, though they have learned to suppress short latency responses. The other groups, while varying in their degree of accuracy, all develop a temporal discrimination.

In order to obtain more information about intergroup similarities in patterns of responding during DRL acquisition, the shapes of the response histograms generated by each group were correlated with each other. The correlations were computed for the histograms generated during the last six days of acquisition (dotted line in Figure III-5). Rank order correlations are particularly valuable in this respect since they do not emphasize absolute values of modal points in the

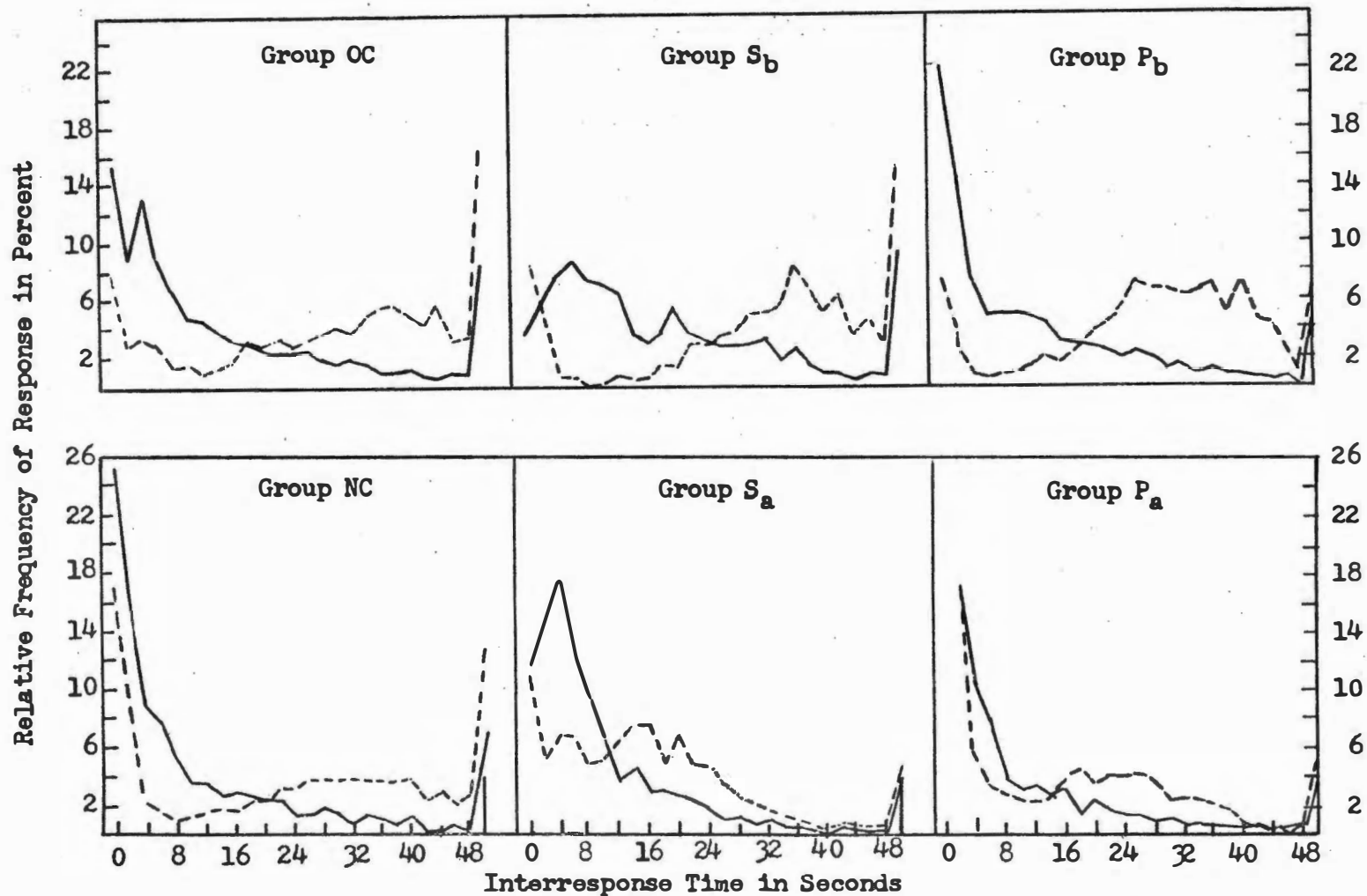


Figure III-5. IRT histograms generated during the first 6 days (—) and last 6 days (---) of DRL acquisition.

distributions, but rather the relative values, thus indicating how a group distributed its responses over time relative to another group.

The shapes of the distributions generated by Groups S_a and P_a were significantly correlated with each other ($r_s = .59$, $P < .01$), but were not related to the distribution generated by Group NC ($r_s = -.25$, $P > .01$; $r_s = .34$, $P > .01$ respectively). The remaining groups generated distributions that were significantly correlated with each other, and with the distribution generated by the normal controls ($W = .84$, $r_{sav} = .78$, $\chi^2 = 83.9$, $df = 25$, $P < .01$).

It can be concluded that damage to the anteromedial septum and diagonal band, or damage to gyrus preceus (which includes its ventral sector) disrupts patterns of responding during DRL acquisition. In addition, the patterns of responding that develop after either lesion are similar to each other.

DRL Performance During the Periods of Feedback and Feedback Withdrawal

Figures III-6, III-7, and III-8 show the group mean efficiencies, reinforcements and response rates respectively for the fifteen day periods of cue presentation and withdrawal. The effects of the feedback stimulus (indicating the availability of reinforcement) are clear. All groups increased their efficiency and number of reinforced presses, while reducing their response rates. There were no significant differences between the group means for any measure of DRL performance during the last six days of feedback training. It can be concluded that the presentation of a feedback stimulus, indicating the availability of reinforcement, ameliorates the deficit on DRL so evident during acquisition in Groups S_a and P_a .

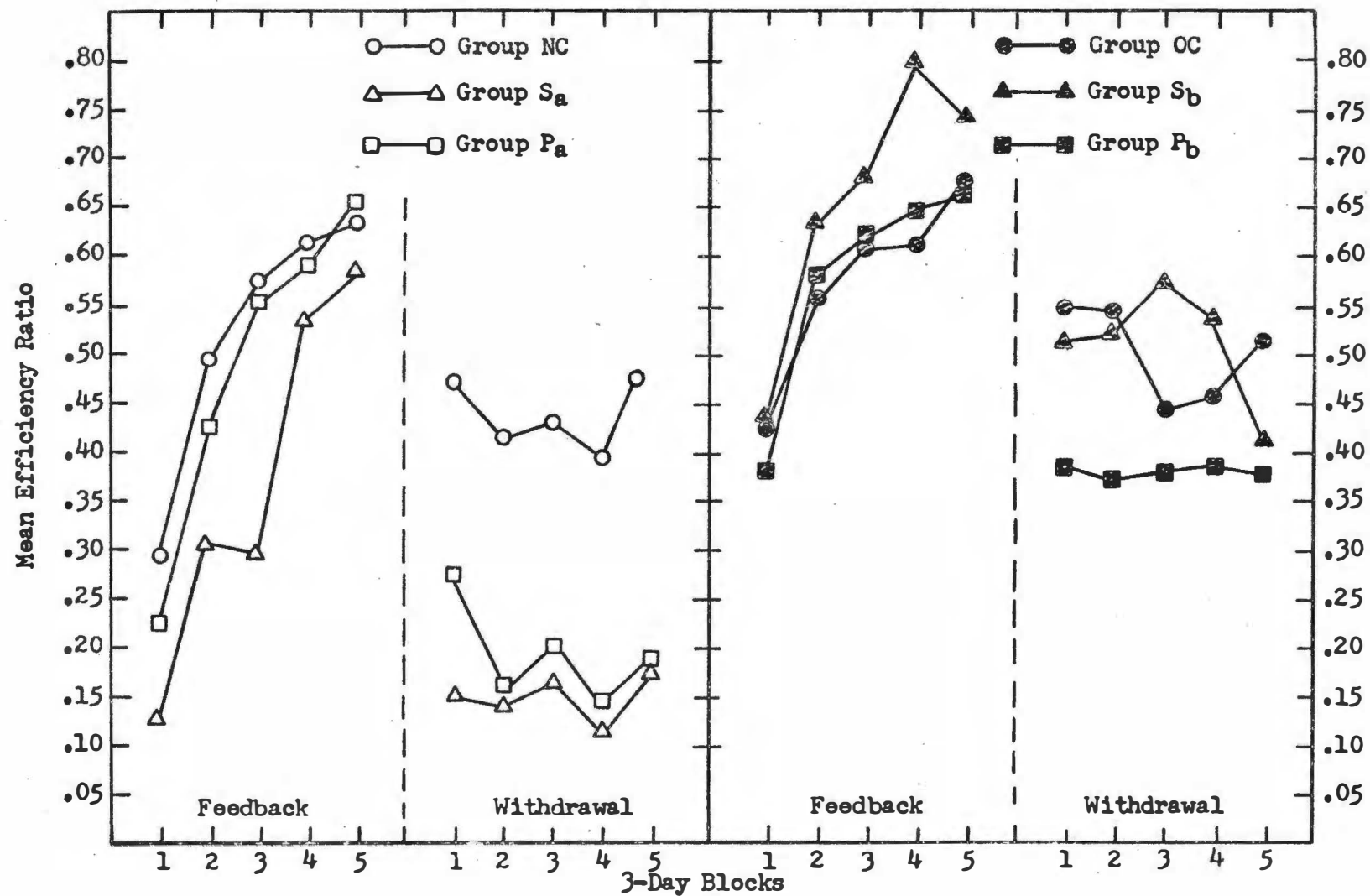


Figure III-6. Mean efficiency ratios during feedback and feedback withdrawal.

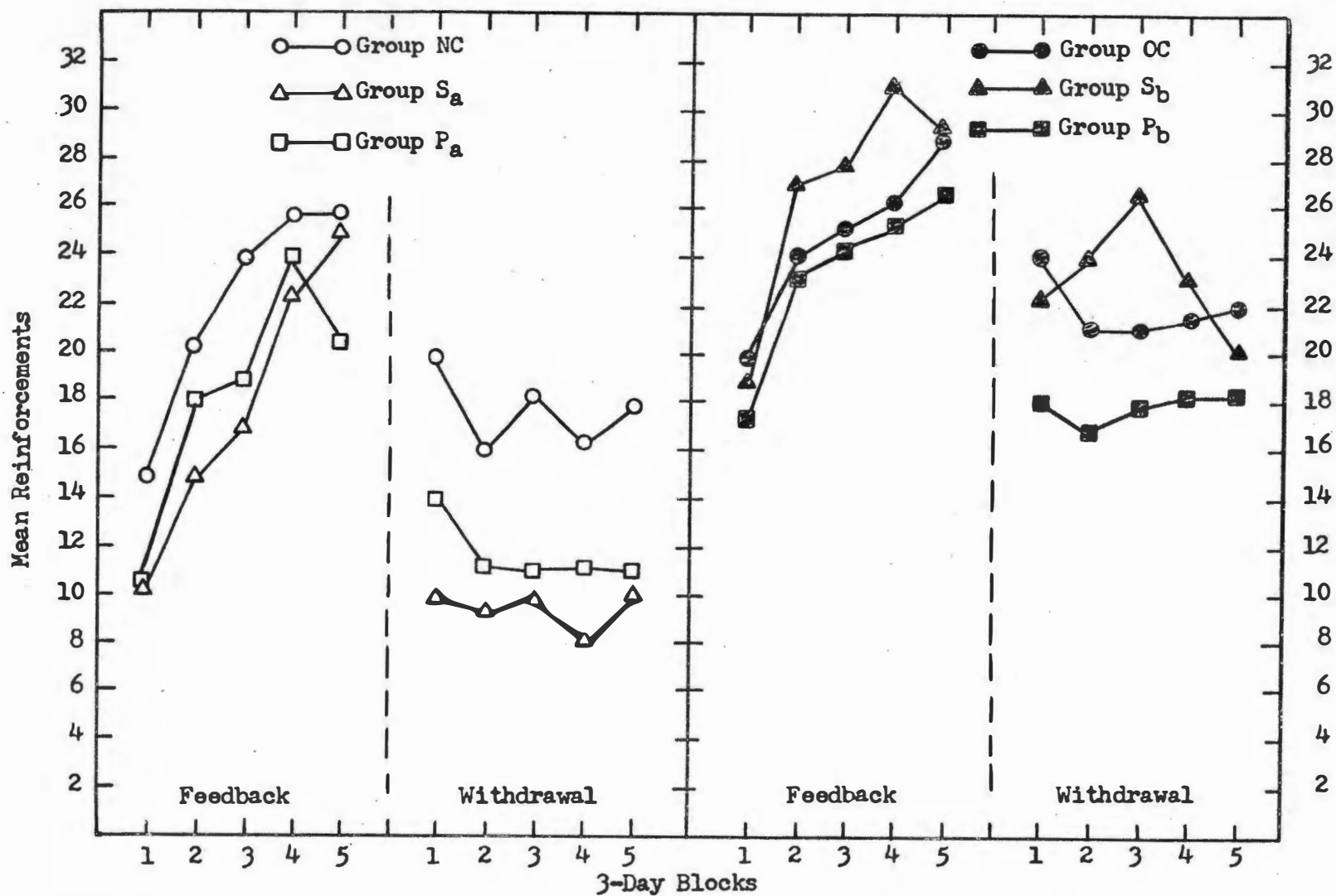


Figure III-7. Mean reinforcements during feedback and feedback withdrawal.

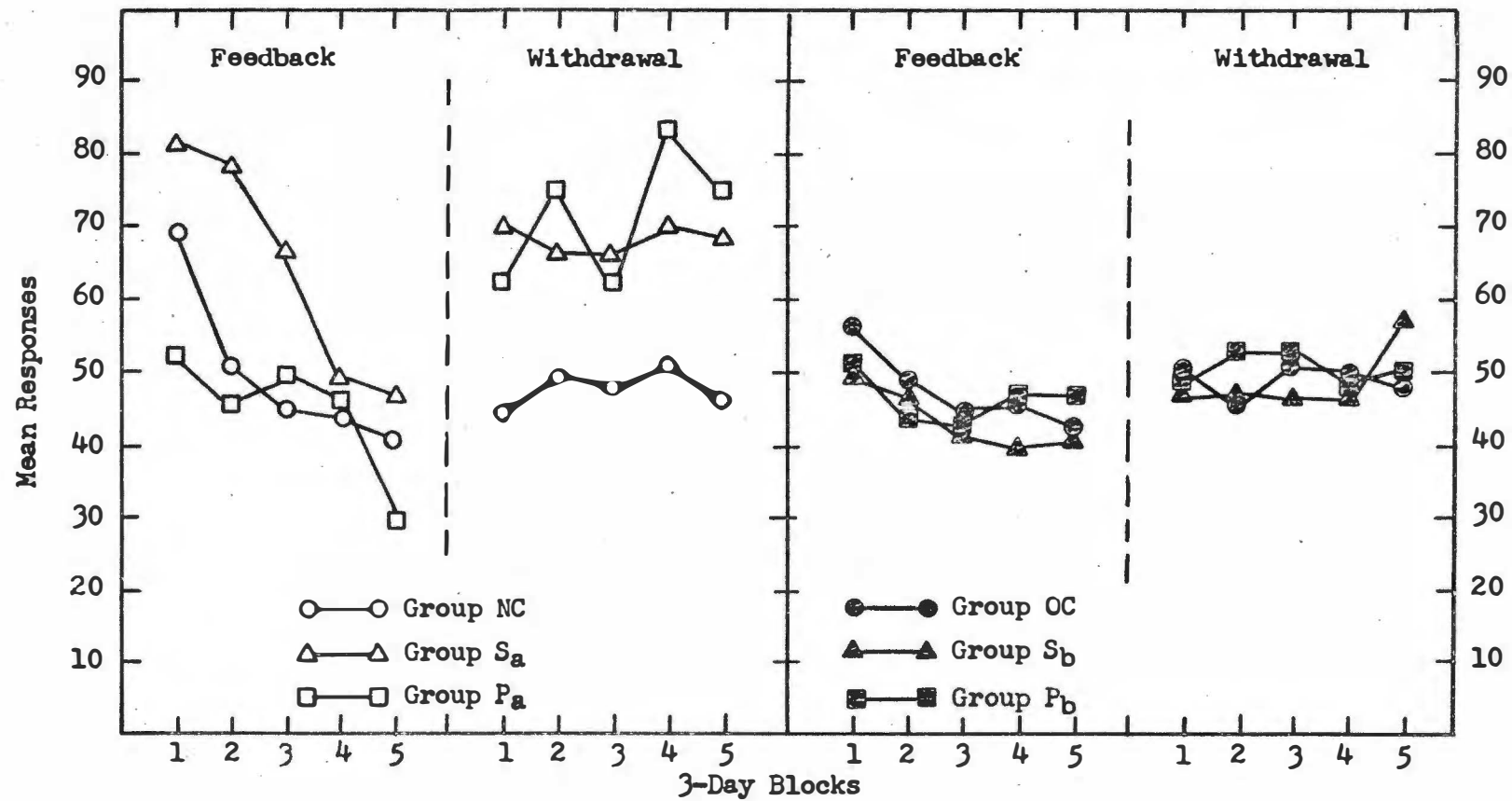


Figure III-8. Mean responses during feedback and feedback withdrawal.

During the fifteen days of feedback withdrawal all groups performed somewhat better than during the thirty days of DRL acquisition, but less well in comparison to their performance during the feedback condition. This decrement in performance was most pronounced for Groups S_a and P_a . These groups obtained fewer reinforcements and emitted more responses than any other group throughout the withdrawal period. During the last six days of feedback withdrawal Groups NC, OC, S_b and P_b all performed more efficiently (Figure III-6, p. 112) than Group S_a ($P < .05$, $df = 6$, $t = 2.14$; $P < .05$, $df = 5$, $t = 3.2$; $P < .05$, $df = 4$, $t = 2.89$; $P < .05$, $df = 5$, $t = 3.0$ respectively) and Group P_a ($P < .05$, $df = 6$, $t = 2.02$; $P < .05$, $df = 5$, $t = 3.05$; $P < .05$, $df = 4$, $t = 2.7$; $P < .05$, $df = 5$, $t = 2.79$ respectively). No other paired comparisons yielded significant t 's.

Figure III-9 illustrates, for each group, the average interresponse time histograms generated during the last six days of feedback (solid line) and the last six days of feedback withdrawal (dotted line). By the end of feedback training all groups showed a sharp rise in IRT frequency around the 42 second class interval. In other words, all peaks occurred after the cue light had been turned on. The fact that there was a rather sharp decline in IRT frequency on either side of this interval, indicates that the onset of the cue light at the end of 40 seconds acted as a discriminative cue for bar pressing. When the use of the cue light was discontinued all distributions tended to shift towards the left and showed a marked reduction in peakedness. These changes were most pronounced for Groups S_a and P_a , which generated distributions that were platykurtic with a sharp decline in response

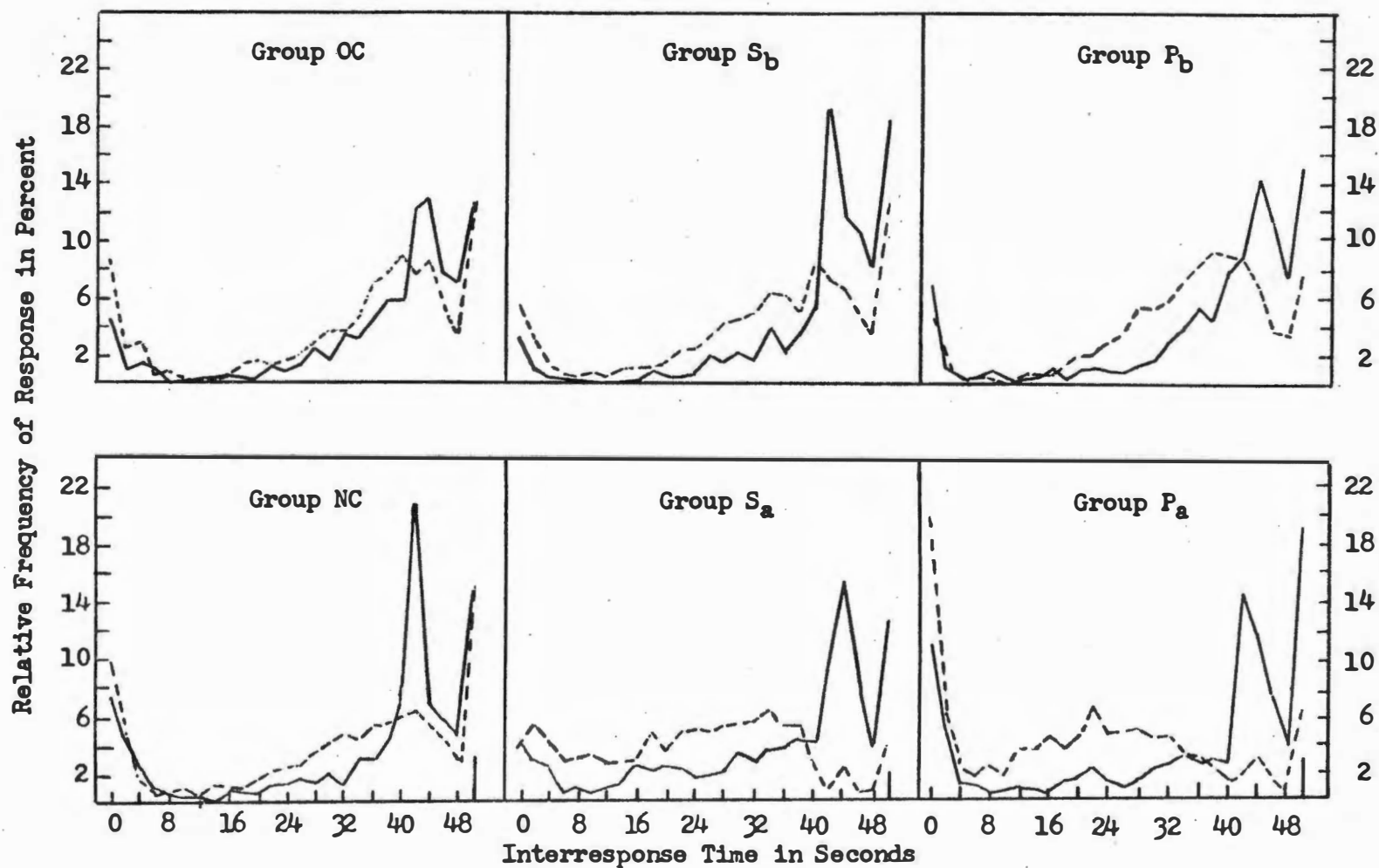


Figure III-9. IRT histograms generated during the last 6 days of feedback (—) and the last 6 days of feedback withdrawal (— —).

frequency following the 34 second IRT interval. All other groups generated distributions that were leptokurtic, with peaks between 38 and 40 seconds.

During the last six days of feedback training (solid line in Figure III-9, p. 116) the shape of the IRT histogram generated by group NC was significantly related to Group S_a ($r_s = .858$, $P < .01$) and Group P_a ($r_s = .881$, $P < .01$) distributions, which in turn were related to each other ($r_s = .887$, $P < .01$). However, during the last six days of feedback withdrawal (dotted line in Figure III-9, p. 116) the situation was identical to that which occurred during the last six days of DRL acquisition. While the shape of the interresponse time distributions generated by Groups S_a and P_a were significantly related ($r_s = .552$, $P < .01$), neither distribution was related to that generated by the normal controls ($r_s = .147$, $P > .01$; $r_s = .121$, $P > .01$ respectively).

The remaining groups generated distributions that were significantly related to each other, and to the distribution generated by Group NC both during feedback ($W = .92$, $r_{sav} = .89$, $\chi^2 = 92$, $df = 25$, $P < .01$) and during withdrawal ($W = .94$, $r_{sav} = .92$, $\chi^2 = 94$, $df = 25$, $P < .01$).

Collateral Behavior

Though quantitative measures of collateral behavior were not recorded, frequent observational periods were scheduled in order to detect the presence or absence of such behavior. All animals tended to develop some form of collateral behavior between responses. The most characteristic form of collateral behavior that developed consisted

of motor responses. For example, many animals would walk from the response lever to the food well, paw at the food well, return back to the response lever, circle it a few times, and then respond anew. In other animals collateral responses consisted simply of pacing, circling and wall scratching. Rapid pacing and circling responses were most obvious in Groups P_a and S_a . A few animals developed a mixed motor-vocal response pattern. The presence of excessive vocalization was most prominent in cat S-95 of Group S_a and P-40 of Group P_a . Cat S-74 of Group S_b also tended to emit a large number of vocalizations.

During acquisition and cue withdrawal the frequency of collateral behavior was greatest directly following a response, or the consummation of the reinforcer. As time since the last response increased, the amount of collateral behavior tended to decrease. Most animals did not emit any collateral responses just prior to responding anew, but rather remained poised and still in front of the response bar.

During cue presentation, collateral behavior was greatly diminished for all groups throughout the DRL interval. The animals tended to poise themselves near the response bar and await the onset of the cue light.

CHAPTER IV

GENERAL DISCUSSION AND CONCLUSIONS

The results obtained in the present experiment demonstrated that damage to the anteromedial septum and diagonal band or severe damage to gyrus preceus which includes its ventral sector impairs the performance of cats on a DRL 40 second schedule of reinforcement. This deficit is alleviated when an external cue is presented indicating the availability of reinforcement, but reasserts itself when the cue is no longer available. In contrast, damage to anterior limbic cortex leads to a moderate facilitation on this task. This latter effect appears to be related to a reduction in response rate that occurs after anterior limbic damage. Damage to the lateral septum alone, the dorsal portions of gyrus preceus, or neural tissue surrounding gyrus preceus (e.g., coronal gyrus, anterior sigmoid gyrus and pericruciate area) does not affect DRL performance. (Table IV-1 summarizes these main effects.)

The fact that septal or preceal damage in cats does not impair response regulatory processes equally in all operated animals has been reported previously. For example, Zucker (1965) and Zucker and McCleary (1964) have reported that septal damage in cats leads to deficient performance on the reversal of a spatial discrimination in only one-half of their operated animals, the remainder performed normally. These investigators, however, did not attempt a rigorous anatomical investigation, rather, they grouped their animals on the basis of prior passive avoidance performance. Warren et al. (1969) found a similar effect

TABLE IV-1

SUMMARY OF THE RELATIVE PERFORMANCE OF EACH GROUP
DURING DIFFERENT STAGES OF THE EXPERIMENT

Group	N	Performance During Different Stages of the Experiment			
		CRT	Acquisition	Feedback	Withdrawal
NC-OC	9	NI	NI	NI	NI
S _a -P _a	6	NI	I	NI	I
S _b	3	I*	NI	NI	NI
P _b	4	NI	NI	NI	NI

NI - No Impairment

I - Impairment

*Lower response rate than any other group.

after proreal ablation in cats. These investigators, however, were able to relate performance to extent of damage. They found that extensive damage to gyrus proraus increased resistance to extinction of a manipulatory response, and impaired performance during successive reversals of a spatial discrimination. Moderate damage to gyrus proraus, however, did not lead to deficient performance. In addition, the histological reconstructions presented by Warren et al. (1969, p. 247) show severe damage to the ventral sector of gyrus proraus in those animals that were deficient, and only minor injury to this area in non-deficient cats. In further support, the histological results of Divac (1972, pp. 520-521) suggest a similar trend relative to the effect of proreal ablation in cats on the retention of a delayed alternation task. These latter two findings are in direct agreement with the present analysis and stress the importance of the ventral sector of gyrus proraus in response regulation.

Previous reports (Burkett and Bunnell, 1966; Carey, 1968; Ellen and Butter, 1969) have emphasized the role of the anteromedial septum and diagonal band nuclei in DRL performance. These investigations, however, could not be generalized since the rat was studied in all cases. The present results corroborate these findings and extend the results to include the cat. In addition, the present findings, indicating that damage to other areas of the septum, and anterior limbic cortex does not impair DRL performance, and in addition may lead to moderate facilitatory effects, supports the position that response regulation is mediated, in part, by opposing neural processes in and around the septum (Burkett and Bunnell, 1966; Raisman, 1966; Carey,

1968). The results, therefore, provide evidence against a conceptualization of the septum as a unitary structure subserving a general function.

Studies related to the role played by frontal cortex in DRL performance have been scarce. Glickstein et al. (1964) found that damage to the dorsolateral frontal cortex in monkeys impaired DRL performance. The present analysis extends these results to include the cat. On the other hand, Schmaltz and Isaacson (1968) found that frontal-polar lesions in rats did not impair the retention or relearning of a DRL operant. In reference to this latter finding, however, it should be emphasized that recent anatomical (Leonard, 1969) and behavioral (Divac, 1971) investigations have suggested that medial cortex, anterior to the genu of the corpus collosum, rather than frontal-polar cortex, is the rat analogue of frontal cortex in higher organisms. Research just completed in our laboratory (Numan, Seifert, and Lubar, 1972) is in support of these findings. We have shown that frontal ablation, when restricted to medial cortex, does in fact, impair DRL performance in the rat. These findings, taken together, strongly implicate the frontal cortical areas, irrespective of species, in response regulatory processes.

The present experiment, in contrast to previous efforts, was specifically designed to compare the behavioral effects of both frontal and septal ablation within the same experimental paradigm. It was argued that such a design would enhance understanding of the similarities and differences between septal and frontal function. The present findings have shown that the deficit pattern on DRL exhibited by proreal and septal cats was virtually identical—there being only one exception. It was found, during DRL acquisition, that Group S_a cats responded at

a higher rate than any other groups, while Group P_a cats responded within the normal range (Figure III-4, p. 104). It is not clear whether this effect is due to a secondary impairment produced by septal ablation, but not by proreal ablation (e.g., increased activity), or whether it reflects a more extreme case of a unitary impairment common to both septal and proreal animals. The present results tend to favor the latter alternative, since during the period of cue withdrawal, groups S_a and P_a showed comparable response rates, and both groups responded at a higher rate than the normal controls (Figure III-8, p. 114).

Further evidence in support of the view that the septum and the gyrus preceus are functionally related is provided by the analysis of the IRT histograms in the present experiment. The shapes of the response histograms (indicative of patterns of responding) generated by the septal and proreal cats were found to be significantly related to each other, but unrelated to the histograms generated by normal animals.

Furthermore, the presentation of an external stimulus, indicating the availability of reinforcement, ameliorated the performance deficits for both the proreal and septal cats (Figure III-6, p. 112). These results, taken together, suggest that both the septum and frontal cortical areas subserve a similar function relative to response control, i.e., the modulation of response tendencies when meaningful exteroceptive stimuli are lacking.

Previous investigators have attempted to explain deficient performance on DRL schedules in terms of (1) changes in motivational state (Harvey and Hunt, 1965) and (2) response disinhibition (Carey, 1968). The first of these alternatives, as indicated earlier, receives virtually

no support. The findings of Conrad et al. (1958) and Segal (1962) also argue against an explanation in terms of motivational changes. The former investigators found that DRL performance in normal animals is relatively insensitive to changes in motivation; the latter investigator found that response patterns similar to those found in the present experiment after frontal or septal ablation, are produced by the stimulant amphetamine at dose levels which reduce food intake.

An explanation in terms of response disinhibition is also inadequate. The results of the present experiment clearly show that when an exteroceptive cue is presented, both septal and proreal cats inhibit their response tendencies as well as normal animals (Figure III-8, p. 114 and Figure III-9, p. 116). Only in the absence of meaningful exteroceptive stimuli does the behavior of septal and proreal animals degenerate.

The present findings, and those of previous investigations (Wagman, 1968; Ellen and Butter, 1969) support the view that deficient performance on DRL is due to an inefficient utilization of proprioceptive cues. More specifically, it is proposed that after septal or frontal damage, animals can no longer utilize proprioceptive cues derived from collateral responses. Collateral responses, as discussed earlier, probably facilitate timing behavior by bridging the temporal interval between reinforced bar presses (Laties et al., 1969).

In the present experiment, all animals tended to develop collateral behavior between responses. However, these collateral responses did not improve the performance of S_a and P_a animals. This finding indicates that septal and proreal damage in cats, while not effecting collateral

behavior per se, impairs the formation of consistent patterns of such behaviors which in turn would be necessary for accurate timing.

The results obtained during the period of cue presentation also lend support to this point of view. The onset of the cue light, acting as a discriminative stimulus for bar pressing, was found to alleviate the deficit in S_a and P_a cats. It was also noted, that collateral behavior drastically diminished in all animals during this stage of the experiment. These findings support the view that collateral responses were indeed acting as mediating stimuli, since their frequency of emission was reduced when no longer necessary. In addition, these results suggest that when septal and prefrontal cats do not have to rely on proprioceptive cues for response control, they perform as well as normal animals.

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APPENDICES

APPENDIX A

The following tables present individual data for each cat throughout the various stages of the experiment.

TABLE A-1

EFFICIENCY RATIOS FOR ALL SUBJECTS DURING DRL ACQUISITION

Cat Number	Days in Blocks of Three									
	1	2	3	4	5	6	7	8	9	10
C-7	.09	.15	.16	.25	.36	.49	.38	.59	.43	.46
C-68	.07	.16	.10	.07	.09	.07	.18	.19	.24	.34
C-55	.24	.23	.18	.26	.37	.39	.24	.25	.21	.21
C-2	.07	.07	.11	.15	.16	.20	.22	.38*	.33	.31
C-37	.05	.06	.05	.06	.12	.07	.08	.07	.11	.23
S _a -6	.06	.04	.02	.01	.02	.04	.02	.03	.03	.02
S _a -69	.06	.04	.06	.05	.02	.04	.02	.02	.03	.03
S _a -95	.03	.04	.05	.04	.04	.05	.11	.08	.07	.22
S _b -75	.17	.15	.27	.30	.25	.34	.27	.15	.27	.13
S _b -74	.14	.11	.19	.31	.46	.15	.11	.34	.32	.63
S _b -70	.25	.19	.18	.28	.36	.47	.33	.66	.56	.54
S _c -71	.09	.15	.12	.07	.14	.22	.17	.17	.33	.61
P _a -41	.06	.08	.05	.05	.07	.09	.07	.10	.10	.09
P _a -40	.09	.10	.06	.10	.05	.07	.07	.07	.08	.12
P _a -22	.07	.07	.08	.11	.06	.21	.07	.05	.13	.14
P _b -10	.07	.07	.08	.12	.15	.13	.15	.13	.22	.15
P _b -56	.10	.10	.15	.24	.26	.19	.15	.18	.15	.10
P _b -81	.08	.11	.18	.57*	.10	.12	.26	.38	.48	.37
P _b -80	.10	.06	.14	.19	.22	.26	.25	.39	.43	.39
P _c -79	.14	.24	.24	.30	.37	.22	.26	.83*	.17	.23
O-50	.08	.16	.16	.14	.24	.36	.34	.65	.65	.61
O-52	.09	.08	.05	.09	.08	.15	.14	.14	.36	.22

*Sick - Not averaged in group data.

For subscript designations see Table III-1 on page 83.

TABLE A-2

REINFORCEMENTS OBTAINED FOR ALL SUBJECTS DURING DRL ACQUISITION

Cat Number	Days in Blocks of Three									
	1	2	3	4	5	6	7	8	9	10
C-7	2	5	15	15	18	19	15	22	19	19
C-68	8	12	11	11	14	12	18	16	19	21
C-55	7	7	7	9	18	17	15	15	13	12
C-2	8	10	12	13	14	14	14	14*	19	18
C-37	7	7	6	6	10	7	7	6	9	14
S _a -6	4	6	3	2	3	5	3	4	3	2
S _a -69	8	5	8	7	3	5	3	2	3	4
S _a -95	6	7	7	6	6	7	9	9	8	13
S _b -75	11	11	14	14	14	16	13	13	18	10
S _b -74	3	6	11	15	10	9	8	19	17	23
S _b -70	14	13	12	15	16	22	17	23	21	21
S _c -71	3	6	11	7	11	12	12	12	18	22
P _a -41	3	3	2	4	3	4	3	6	5	6
P _a -40	9	12	8	10	7	7	6	7	7	9
P _a -22	8	9	9	11	6	13	7	6	10	8
P _b -10	11	11	9	9	11	10	12	10	13	11
P _b -56	8	9	11	14	15	11	9	10	9	6
P _b -81	8	6	11	12*	8	7	13	16	19	14
P _b -80	11	8	13	15	15	16	16	20	21	20
P _c -79	9	16	16	16	17	12	15	21*	10	13
O-50	8	9	10	8	14	18	18	26	25	25
O-52	8	11	8	11	13	12	13	11	17	18

*Sick - Not averaged in group data.

For subscript designations see Table III-1 on page 83.

TABLE A-3

RESPONSES EMITTED BY EACH SUBJECT DURING CRF TRAINING AND DRL ACQUISITION

Cat Number	CRF Days in Blocks of Three		DRL Acquisition Days in Blocks of Three									
	1	2	1	2	3	4	5	6	7	8	9	10
C-7	44	68	30	36	93	66	53	40	45	38	50	44
C-68	91	139	120	79	128	163	152	179	109	95	80	66
C-55	64	89	34	31	45	35	49	51	63	60	62	58
C-2	62	78	103	141	110	92	91	74	70	37*	61	63
C-37	67	65	133	129	132	121	88	97	92	88	80	61
Sa-6	91	115	76	147	176	187	135	129	134	109	109	108
Sa-69	103	107	122	144	142	151	140	129	131	125	124	122
Sa-95	75	92	176	172	146	153	160	144	103	112	104	78
Sb-75	51	65	72	76	52	49	58	50	72	87	67	77
Sb-74	34	39	23	51	64	52	37	65	73	58	53	38
Sb-70	39	44	54	75	65	58	56	48	58	35	38	41
Sc-71	108	85	29	44	99	109	76	71	67	73	56	39
Pa-41	115	85	60	43	43	70	62	44	45	59	49	66
Pa-40	81	72	108	119	126	103	138	105	89	94	81	75
Pa-22	91	76	115	126	115	99	105	61	99	115	77	92
Pb-10	94	140	165	129	108	84	77	77	78	75	66	71
Pb-56	75	71	81	92	72	57	57	57	57	53	61	58
Pb-81	36	34	110	63	64	28*	75	65	49	45	42	39
Pb-80	94	115	123	145	97	77	71	64	63	53	54	53
Pc-79	64	62	62	66	67	54	50	55	51	25*	59	58
O-50	101	131	97	60	64	54	60	52	53	40	40	41
O-52	93	95	85	143	165	125	126	84	93	80	56	84

*Sick - Not averaged in group data.

For subscript designations see Table III-1 on page 83.

TABLE A-4

EFFICIENCY RATIOS FOR ALL SUBJECTS DURING FEEDBACK TRAINING AND FEEDBACK WITHDRAWAL

Cat Number	Feedback Days in Blocks of Three					Feedback Withdrawal Days in Blocks of Three				
	1	2	3	4	5	1	2	3	4	5
C-7	.60	.60	.54	.38	.39	.35	.69	.58	.50	.76
C-68	.15	.40	.60	.75	.70	.58	.52	.50	.33	.46
C-55	.28	.62	.75	.83	.82	.49	.37	.33	.30	.29
C-2	.36	.68	.74	.76	.75	.60	.34	.60	.71	.64
C-37	.09	.10	.24	.35	.50	.33	.14	.15	.11	.21
S _a -6	.26	.76	.58	.87	.72	.12	.09	.19	.12	.28
S _a -69	.08	.07	.15	.37	.59	.17	.19	.17	.11	.15
S _a -95	.09	.09	.16	.36	.44	.16	.14	.14	.12	.11
S _b -75	.18	.34	.59	.89	.91	.44	.40	.39	.32	.26
S _b -74	.54	.80	.69	.72	.50	.37	.70	.70	.65	.28
S _b -70	.57	.76	.76	.78	.82	.72	.46	.64	.64	.70
S _c -71	.54	.59	.74	.68	.64	.59	.82	.44	.36	.61
P _a -41	.07	.21	.17	.38	.58	.20	.13	.33	.10	.18
P _a -40	.30	.58	.66	.84	.79	.30	.19	.12	.11	.15
P _a -22	.30	.49	.84*	.54	.59	.31	.16	.15	.22	.22
P _b -10	.22	.29	.33	.22	.24	.22	.15	.20	.21	.31
P _b -56	.30	.55	.60	.69	.81	.37	.34	.17	.34	.24
P _b -81	.48	.80	.64	.80	.84	.53	.65	.66	.57	.46
P _b -80	.51	.68	.90	.87	.75	.41	.33	.49	.45	.48
P _c -79	.44	.75	.65	.64	.76	.59	.50	.41	.40	.43
O-50	.60	.64	.64	.66	.75	.61	.61	.63	.69	.74
O-52	.12	.24	.38	.46	.55	.39	.24	.28	.36	.26

*Sick - Not averaged in group data.

For subscript designations see Table III-1 on page 83.

TABLE A-5

REINFORCEMENTS OBTAINED FOR ALL SUBJECTS DURING FEEDBACK TRAINING AND FEEDBACK WITHDRAWAL

Cat Number	Feedback Days in Blocks of Three					Feedback Withdrawal Days in Blocks of Three				
	1	2	3	4	5	1	2	3	4	5
C-7	23	16	17	14	13	8	12	16	10	13
C-68	12	23	28	35	33	25	22	22	20	22
C-55	14	27	35	34	35	22	17	16	16	14
C-2	18	28	26	26	25	25	19	26	28	26
C-37	8	7	14	20	23	18	10	11	8	14
S _a -6	16	28	26	28	25	7	7	9	8	12
S _a -69	7	7	12	21	27	10	11	10	7	9
S _a -95	8	9	12	18	23	12	10	10	9	9
S _b -75	12	20	26	35	35	21	20	21	17	15
S _b -74	21	31	29	28	24	18	32	29	26	17
S _b -70	23	30	28	30	29	28	20	30	26	28
S _c -71	23	22	26	26	25	24	20	22	17	25
P _a -41	3	10	14	20	12	14	12	15	14	15
P _a -40	15	25	27	34	34	14	11	8	7	9
P _a -22	13	19	15*	18	15	14	11	10	13	9
P _b -10	14	17	19	15	15	13	10	13	13	17
P _b -56	14	22	26	27	31	16	15	9	16	14
P _b -81	18	25	19	26	29	22	25	25	21	17
P _b -80	23	28	33	33	31	21	17	24	23	25
P _c -79	20	30	27	27	31	25	23	19	18	19
O-50	25	28	27	30	33	26	25	26	30	28
O-52	11	16	21	22	26	21	16	17	21	16

*Sick - Not averaged in group data.

For subscript designations see Table III-1 on page 83.

TABLE A-6

RESPONSES EMITTED BY EACH SUBJECT DURING FEEDBACK TRAINING AND FEEDBACK WITHDRAWAL

Cat Number	Feedback Days in Blocks of Three					Feedback Withdrawal Days in Blocks of Three				
	1	2	3	4	5	1	2	3	4	5
C-7	39	33	33	38	32	23	21	28	22	18
C-68	108	53	50	47	47	44	51	43	62	48
C-55	52	44	43	41	43	45	45	49	55	50
C-2	54	41	35	34	32	43	55	43	40	41
C-37	91	80	63	56	47	61	75	76	75	70
S _a -6	68	37	45	32	38	76	70	59	65	51
S _a -69	90	100	81	58	46	56	57	61	68	63
S _a -95	86	97	72	58	55	78	73	79	77	90
S _b -75	68	60	46	40	39	50	49	53	53	66
S _b -74	39	40	42	40	51	52	45	43	43	62
S _b -70	41	39	37	39	36	39	45	41	41	40
S _c -71	44	38	36	39	41	43	25	51	49	41
P _a -41	46	49	88	61	19	79	95	49	141	85
P _a -40	55	44	42	41	43	56	59	68	65	69
P _a -22	56	43	18*	34	26	51	71	70	44	69
P _b -10	64	60	59	73	72	59	72	65	61	54
P _b -56	50	41	45	43	38	43	46	55	50	57
P _b -81	37	32	30	32	35	43	39	39	37	36
P _b -80	49	41	36	38	41	53	53	48	50	52
P _c -79	46	40	42	42	41	43	45	47	46	45
O-50	41	45	42	45	39	43	42	44	44	39
O-52	92	68	56	55	48	71	68	63	60	65

*Sick - Not averaged in group data.

For subscript designations see Table III-1 on page 83.

APPENDIX B

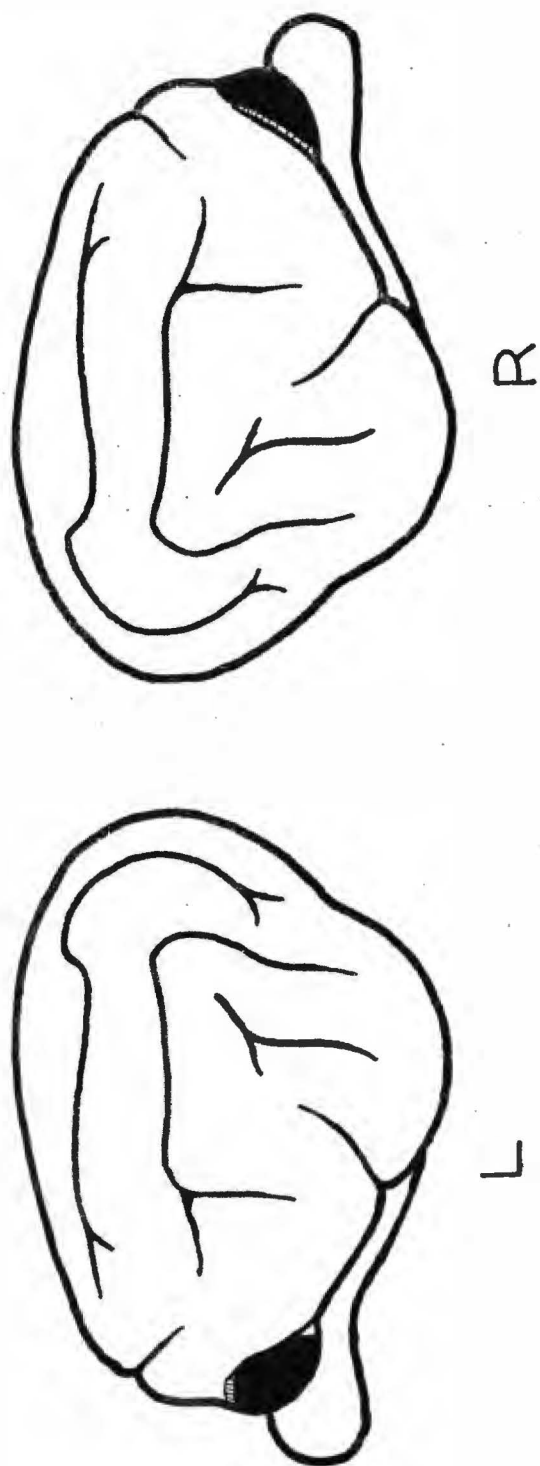
Figure B-1. Reconstructions of brain damage for proreal and operated control cats.



Lesion invades underlying white matter.



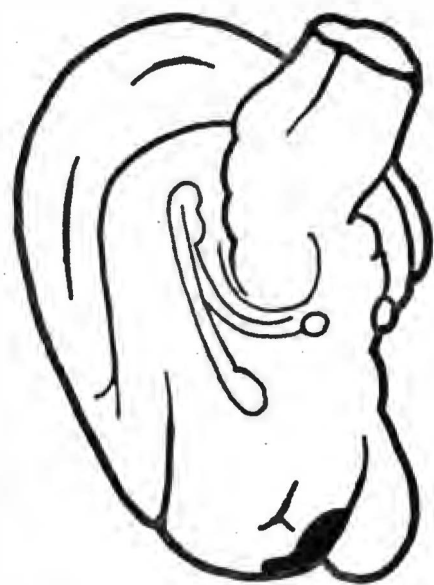
Lesion spares underlying white matter.



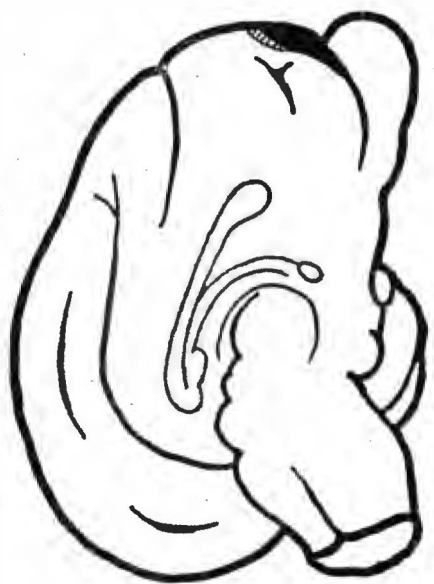
LATERAL

P-41

Figure B-1 (continued).



R

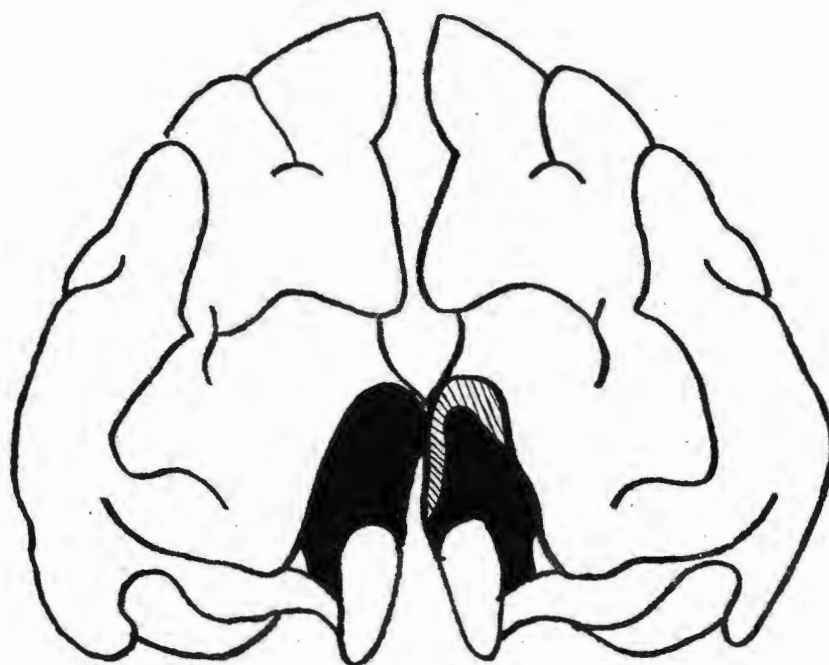


L

MEDIAL

P-41

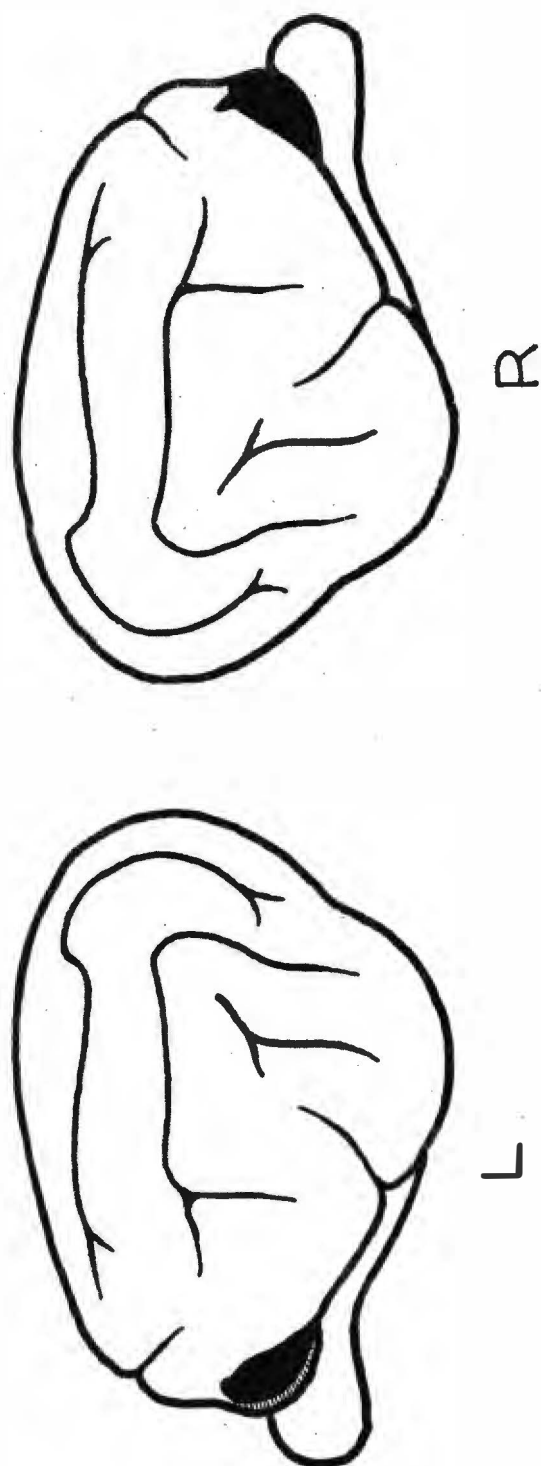
Figure B-1 (continued).



FRONTAL

P-41

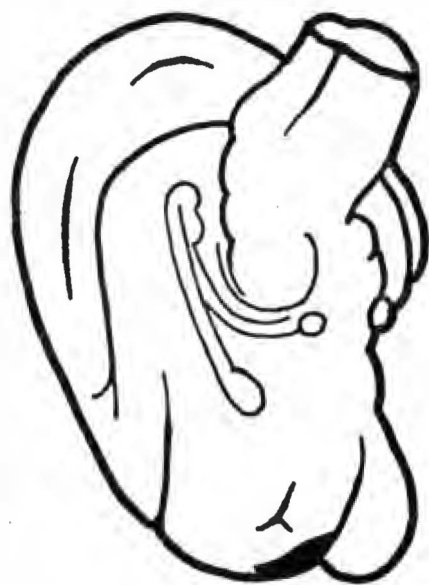
Figure B-1 (continued).



LATERAL

P-40

Figure B-1 (continued).



R

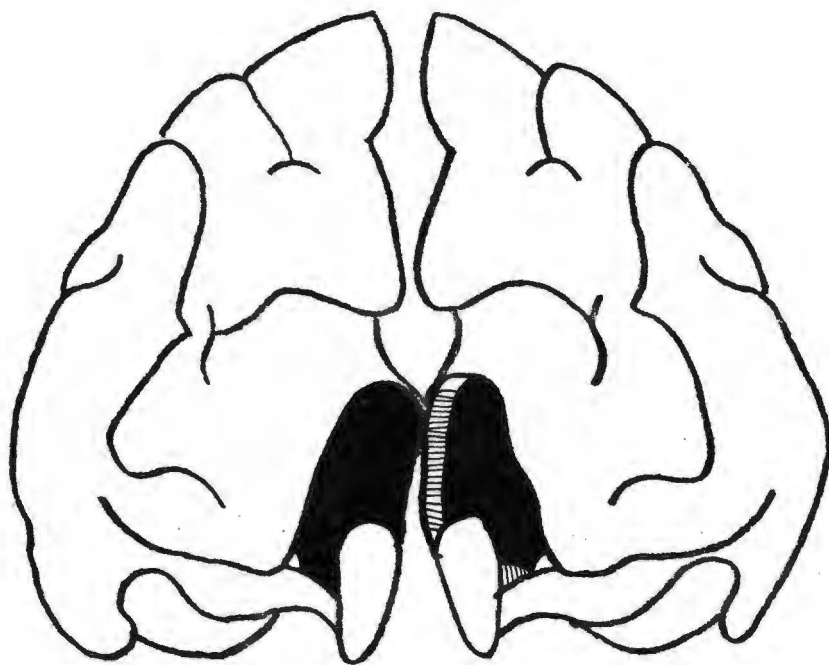


L

MEDIAL

P-40

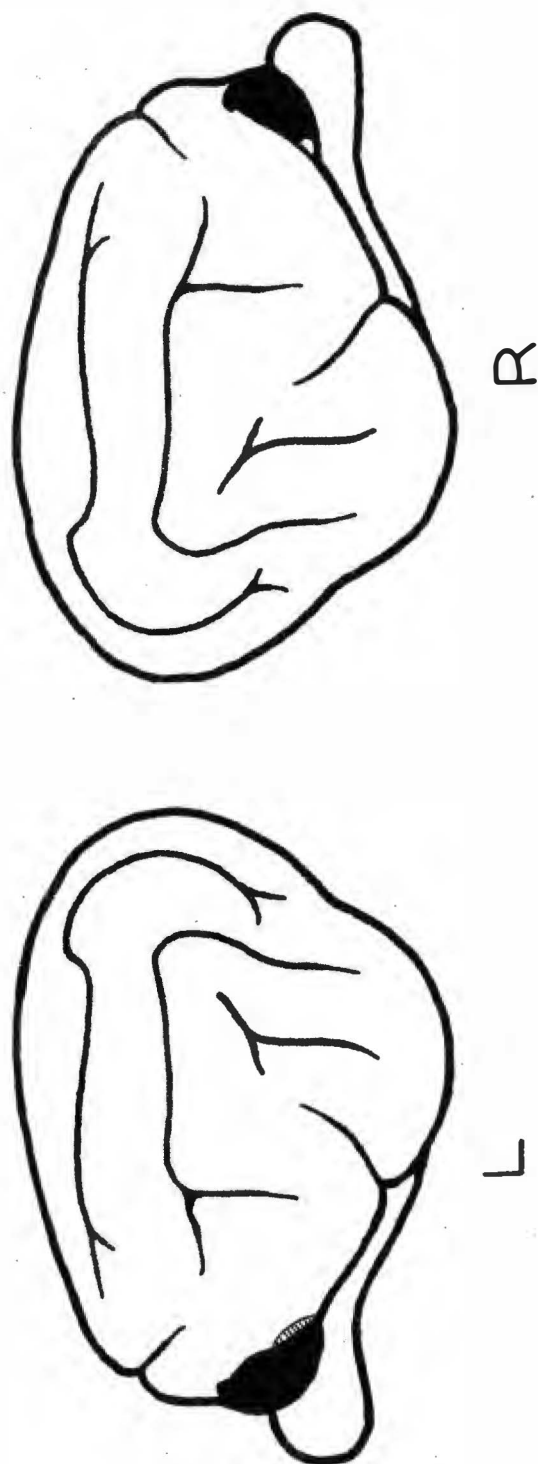
Figure B-1 (continued).



FRONTAL

P-40

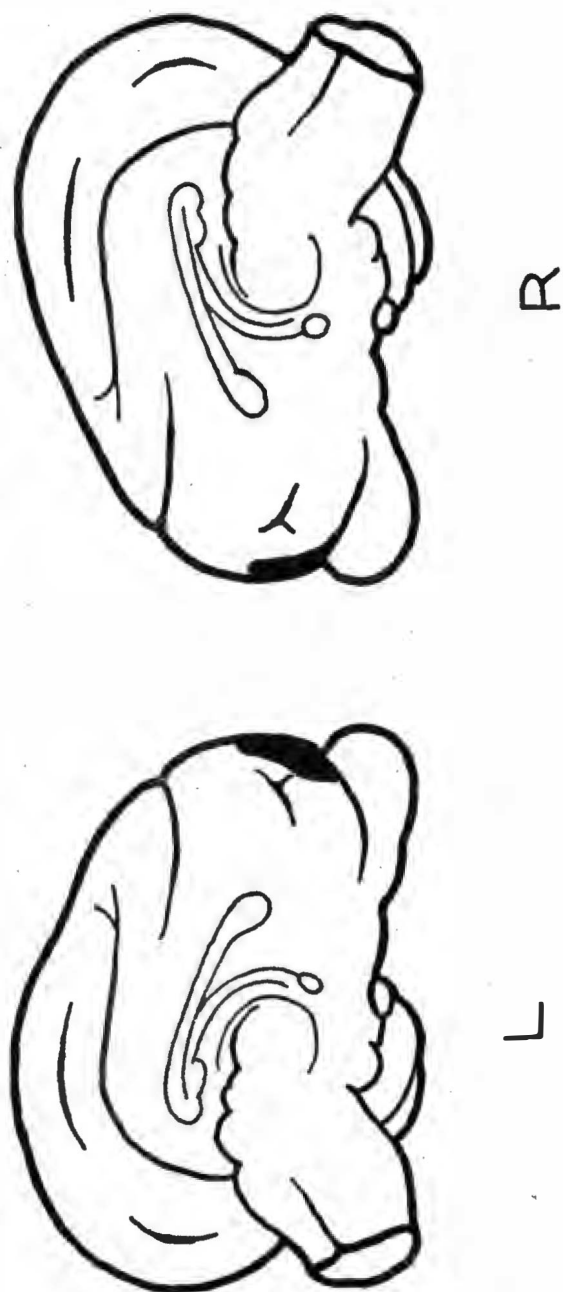
Figure B-1 (continued).



LATERAL

P-22

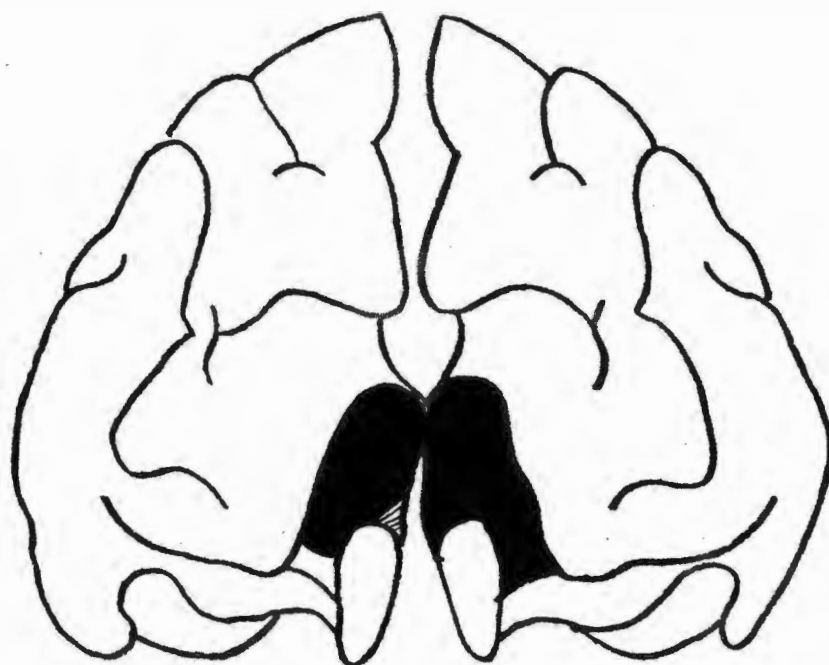
Figure B-1 (continued).



MEDIAL

P-22

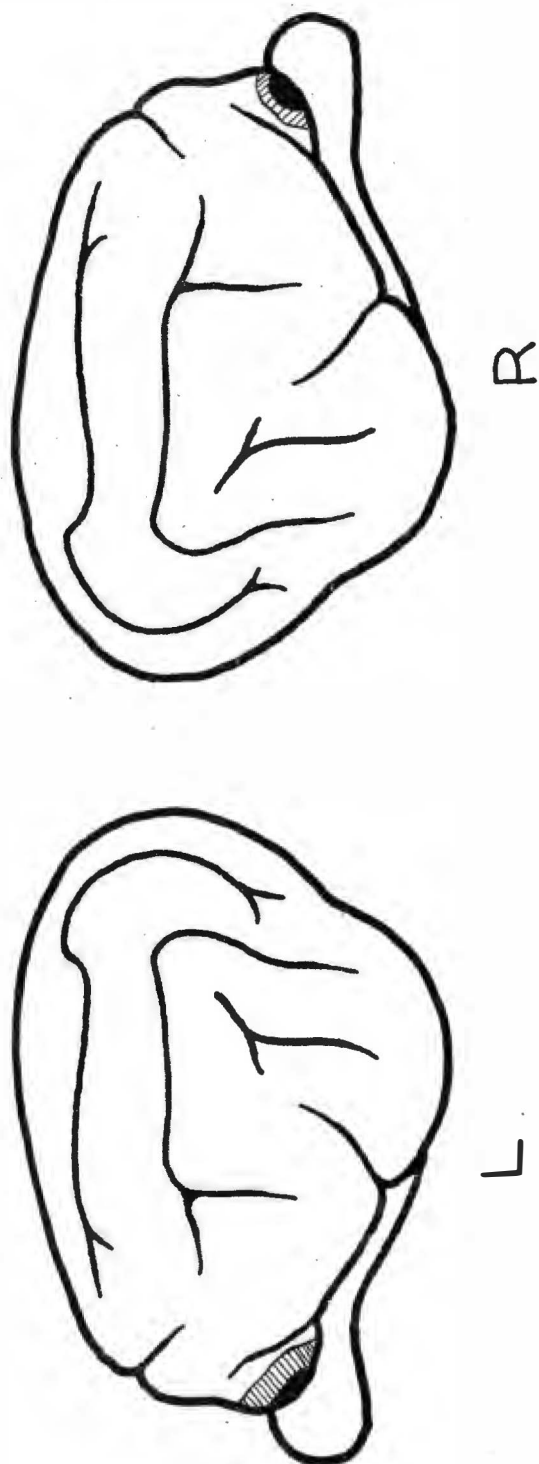
Figure B-1 (continued).



FRONTAL

P-22

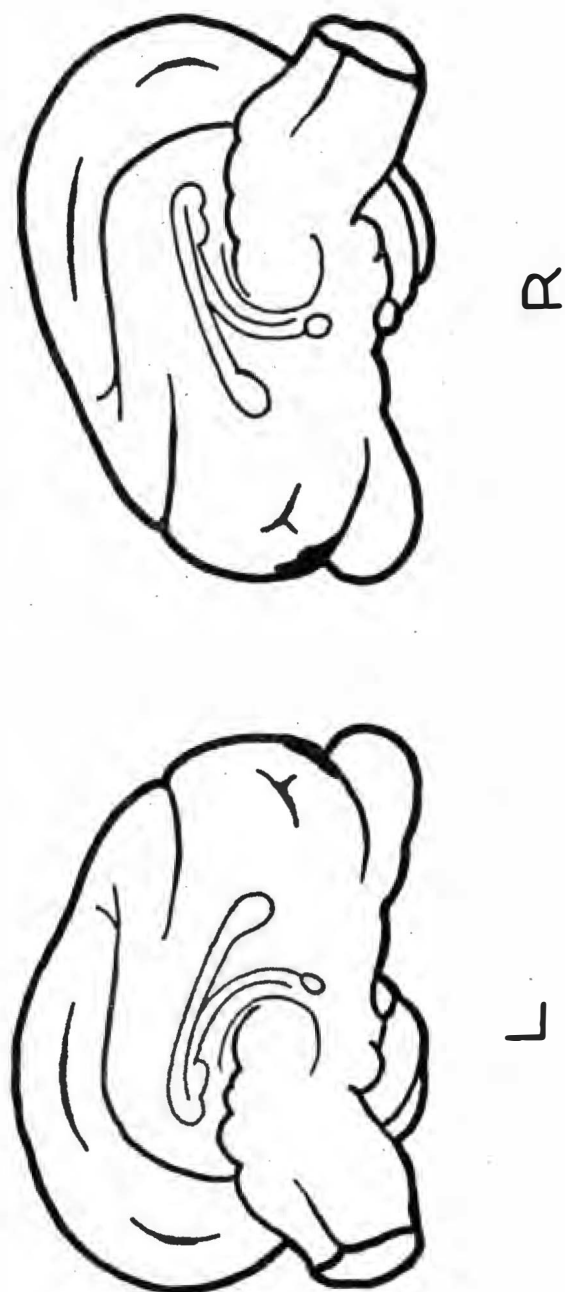
Figure B-1 (continued).



LATERAL

P-10

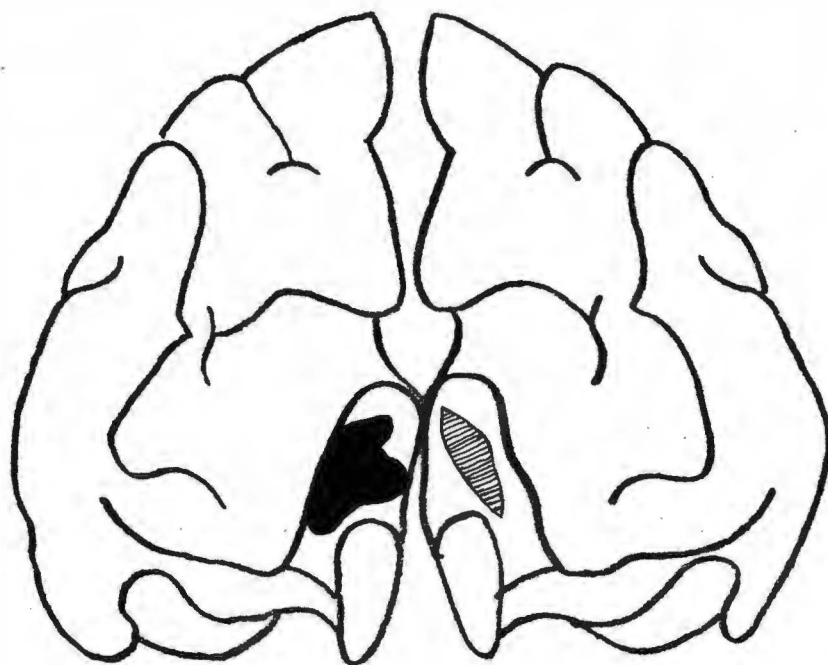
Figure B-1 (continued).



MEDIAL

P-10

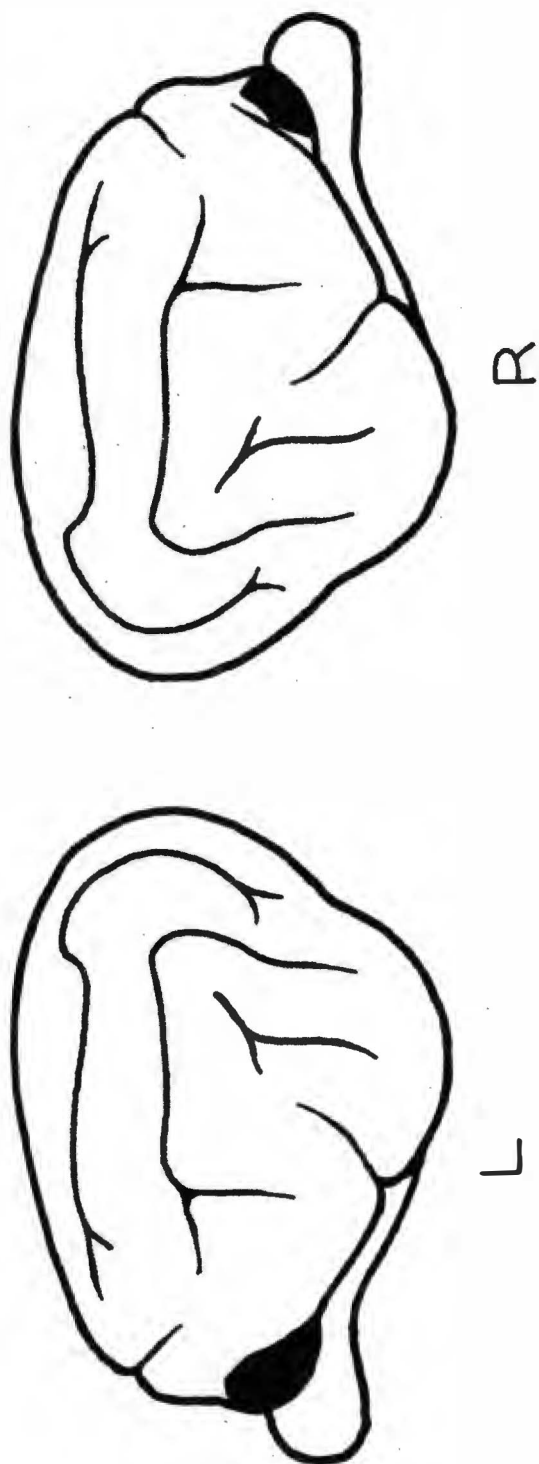
Figure B-1 (continued).



FRONTAL

P-10

Figure B-1 (continued).



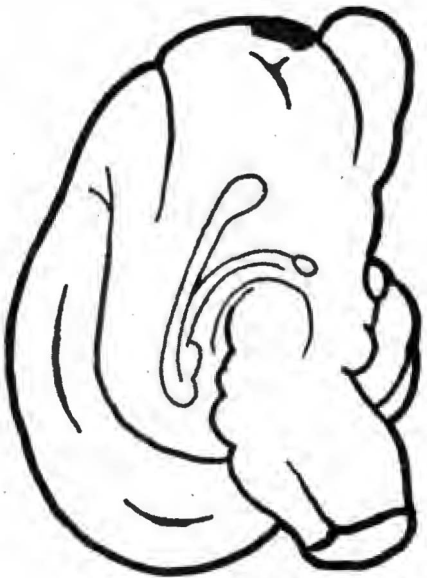
LATERAL

P-56

Figure B-1 (continued).



R

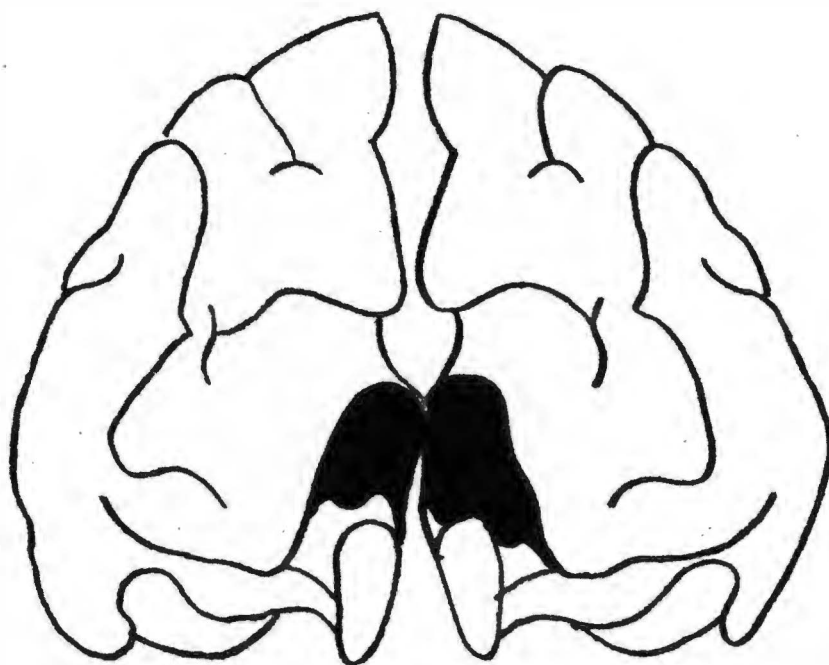


L

MEDIAL

P-56

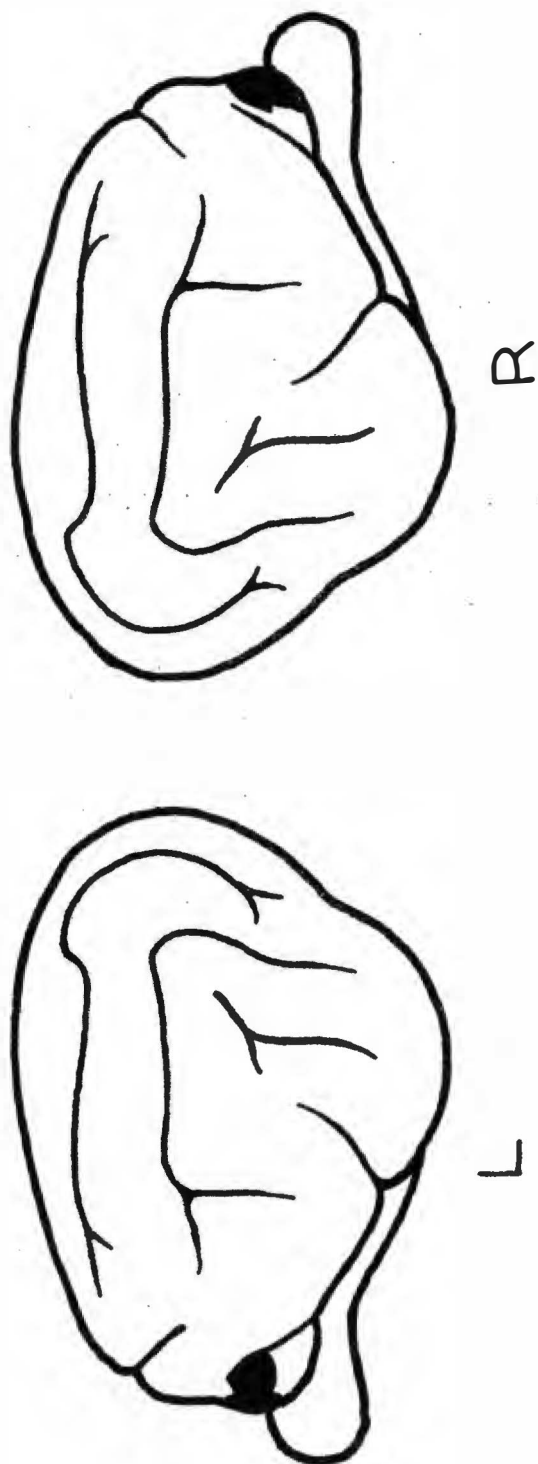
Figure B-1 (continued).



FRONTAL

P-56

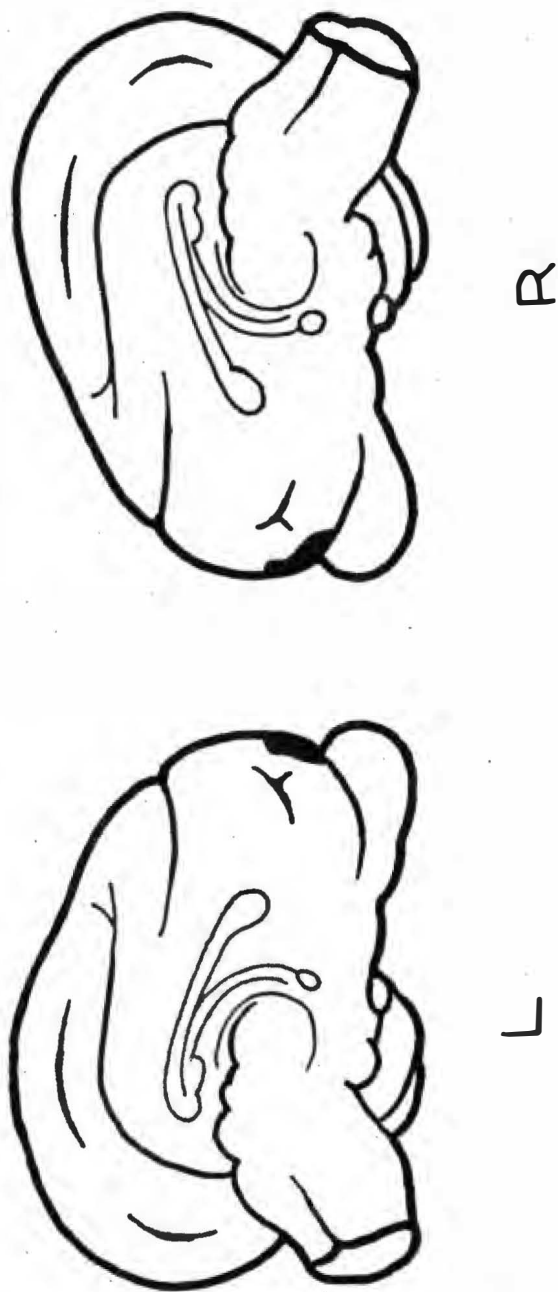
Figure B-1 (continued).



L A T E R A L

P-81

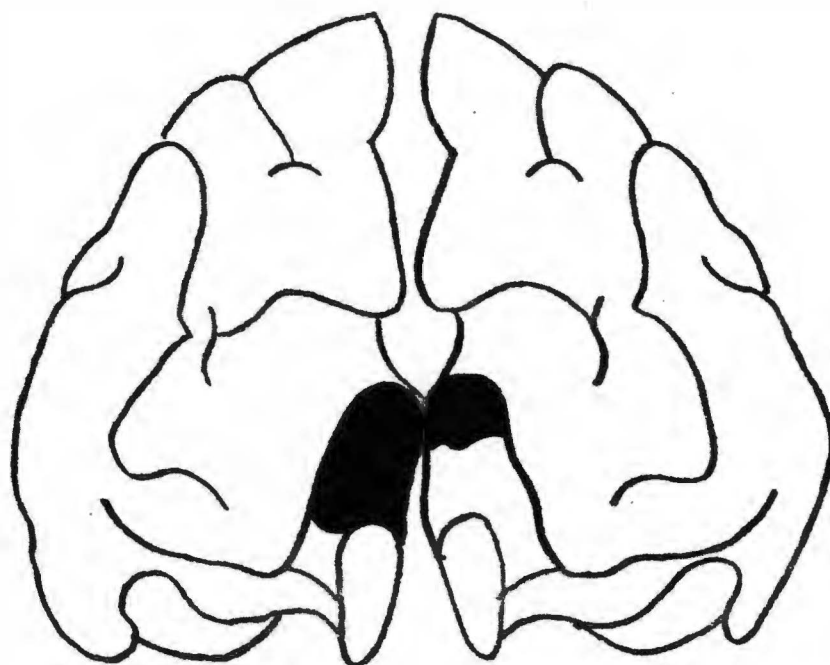
Figure B-1 (continued).



MEDIAL

P-81

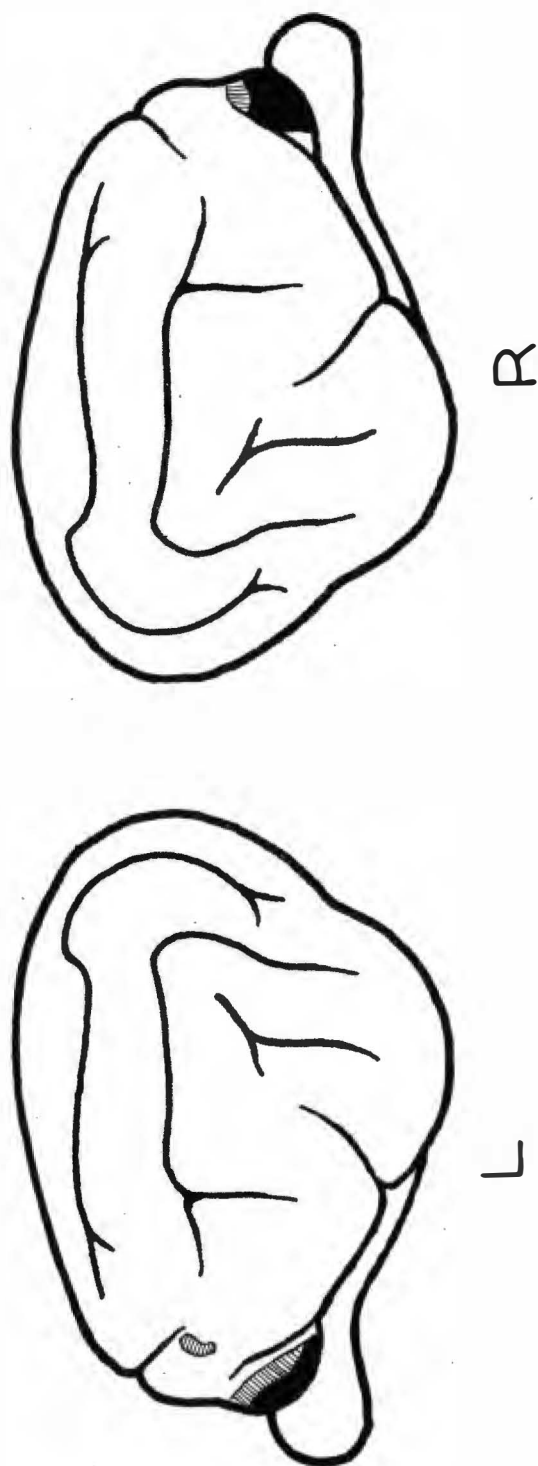
Figure B-1 (continued).



FRONTAL

P-81

Figure B-1 (continued).



LATERAL

P-80

Figure B-1 (continued).



R

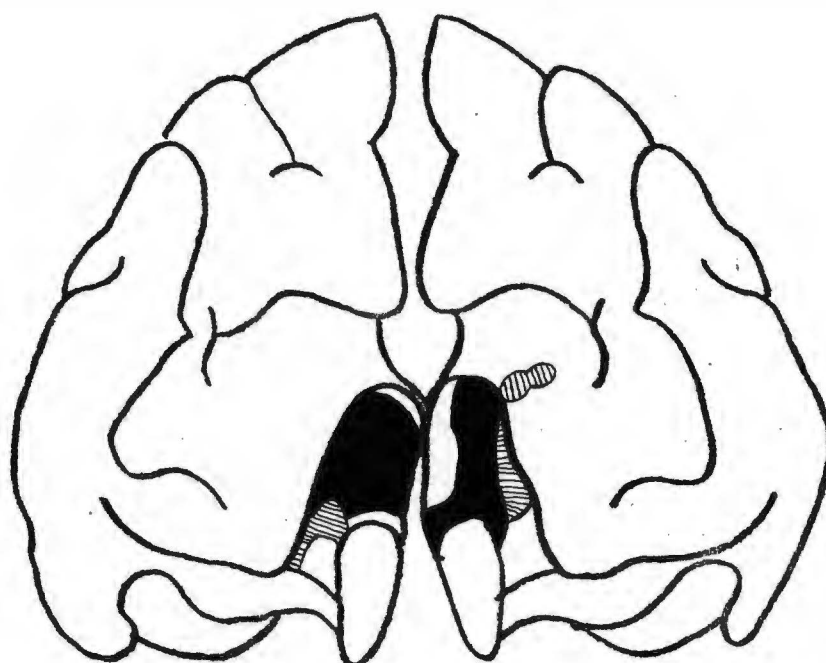


L

MEDIAL

P-80

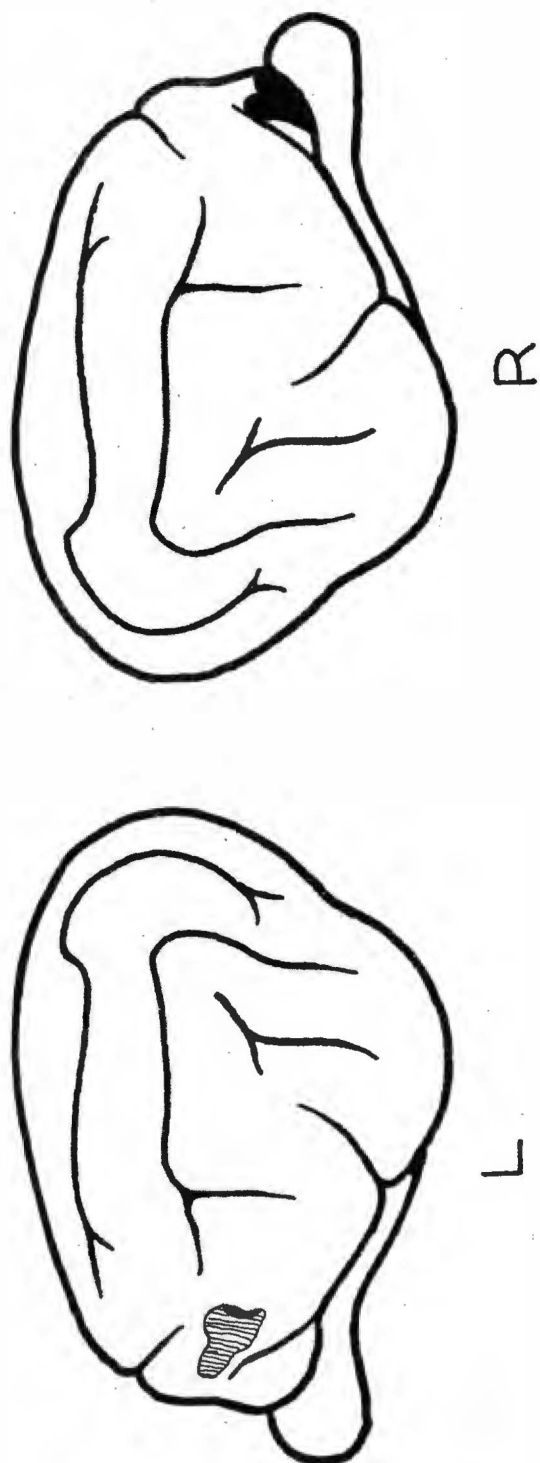
Figure B-1 (continued).



FRONTAL

P-80

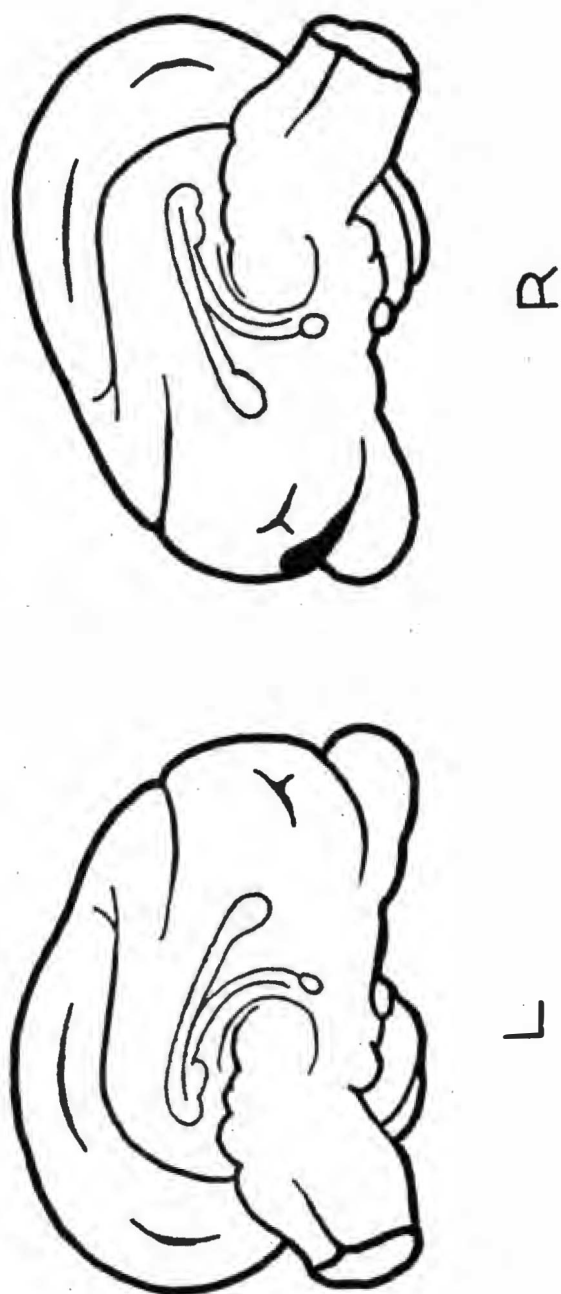
Figure B-1 (continued).



LATERAL

P-79

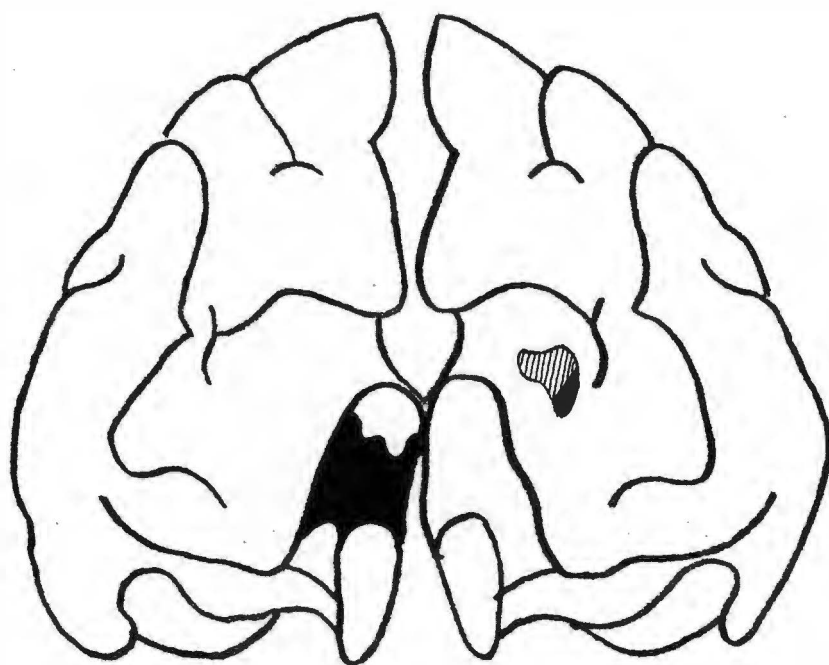
Figure B-1 (continued).



MEDIAL

P-79

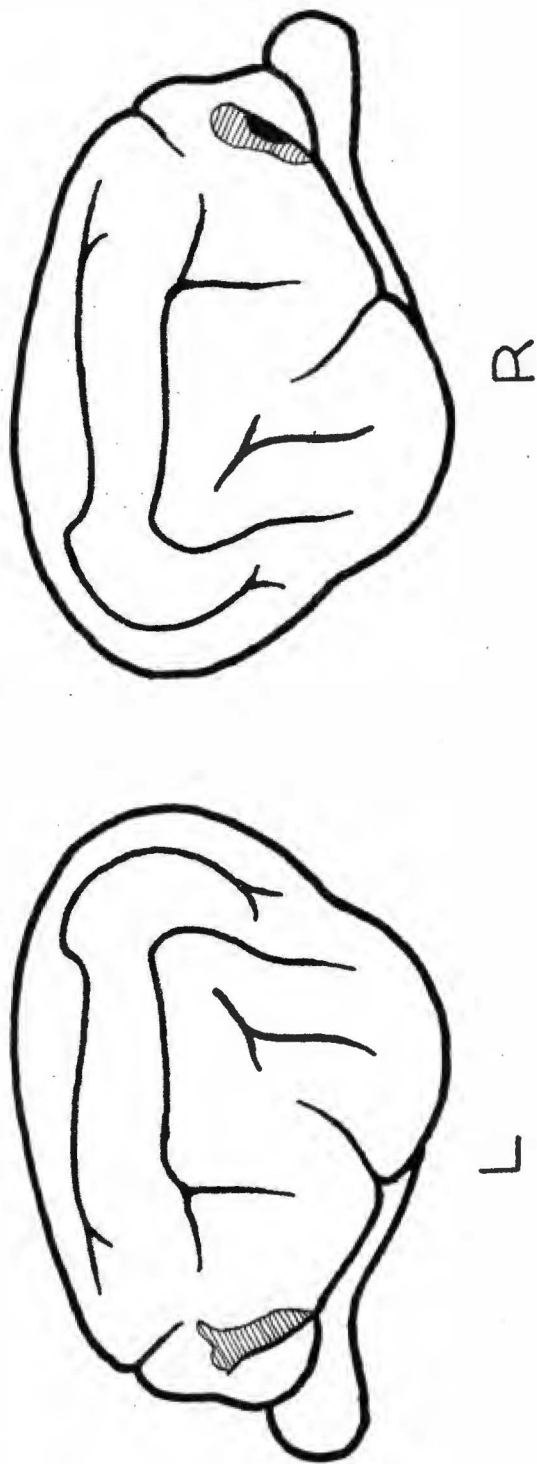
Figure B-1 (continued).



FRONTAL

P-79

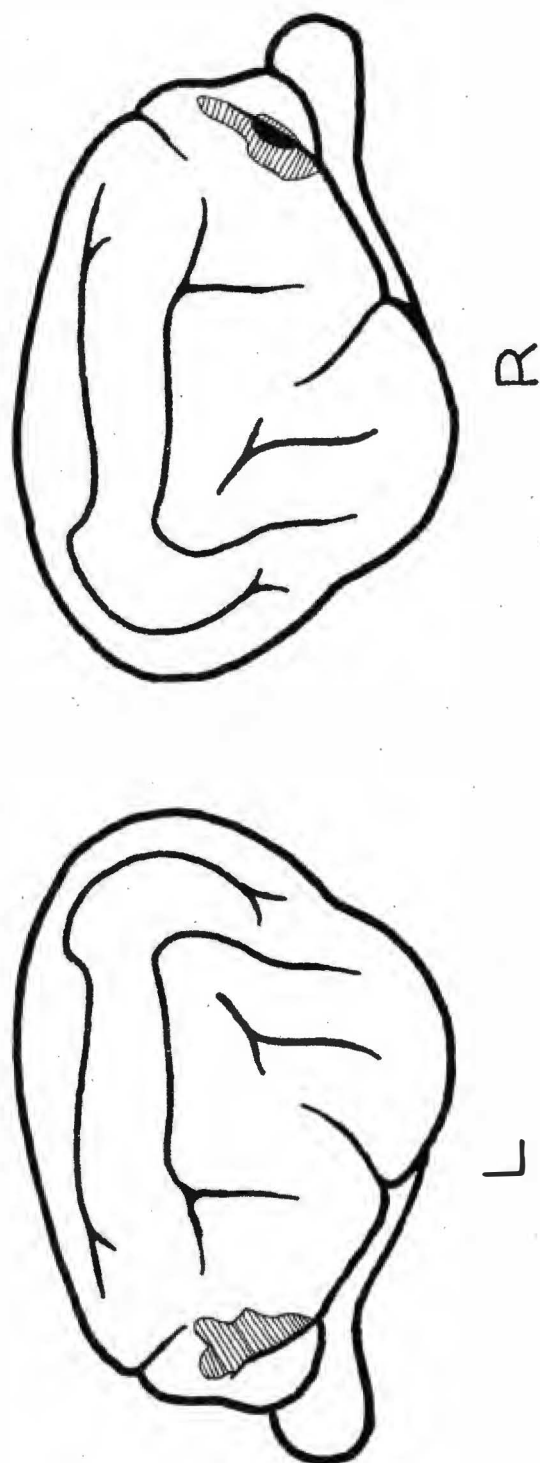
Figure B-1 (continued).



L A T E R A L

0-50

Figure B-1 (continued).



L A T E R A L

O-52

Figure B-1 (continued).

VITA

Robert Numan was born on March 2, 1946, in Brooklyn, New York. He received a Bachelor of Science degree, with a major in Biology, from Brooklyn College of the City University of New York in January, 1968. Upon completing his undergraduate training he was employed as a research assistant by the Sloan Kettering Institute for Cancer Research in New York City. He entered graduate school at the University of Tennessee in September, 1968, and received the Doctor of Philosophy degree with a major in Psychology in December of 1972. He is a member of the American Association for the Advancement of Science.