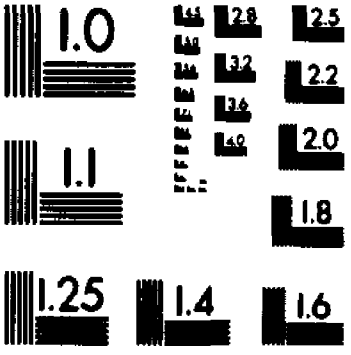


MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS
STANDARD REFERENCE MATERIAL 1010a
(ANSI and ISO TEST CHART No. 2)

Brutus, Martin

AN ANALYSIS OF THE MECHANISMS UNDERLYING SEPTAL AREA AND CINGULATE GYRUS CONTROL OF HYPOTHALAMICALLY ELICITED AGGRESSION IN THE CAT

City University of New York PH.D. 1986

PLEASE NOTE:

In all cases this material has been filmed in the best possible way from the available copy. Problems encountered with this document have been identified here with a check mark __✓__.

1. Glossy photographs or pages __✓__
2. Colored illustrations, paper or print _____
3. Photographs with dark background __✓__
4. Illustrations are poor copy _____
5. Pages with black marks, not original copy _____
6. Print shows through as there is text on both sides of page _____
7. Indistinct, broken or small print on several pages __✓__
8. Print exceeds margin requirements _____
9. Tightly bound copy with print lost in spine _____
10. Computer printout pages with indistinct print _____
11. Page(s) _____ lacking when material received, and not available from school or author.
12. Page(s) _____ seem to be missing in numbering only as text follows.
13. Two pages numbered _____. Text follows.
14. Curling and wrinkled pages _____
15. Dissertation contains pages with print at a slant, filmed as received __✓__
16. Other _____

_____

_____

AN ANALYSIS OF THE MECHANISMS UNDERLYING SEPTAL AREA AND CINGULATE GYRUS CONTROL OF HYPOTHALAMICALLY ELICITED AGGRESSION IN THE CAT.

by

MARTIN BRUTUS

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1986

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

30 Dec 85
date

Chairman of Examining Committee

January 2 1986
date

Executive Officer

Dr. Lou Gerstman

Dr. Donald Mintz

Dr. Richard Bodnar

Dr. Allan Siegel
Supervisory Committee

The City University of New York

ABSTRACT

AN ANALYSIS OF THE MECHANISMS UNDERLYING SEPTAL AREA AND CINGULATE GYRUS CONTROL OF HYPOTHALAMICALLY ELICITED AGGRESSION IN THE CAT

by

Martin Brutus

Adviser: Professor Solomon Steiner

This experiment was performed in order to examine several of the underlying mechanisms by which the septal area and adjacent regions regulate quiet biting attack behavior elicited from electrical stimulation of the hypothalamus in the cat. This behavior begins with quiet stalking of the rat and ends with a lethal bite directed at the back of a rat's neck. There is little sympathetic nervous system involvement other than some pupillary dilatation.

The results indicate that stimulation of the septal area and anterior cingulate gyrus increased the latency for the occurrence of quiet biting attack behavior. Those sites within the septal area from which inhibition of attack can be produced are linked to sensory mechanisms associated with trigeminal reflexes activated during hypothalamic stimulation. Stimulation of these septal area sites decreased the lateral extent of the "effective sensory fields of the lipline established during hypothalamic stimulation, but did not appear to have any effect upon the latency of the hypothalamically-elicited jaw opening response.

[^{14}C]-2-deoxy-D-glucose is a labeled structural analogue of glucose which can serve as a marker for increased glucose utilization. Since it has been established that a close relationship exists between energy metabolism and functional activity in central nervous system tissues, it has been possible to provide pictorial representations of the relative rates of glucose utilization during different stimulation elicited behaviors. Deoxyglucose autoradiography revealed that the inhibition resulting from stimulation of the lateral septal area may be due to either the monosynaptic activation of the lateral hypothalamus or the polysynaptic activation of this area utilizing a circuit involving the nuclei of the diagonal band of Broca.

It would appear that such limbic system structures as the septal region and cingulate gyrus provide tonic and/or phasic inhibitory control over hypothalamic organization of aggressive behavior, thereby reducing aggressive behavior to levels appropriate to the organism's stimulus environment. They do this in part, by modulating the trigeminal sensory components of the attack response. A fuller understanding of the neuropathology, neuropharmacology and neuroanatomy of aggression can allow for noninvasive drug or other therapeutic strategies to control nonadaptive aggressive behavior.

ACKNOWLEDGMENTS

I would first like to thank Dr. Robert Ackermann, whose excellent teaching inspired me to pursue a career in neuroscience. Thank you Dr. Dennis Kelly for the intellectual environment you provided at N.Y.S. Psychiatric Institute, which helped to shape my scientific thinking. My sincere gratitude is also offered to the members of this dissertation committee. I am grateful to Dr. Sol Steiner, Dr. Lou Gerstman and Dr. Don Mintz for the time and effort they have spent on this dissertation. Special thanks goes to Dr. Richard Bodnar for his continued intellectual and emotional support of my effort through these many long years. I thank him for his enthusiasm and his sharing of both his experience and knowledge so that I might realize this goal. I am most thankful to Dr. Allan Siegel of the Dept. of Neuroscience at New Jersey Medical School for the support, criticism and facilities necessary for the successful completion of this research. I would also like to thank him for sharing his intellectual thoughts about behavior and its neural basis and his encouragement and friendship. Thank you Rose Adler for your warmth and intellect and for rescuing this dissertation from last minute throes of incompletion.

Thank you Delia Aponte for the example of dignity and love you gave us all at the difficult end of your journey in this life. The life of this dissertation took many paths and was finally completed on the day you took your Samadhi.

Vaya con Dios. Ädiedäh Ema ja Isa. Mina armastan teid. Thank you Dr. Peter Dubno. With deep love and great respect, I acknowledge my wife Thelma Nin, who in the short time I have known her has transformed my life in every way. I love you. Om Namah Shivaya.

Table of Contents Page

Page

Page

Page

List of Tables and Figures Page

Page

INTRODUCTION

The problems generated by human violence and aggression have provided the impetus for the sustained research efforts in the fields of psychiatry and neuroscience of aggression during the past half century. Although much has been learned about violence and aggression, the neural bases underlying control of aggressive behavior, is still largely undetermined and therefore practical applications of such knowledge remains limited. Attempts to control or manipulate aggression essentially require an understanding of the extrinsic stimulus events that elicit it and the functional organization within the brain that allows for its expression.

Although there are many general similarities in the response topography and behavioral end-points of aggression, the particular patterns of aggressive behavior do differ. This would suggest that the neural circuits utilized are to some degree similar or overlapping but also different. On the other hand, the stimulus situations that elicit aggressive or agonistic behavior may vary considerably. These different kinds of environmental situations or triggers that elicit aggressive behavior have therefore been used to define the various types of responses (Moyer, 1976). Aggression is associated with the need for food (predatory), fear of environmental threats (defensive), protection of one's territory (territoriality), social dominance (intermale), protection of one's young (maternal), environmental

frustrations or obstacles (irritable), sexual contact (sex-related) and positive or negative affect or reinforcement (instrumental). Perhaps even other types of aggression exist. In the natural environment, a particular instance of aggression may involve a combination of these classes.

To study the neural mechanisms of aggression in the laboratory, animal models have been developed to control for the experimental variability found in the natural setting or in ethological experiments (Flynn, 1967; Flynn, 1972; Flynn, 1976; Flynn et al., 1970; Clemente & Chase, 1973; Goldstein, 1974; Moyer, 1976). Examples of these include isolation-induced aggression, frustration-induced aggression, pain-induced aggression, aggression due to overcrowding, spontaneous aggression, predation, intra-species fighting and electrical brain stimulation induced aggression.

The blocking of ongoing goal-oriented behavior can produce frustration-induced aggression (Dollard et al., 1939; Buss, 1961; Berkowitz, 1962, 1969; Miller, 1941; Bateson, 1941). Korn & Moyer (1968) placed a rat in isolation in a single cage for a month. This resulted in frantic escape attempts when the experimenter attempted to handle or restrain the rat. If cornered, the rat repeatedly tried to bite the experimenter. Largerspetz and Murmi (1964) taught mice to obtain food at the end of a runway. They blocked the goal box after the response had been well learned. The procedure resulted in aggression only when another mouse was present in the chamber. However, if the goal object is not

available, the experimental subject is said to be deprived (Berkowitz, 1962, 1969). Social deprivation or isolation can also result in aggression (Harlow, 1962). Almost all species show aggression after isolation (Valzelli, 1969; Hatch et al., 1963; Brain, 1973; Platt et al., 1967; Kuo, 1967). Application of a painful stimulus such as footshock (Johnson et al., 1972; Ulrich, 1967; Ulrich et al., 1965) will result in pain-induced aggression. The most common procedure utilized, involves the application of shock to the feet of two rats in a box with a grid floor. Application of shock makes the rats assume a boxing or fighting posture. Monkeys have also been shown to attack mice, rats and even other monkeys when shocked (Azrin et al., 1964). Insufficient space or high population density can also lead to fighting (Scott, 1944). Bevan et al., (1960) divided aggression into two classes: spontaneous aggression and competitive aggression. The only identifiable stimulus in spontaneous aggression appears to be the physical proximity of another animal. Competitive aggression occurs when two or more animals pursue the same goal object simultaneously. Valzelli (1967) includes both intra- and interspecies aggression under the category of spontaneous aggression. Predatory aggression is attack behavior directed against an animal's natural prey. It leads to the destruction or injury of the prey (Myer & White, 1965; Karli & Vergnes, 1963; Bandler, 1961; Karli, 1956). One type of intraspecies fighting includes inter-male aggression. This involves the

hostility of a male in one species with another male conspecific to which the attacker has not become habituated. Examples include a male mouse which will attack another male mouse, but not a young mouse or a female (Scott & Fredericson, 1951). Also a rat will attack a strange member of the same species, but will rarely attack a member of its own group (Barnett, 1963; Eibl-Eibesfeldt, 1961). In electrical brain stimulation - induced aggression stimulation of the lateral or ventromedial hypothalamus of the cat will result in quiet biting or predatory attack and affective or irritable aggression (Wasman & Flynn, 1962), respectively.

It is appropriate to analyze neural mechanisms in the somewhat simpler animal models of aggression such as in the rat or cat and then to cautiously extrapolate to or apply these insights to those mechanisms underlying the vastly more complex neural substrates of aggression in man (Goldstein, 1974; Siegel and Edinger, 1979). The animal and clinical literature suggest that there exist functionally discrete brain regions that play a critical role in the expression of both offensive and defensive aggressive behaviors. The hypothalamus appears to play a central role in the organization of naturally occurring and also electrical brain stimulation models of aggressive behaviors in both man and animals (Wasman & Flynn, 1962; Flynn, 1976; Clemente and Chase, 1973; Moyer, 1976).

In the laboratory, electrical stimulation of separate regions of the feline (Wasman & Flynn, 1962), rodent (Panksepp, 1971) and oppossum (Roberts et al., 1967) hypothalamus is known to elicit two forms of species specific aggressive behavior: quiet biting attack and affective attack behavior (which is also called affective defense or display).

Behavioral Studies

Affective Attack (Defense). An experimental model for defensive aggression that can be readily employed within the laboratory is the feline affective display (AD) response, which is similar to the caricatured response of the black "halloween" cat with arched back, hair standing on end (piloerection), spitting and hissing. An illustration of this form of aggression is depicted in Fig. 1. In the laboratory setting, the AD response can readily be elicited by electrically stimulating the medial portions of the hypothalamus (Hess and Brugger, 1943; Wasman and Flynn, 1962; Ranson, 1936-37). These studies have revealed that affective reactions could be elicited from the dorsomedial, perifornical and the ventromedial regions of the hypothalamus. Brainstem regions such as the midbrain central gray, the lateral tegmental fields adjacent to the brachium of the inferior colliculus (Magoun et al., 1930; Hunsperger, 1956; Skultety, 1963) and medial portions of the pons and medulla (Coote et al., 1973) also produce affective defense during

Fig. 1. Typical affective attack response elicited by electrical stimulation of the ventromedial hypothalamus (Flynn, 1972).

Fig. 1.

stimulation. Detailed maps of hypothalamic sites from which affective defense reactions can be elicited have been provided by Nakao (1958), Gluzman and Roizin (1960), Wasman and Flynn (1962), Skultety (1963), Hunsperger (1956) and others.

Stimulation of the ventromedial hypothalamic nucleus in the cat results in sympathetic nervous system activation producing pupillary dilation (mydriasis), piloerection, ear retraction, urination, growling or vocalization, hissing, finally culminating in a paw strike or defensive attack behavior (Ranson 1934; Hess & Brugger, 1943; Wasman & Flynn, 1962). While the end result of this response pattern during electrical stimulation is aggressive in nature, the attack response does not appear to be either solely directed at the natural prey object nor is it done so with lethal intent. The response may be directed at any moving object available in the visual field of the cat. In addition to preparing the organism for a fight situation, the recruitment of an increasing number of the various sympathetic response systems described above can serve as a warning stimulus to environmental threats. Therefore it is likely that it is largely a defensive response which begins as a fear response only to change to rage at the end. This warning signal enables the organism to ward off potential involvement in aggressive confrontations and provides a natural adaptive mechanism that minimizes energy loss and therefore has survival value. This response is clearly expressed to different degrees in the presence of various environmental

threats and is required for the defense of one's territory, protection of one's young, in situations involving social dominance and even in situations involving sexual contact or environmental frustrations (Moyer, 1976).

The AD response is also associated with aversive events (Adams & Flynn, 1966; Panksepp, 1971) and animals will therefore escape (Panksepp, 1971) from this type of electrical brain stimulation. As a matter of fact, in the natural setting, the natural outcome of an unsuccessful AD response (as evaluated by the threatened organism) to an imposing or life threatening stimulus is flight behavior.

Quiet Biting Attack. A form of aggressive or predatory behavior (Wasman & Flynn, 1962) called quiet biting attack (QBA) is prevalant in carnivores, and bears a resemblance to the behavioral pattern of a lion in a natural setting, stalking, attacking and killing an antelope (Berntson et al., 1976). QBA can be used as an experimental model for offensive aggressive behavior in the laboratory. This attack response can be elicited by electrical stimulation of portions of the feline hypothalamus lateral to a nerve fiber bundle called the fornix, from the preoptic area throughout the rostro-caudal extent of the hypothalamus. QBA can also be elicited by stimulation of the midbrain ventral tegmental area (Bandler et al., 1972), the pontine tegmentum (Berntson, 1973) and such thalamic nuclei as the mediodorsal nucleus (posterior aspects of it) and the nucleus reuniens (MacDonnell and Flynn, 1968). In the cat, this response is

characterized by an initial crouching, followed by searching and stalking of the prey in a clearly directed or calculated manner as compared to the more variable affective defense response. Latency to attack is used as the dependent variable and is defined as the time from onset of stimulation to the moment the cat's teeth make contact with the back of a rat's neck. This response culminates in a vigorous and generally fatal bite to the nape of the neck of an anesthetized rat or other anesthetized prey. Other than some mydriasis (pupillary dilation), other overt sympathetic signs are not visible. This serves to enhance the success of this largely cold blooded response. Sympathetic arousal evident during affective display would presumably only serve to warn the prey of the predator's presence and obstruct the outcome. Illustration of this form of aggression can be seen in Fig. 2.

Although predatory behavior by definition involves the hunting of prey for food, electrical stimulation of the lateral hypothalamus can be differentiated from feeding behavior (Flynn et al., 1970; personal observations). In our hands (Siegel, 1982), QBA is a very specific behavioral sequence and feeding behavior is rarely if ever elicited from sites eliciting quiet attack. During stimulation of the hypothalamus, most cats displayed QBA behavior only, and typically passed by a dish of cat chow placed between the cat and the anesthetized rat. In addition, experimental procedures which affect feeding, such as food-deprivation,

Fig. 2. Quiet biting attack response elicited by electrical stimulation of the lateral hypothalamus(courtesy of Allan Siegel).

Fig. 2.

do not appear to affect electrically elicited predatory attack (Flynn, 1970; Paul, 1972). Twenty-four to forty-eight hour food-deprived cats, which by-passed food to attack a rat during their normal diet, interrupted eating horsemeat to attack a rat following electrical stimulation of a hypothalamic attack site (Flynn et al., 1970). Stimulation of the lateral aspects of the hypothalamus of the cat therefore seems to activate clearly defined aggressive components of the predatory response and not the end point of this behavioral sequence, namely feeding. It has also been our experience and that of others (Levinson & Flynn, 1965) that cats will attack (QBA) a live or anesthetized rat more frequently than a dead rat or objects that are progressively less similar to this natural prey, such as stuffed animals, dogs or styrofoam blocks. In the presence of the appropriate prey object, the predator will discriminate and attack species-specific stimulus targets (discriminative stimuli), whereas in their absence there will be response generalization and attack of prey objects according to their similarity in physical appearance and other parameters (such as odor, texture, etc.), to their natural prey (discriminative stimulus) (Siegel & Edinger, 1979; Levinson & Flynn, 1965).

Although some researchers indicate the specificity of the quiet attack response as an aggressive response, others suggest that feeding can also be elicited from their attack sites in the rat (Panksepp, 1971) and cat. Rats exhibiting

quiet attack behavior will eat food pellets or gnaw a block of wood when mice are not available (Panksepp, 1971). Cats are also known to initiate feeding behavior from placements eliciting quiet attack if current intensities are lowered (Hutchinson & Renfrew, 1966).

Valenstein's (1968) data on eating, drinking or gnawing in the rat also challenged the hypothesis that specific hypothalamic substrates subserve separate response topographies based on the fact that electrically elicited behavioral responses are expressed in the presence of appropriate environmental triggers. In the absence of a particular class of triggers, other behaviors similar in nature will be expressed during the stimulation, appropriate to the stimulus conditions remaining. This is reminiscent of recent research on environmental triggers of endogenous pain-inhibitory systems (Bodnar, 1985; Terman et al., 1984) which suggest that the diversity and complexity of environmental stimulus events has allowed multiple neural systems to evolve in order to receive and activate differential analgesic responses, thus providing optimal coping and adaptive behavior. Therefore at least quiet attack behavior in the rat may not be subserved by fixed brain circuits because it has not provided as high a degree of survival value during evolution. It is likely therefore, that it would be more difficult to elicit only quiet attack during electrical stimulation or when appropriate environmental stimuli are present. The carnivore on the other hand has physically

evolved to be able to stalk and emit clearly defined biting attack behavior when electrically stimulated or environmentally triggered. Although the environmental triggers of attack behavior have been studied in some species, numerous others have not and therefore this certainly leaves the issue of attack response topographies for most species other than in the carnivore open to some degree.

An alternative explanation of mixed responses, both aggression and feeding, from stimulation of a single hypothalamic site is that the electrode was implanted in a region bordering both an attack and feeding substrate (personal observations). In this circumstance, since the electrode placement is not exclusively stimulating either system, some environmental triggers may be more influential than others in accessing those afferent systems in eliciting one response pattern over the other. A third explanation could be that variability in hypothalamic current intensity (e.g. increases or decreases) and therefore spread of current, could access larger or smaller areas of tissue with more or less involvement of one behavior over the other. Finally, stimulation of the smaller rat brain at controlled current intensities would likely involve the activation of more cells and fiber bundles than similar stimulation of the region in question in the comparatively larger cat brain.

Another aspect of quiet biting attack behavior, unlike the affective defense response (Adams & Flynn, 1966; Panksepp, 1971) is the likelihood that it is positively re-

inforcing. Although it is not true for all cases, rats are known to self-stimulate from brain sites that also elicit attack behavior (Panksepp, 1971). Finally, rats will also learn a discrimination task in order to obtain the opportunity to kill (Myer & White, 1965).

Lesion Studies and Aggression

Lesion or ablation studies attempt to determine whether a specific brain region mediates a behavioral response. The presence or absence of the behavior in question, following the surgical removal of the brain locus, therefore, provides a limited answer to this problem. An increase in the behavioral response would suggest that the region normally inhibits the behavior. A decrease in the behavioral response would suggest that the region normally stimulates or disinhibits the behavior.

Early work involving cortical ablations was found to increase aggressive displays in dogs (see Goltz, 1982). Woodworth and Sherrington (1904) were able to elicit the behavior characteristic of a highly emotional state in a decerebrate cat. They suggested the response be called "pseudo-affective" since it closely resembled the normal aggressive cat, but the eliciting stimulus was electrical brain stimulation as opposed to a natural stimulus. Similar behavior was termed "sham rage" by Bard (1928). In the enraged cat, retraction of lips, exposure of canines, pupillary dilation, piloerection or arching of the back are pre-

sumably expressions of an inner feeling (Flynn et al., 1971). Inner feelings are presumed to be cortical or hypothalamic in origin. However inner feelings are not necessary for the expression of rage, since decerebrate (forebrain removed) and hypothalamic (forebrain except for posterior hypothalamus is removed) cats do exhibit rage behavior.

Other early evidence seemed to point to brainstem and diencephalic but not neocortical involvement in the elicitation of rage behavior (Bazett and Penfield, 1922; Keller, 1932; Cannon and Britton, 1925). The posterior hypothalamus and brainstem appeared to be critical for its expression (Bard, 1928; Masserman, 1938; Ingram et al., 1936; Ranson, 1936-37) since lesions placed caudal to the posterior hypothalamus prevented rage behavior during the presentation of somatic or other stimuli which normally elicited this response. Demonstration that bilateral damage to the ventromedial hypothalamus produced a permanently savage cat provided further evidence in support of this role for the hypothalamus (Wheatley, 1944; Glusman, 1974). Since lesions of the ventromedial hypothalamus produced effects similar to electrical stimulation of this region, Glusman (1974) suggested that the neurons in intact regions such as the midbrain central gray, from which affective aggression could still be obtained experienced denervation supersensitivity. When a functional chain of neurons at higher centers in the nervous system (ventromedial hypothalamus) are destroyed,

the activity at lower centers (midbrain central gray) they control is generally increased. The supersensitivity is greatest for the links which immediately follow the severed neurons and progressively less for the more distal elements in this chain. The result of loss of nerve input to a region may cause a deficiency of a given neurotransmitter. This may perhaps result in the increased sensitivity of post-synaptic receptors or an increase in the number of active receptors for the transmitter. Alternative explanations for increased rage included axonal sprouting of ventromedial hypothalamic neurons projecting to the midbrain central gray sites (Glusman, 1974) or perhaps production of an irritative focus in the remaining hypothalamic tissue due to the deposition of metals during the process of making a lesion (Rabin, 1968; Reynolds, 1963). Ventromedial hypothalamic tumors, perhaps serving as irritative foci in humans can also result in threshold reductions for aggressive behavior (Reeves and Plum, 1969). Ellison and Flynn (1968) surgically isolated the hypothalamus in the cat and were still able to elicit affective defense behavior during electrical stimulation of the midbrain central gray or during clamping of the cat's tail. This suggests that the hypothalamus was not essential for elicited rage but probably was essential for spontaneous aggression (Bard, 1928). Given the appropriate experimental conditions, brainstem mechanisms appear to allow for the expression of affective defense behavior while cortical or forebrain systems appear to modulate this

behavior by either enhancing, facilitating or diminishing it.

Electrical Stimulation Induced Aggression

Electrical stimulation studies provide for a reasonably accurate estimation of which brain regions mediate attack behavior. An advantage of this response over lesion studies is that the aggressive response can be reliably reproduced and therefore other experimental (e.g. pharmacological) manipulations can be superimposed upon this procedure.

Quiet Biting Attack. Quiet biting attack behavior can be elicited by stimulating lateral regions of the preoptico-hypothalamic continuum (Wasman and Flynn, 1962), the ventral tegmentum (Bandler, 1972) and pontine tegmentum (Berntson, 1973). The lateral preoptico-hypothalamic continuum and ventral tegmental area also share reciprocal anatomical connections (Chi and Flynn, 1971; Chi and Flynn, 1971b; Nauta, 1958; Troiano and Siegel, 1975; Chi et al., 1976). Since lesions of the ventral tegmental area diminish this attack behavior (Proshansky and Bandler, 1975), it is likely that the medial forebrain bundle is integrally involved in the expression of this behavior. Stimulation of lateral hypothalamic neurons is also known to have excitatory effects on midbrain neurons which are known to course within this system (Edinger et al., 1977; Sutin et al., 1975). Electrical stimulation of the ventral tegmental area produces a

less directed and more stereotyped form of quiet attack. Facilitation of quiet biting attack is associated with stimulation of the lateral (Shaikh et al., 1984) and dorsal (Sheard and Flynn, 1966) half of the tegmentum while suppression of quiet attack is associated with stimulation region near the midline. Lesions of the dorsal tegmentum increase thresholds for such behavior (Berntson, 1972).

The midline thalamic nuclei such as the mediodorsal nucleus (posterior aspects) and the nucleus reuniens also elicit quiet attack when stimulated (Bandler and Flynn, 1974). Anatomical evidence supports the likelihood that attack associated with these two structures may utilize fibers which descend from the posterior aspects of the mediodorsal nucleus to either the midbrain central gray or first synapse in the nucleus reuniens and other midline thalamic structures and then project into the entire extent of the preoptico-hypothalamus (Brutus et al., 1984a; Siegel et al., 1973a).

Affective Defense. Affective defense behavior can be elicited by stimulation of the medial aspect of the preoptico-hypothalamic continuum and also the midbrain central gray in the cat (Hess and Brugger, 1943; Wasman and Flynn, 1962) and rat (Panksepp and Trowell, 1969). It is likely that descending periventricular fibers projecting to the midbrain periaqueductal gray are involved in the organization of this response since lesions of this system can effectively eliminate it (Glusman, 1974). Chi and Flynn

(1971a) also noted a heavy projection to the central gray following lesions of the dorsal and medial hypothalamic regions from which AD can be elicited. Stimulation of the medial aspects of the reticular formation of the pons and medulla can also elicit defensive responding (Coote et al., 1973). Decerebration or sectioning at the superior border of the pons leaves this defense reaction intact while sectioning of the brain between the level of the mesencephalon and diencephalon, leaving the mesencephalon, pons and medulla intact, leaves a more complete affective response (Woods, 1964; Bignall and Schramm, 1974), with biting and striking components intact. The full expression of affective defensive behavior requires an intact hindbrain, midbrain and posterior hypothalamus (Bard, 1928; Karli et al., 1969). In fact, affective defense behavior can be elicited by stimulation of a zone extending from the amygdala, along the stria terminalis and its bed nucleus which projects to the ventromedial hypothalamus to the central gray. (DeMolina and Hunsperger, 1959; 1962; Hunsperger, 1956; 1967). Lesions placed at loci progressively further caudal along this axis are more effective in abolishing affective reactivity.

Effect of Hypothalamic Stimulation on Sensory and Skeletal Motor Systems

Integration and cordination of both sensory and motor systems by associational and modulatory systems in neocortex and the limbic system provide for integrated defensive

posturing or prey killing (Bandler and Flynn, 1971; Bugbee and Eichelman, 1972; MacDonnell and Flynn, 1966a; Smith, 1972; Thor and Ghiselli, 1973; Thor et al., 1974). Sensory systems in this context refers to brain regions which process tactile, visual, olfactory and auditory inputs. Motor systems here refer to the somesthetic cortex, the frontal association cortex (Numan, 1978) and also the cerebellum and basal ganglia, which influence proper sensorimotor cortical sequencing of motor outputs during AD or QBA. Thus, head and body orienting, visual searching, body movements, lunging and biting of prey require cortical systems for proper motor sequencing, while limbic system structures provide for the qualitative appraisal of appropriate environmental stimuli in order to modulate these behaviors. During these behaviors, the organism appears to be aroused and its sensory and skeletal motor systems are prepared in a manner comparable to the sympathetically-mediated preparation of these systems during fight or flight situations (Flynn et al., 1971). Stimulation of hypothalamic sites can modify such sensory components of the quiet attack response which utilize visual, olfactory and tactile cues (MacDonnell and Flynn, 1966b).

Lateral hypothalamic stimulation ordinarily produces a lethal attack upon a rat (Wasman and Flynn, 1962). The jaw opening response is the last behavior emitted or elicited during quiet attack behavior before the cat kills the rat. In the normal cat, stimulation of these hypothalamic attack

sites is associated with alterations in the sensory fields for both the head-orienting and jaw-opening reflexes. The sensory fields for the jaw-opening and head-orienting reflexes are located along the lipline and muzzle regions, respectively, of the cat. The extent or size of these sensory fields is always a fraction of the hypothalamic stimulation intensity. Light touch of the muzzle area located above the lipline, combined with hypothalamic stimulation, initiates head-orienting responses which helps to bring a tactile stimulus to the lips of the cat. The effective sensory field size in the muzzle region is a direct function of hypothalamic stimulation intensity. See Fig. 3 for an illustration of this sensory field. Light tactile stimulation of the lipline during hypothalamic stimulation also produces an increase in the lateral extent or size of the trigger zone along the lip line for opening of the jaw. In the absence of hypothalamic stimulation in the normal cat, stimulation of the lipline does not produce jaw-opening. See Fig. 4 for an illustration of this sensory field.

The distribution for both of these types of sensory fields is largely on the side of the muzzle or lipline contralateral to the side of central nervous system stimulation. Although high levels of hypothalamic stimulation activate sensory fields ipsilaterally, the extent to which they increase, lags behind those on the contralateral side of the body. Hypothalamic stimulation is more effective in

Fig. 3. The maximum extent of the maxillary sensory field (upper shaded area of muzzle) for head-orienting responses during intense stimulation of a hypothalamic attack site (QBA). The sensory fields along the lower jaw, which is innervated by the mandibular branch of the trigeminal nerve as not yet been mapped in detail (Flynn, 1972).

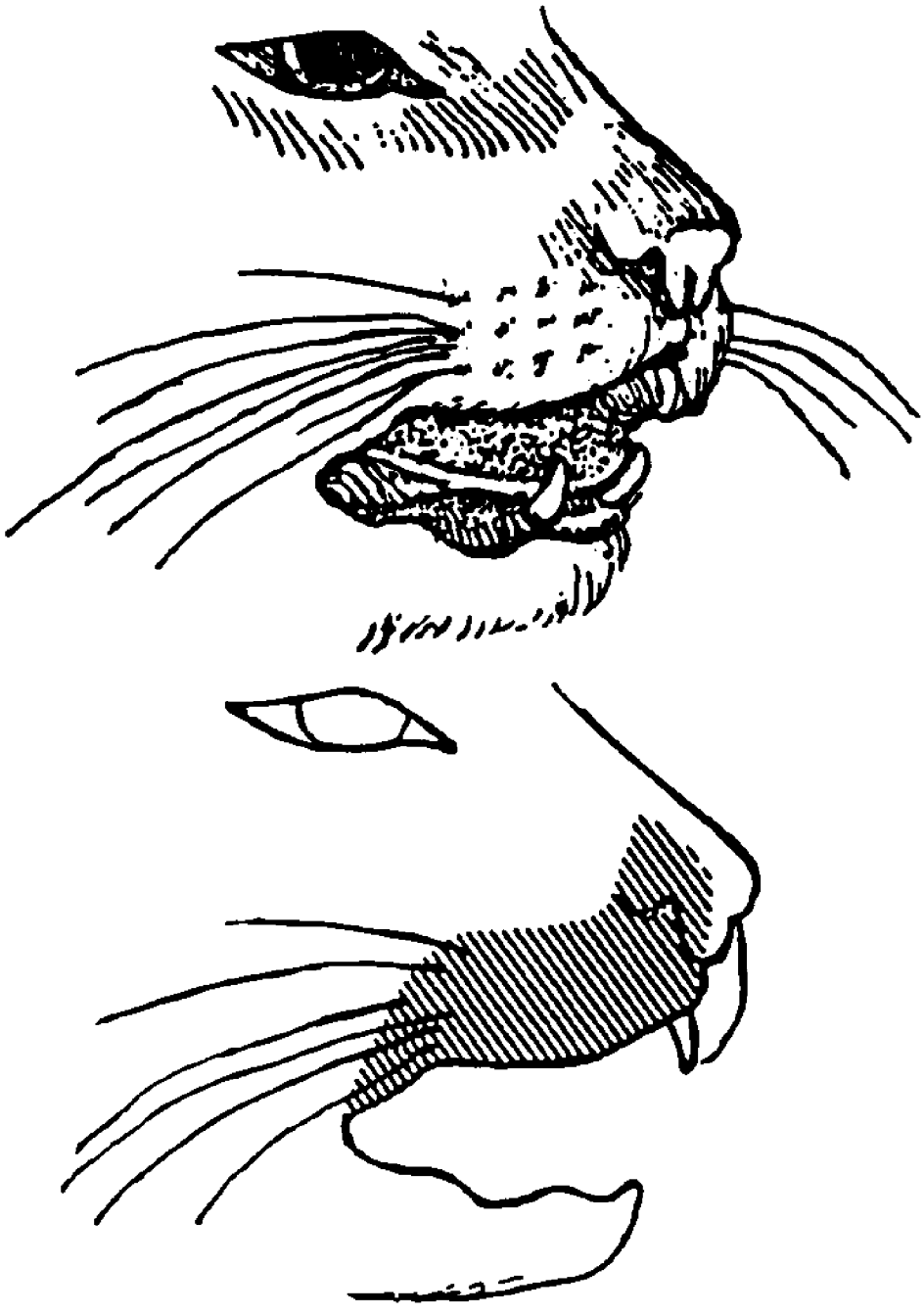


Fig. 3.

Fig. 4. The maximum extent of the sensory field of the lip-line for the jaw-opening response during relatively intense stimulation of a hypothalamic attack site (QBA) (Flynn, 1972).

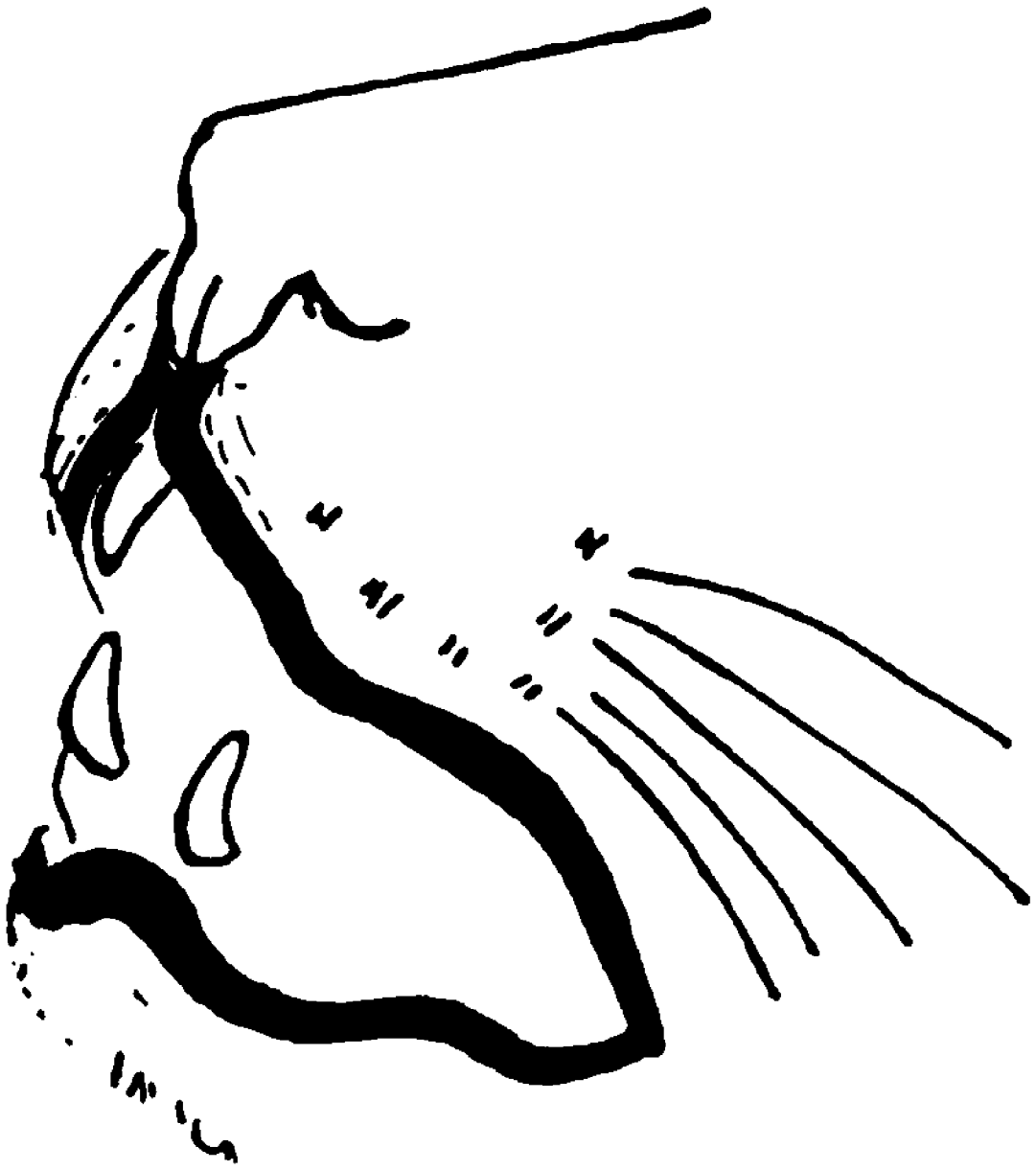


Fig. 4.

altering the size of the contralateral sensory fields of the lip or muzzle than for those located ipsilaterally. This difference in responsiveness between the two sides of the muzzle indicates differential excitation of each side of the body, with one receptive field for the reflex affected more than the other.

Rats with intact vibrissae show increased fighting behavior as compared to devibrissaed or facially anesthetized animals (Bugbee & Eichelman, 1972; Thor & Ghiselli, 1973; Thor et al., 1974). Section of the infraorbital maxillary and infra-alvelolar sensory branches of the trigeminal nerve eliminates hypothalamically elicited biting in the cat (MacDonnell and Flynn, 1966b). Biting frequency in the cat following trigeminal sectioning was found to be diminished, while repetitive biting occurred during stimulation in the normal animal. Blindfolding cats also diminished biting by half, while trigeminal resectioning and blindfolding totally elminated biting attack (Flory and Ulrich, 1965). Olfactory bulb ablation had no effect upon number of attacks. Size of the effective tactile receptive field of the cat's forepaw is also increased by increases in hypothalamic stimulation intensity, resulting in a more pronounced paw strike reflex (Bandler and Flynn, 1972). Components of the cat paw strike reflex include striking, holding, and positioning of the prey. Stimulation effects here are larger for the contralateral paw than the ipsilateral paw. The tactile receptive fields for the reflex

increase in size according to the successive tactile dermatomes (Hekmatpanah, 1961) located on the paw. The correspondence between the receptive fields for paw strike and dermatomes is shown in Fig. 5.

The frequency of a cat's lunge toward a mouse during stimulation of the hypothalamus was greater when the mouse was presented to the contralateral versus ipsilateral eye (Flynn et al., 1971). Visual areas are therefore important in the organization of this patterned reflex (Bandler and Flynn, 1971). Occipital cortical neuron receptive fields are also increased or decreased by hypothalamic stimulation (Flynn et al., 1970), with the more effective stimulation occurring in the contralateral sensory receptive fields. It is therefore likely that an organism's sensory and motor systems are primed to help elicit these patterned reflexes in the presence of suitable environmental stimuli (Flynn et al., 1971).

The Neural Substrates of Aggressive Behavior

Both electrically elicited and natural aggressive behaviors require the utilization of multiple afferent, associational and efferent systems to produce sustained, directed responding that is integrated with the environment. Central to the organization of electrically elicited affective and quiet attack behavior and probably naturally emitted aggression is the lateral and medial hypothalamus as described above. The fimbria-fornix, stria medullaris,

Fig. 5. The first row is a representative map of the extent of the tactile receptive fields on the cat's forelimbs from which striking could be elicited during stimulation of a hypothalamic attack site (QBA). As the intensity of hypothalamic stimulation was increased, the extent of the tactile receptive field expanded from I to V (also see Fig. 2). The second row is a map of the C_5 to T_1 tactile dermatomes of the cat's forelimb, adapted from J. Hekmatpanah (1961). A comparison of rows 1 and 2 suggests that at low intensities of hypothalamic stimulation, the tactile receptive field approximates the area of the C_5 and C_6 dermatomes, and as the intensity of hypothalamic stimulation was increased the tactile receptive field expanded to include the approximate area of the next successive tactile dermatomes, C_7, C_8 and T_1 (Flynn, 1972).

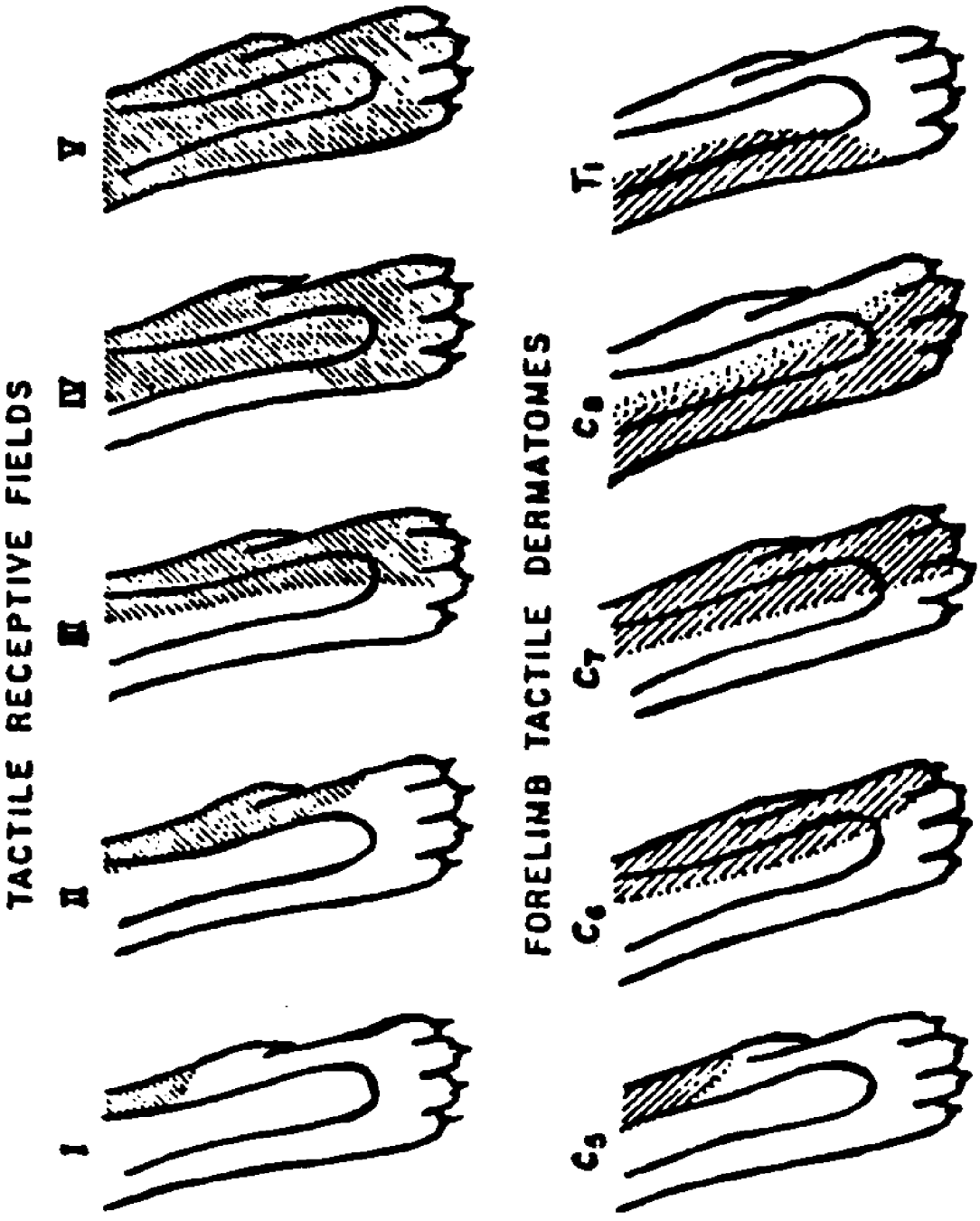

TACTILE RECEPTIVE FIELDS
I
II
III
IV
V
FORELIMB TACTILE DERMATOMES
C5
C6
C7
C8
T1

Fig. 5.

stria terminalis and medial forebrain bundle provide the hypothalamus with its predominant afferent and efferent projections (Troiano & Siegel, 1975; Raisman, 1966; Swanson & Cowan, 1975; Chi & Flynn, 1971). These pathways provide the hypothalamus with reciprocal connections to both forebrain and brainstem limbic system structures which also produce attack behavior when electrically stimulated or modify attack elicited by hypothalamic stimulation. A brief description of the hypothalamic anatomy subserving aggressive behavior will now be described.

Fimbria-Fornix System.

Behavioral experiments clearly indicate that the hippocampal formation differentially regulates hypothalamically elicited attack behavior (Siegel et al., 1974b; Siegel and Flynn, 1986; Watson et al., 1983a). These studies suggest that the dorsal hippocampal formation mainly projects to the dorsomedial aspect of the lateral septal nucleus, while the ventral hippocampal formation projects to the lateral aspect of the lateral septal nucleus (See Appendix I) (Swanson & Cowan, 1975, 1977; Meibach & Siegel, 1977; Watson et al., 1984b). Differentiation of function along the dorso-ventral axis of the hippocampal formation has also been suggested for other types of functional processes as well (Andy et al., 1969; Hughes, 1965; Elul, 1964; Gage and Thompson, 1980). Neuroanatomical studies utilizing degeneration procedures, horseradish peroxidase histo-

chemistry and amino acid radioautography have demonstrated that the efferent pathways from these two regions of the hippocampus, utilize the fimbria-fornix system but project to different regions of the neuroaxis (DeMolina and Hunsperger, 1959; Siegel and Skog, 1970; Siegel et al., 1974b; Siegel et al., 1975; Edinger et al., 1979).

Anatomy. The fornix is a bundle of fibers which reciprocally connects the hippocampal formation septum (Edinger et al., 1979; Meibach and Siegel, 1977a; Swanson and Cowan, 1977; 1979; Watson et al., 1983b), hypothalamus, thalamus (Meibach and Siegel, 1977b; Natua, 1956; Watson et al., 1983b), entorhinal cortex (Swanson and Cowan, 1977) and the midbrain. At the anterior level of the hippocampal formation the fornix is composed of fibers from the fimbria and dorsal fornix. One component of this bundle, the precommissural component descends through the septum, anterior to the level of the anterior commissure into the preoptic area and another component, the post-commissural component descends through the hypothalamus to the anterior thalamic nucleus and mammillary bodies.

The post-commissural fornix fibers which synapse in the mammillary bodies and anterior thalamic nucleus arise exclusively from within the subicular cortex. Although a projection (medial corticohypothalamic projection) from the anterior ventral subicular cortex to the entire ventromedial hypothalamic continuum exists in some species (Valenstein and Nauta, 1959; Meibach and Siegel, 1977b), it does not

appear to exist in the cat (Siegel and Tassoni, 1971a; Edinger et al., 1979). The pre-commissural fornix has also been found to arise directly from subicular cortical cells and project throughout all aspects of the lateral septal nucleus. Hippocampal fibers originating from CA3 and CA4 fields and traveling within the precommissural fornix are known to have a limited bilateral distribution to the caudal aspects of the lateral septal nucleus, the nucleus of the diagonal band and to the preoptic area through the medial forebrain bundle. The fibers passing through the septum to terminate in the preoptic area are joined by fibers arising in the septum and bypass the preoptic region and also project to the midbrain.

Precommissural fornix fibers are known to drive (excite) those septal neurons which synapse upon them directly, whereas they are known to inhibit those septal neurons which receive these inputs via interneurons (Edinger et al., 1973). Fornix fibers from the dorsal hippocampus will therefore excite cells in the dorsomedial aspects of the lateral septum and inhibit other septal cells, while ventral hippocampal fibers will excite far lateral septal neurons and suppress firing of cells in other septal regions.

Therefore, the majority of fiber projections of the hippocampal formation to the septal area and hypothalamus arise from the subicular cortex and not from hippocampal pyramidal cells (Meibach and Siegel, 1977b). It therefore

appears that the majority of fibers which project to the septum and all the fibers which project to those hypothalamic sites which elicit aggressive behavior, originate in the subicular cortex. These projections are organized along the longitudinal axis of the hippocampal formation. Subicular cortical cells located at the septal (dorsal) end of the hippocampal formation project through the medial part of the dorsal fornix and terminate in the dorsomedial quadrant of the lateral septal nucleus and in the dorsal aspects of the pars posterior of the medial mammillary nucleus. Fibers originating from the temporal lobe (or posteroventral) portions of the hippocampal formation project through the more lateral aspects of the dorsal fornix and fimbria and synapse in the lateral and ventral quadrants of the lateral septal nucleus and also in the ventral portions of the medial mammillary nucleus (pars posterior). The prosubiculum and subiculum therefore project through the pre- and post- commissural fornix. Hippocampal pyramidal cells from all CA fields have a limited projection within the precommissural fornix terminating in the caudal septum while the presubiculum projects solely in the postcommissural fornix.

2-Deoxyglucose Experiments. The recently developed [^{14}C]-deoxyglucose technique (Sokoloff et al., 1977) is able to simultaneously measure the rate of energy metabolism in specific brain regions of normal conscious animals as well as animals under experimentally altered states of cerebral

functional activity. The excellent spatial resolution offered by the quantitative autoradiographic technique developed for measuring local cerebral blood flow (Landau et al., 1955; Reivich et al., 1969) enables the [^{14}C]-deoxyglucose procedure to provide pictorial representations of both increased and decreased rates of energy metabolism during experimentally and pathologically altered states of the brain. (See Appendix II for details of [^{14}C]-deoxyglucose metabolism).

Data from recent experiments utilizing the 2-deoxyglucose procedure and electrical brain stimulation are consistent with established anatomical projections of the precommissural fornix (Meibach and Siegel, 1977b; Swanson and Cowan, 1977; Watson et al., 1983b). Stimulation of the ventral hippocampal sites metabolically activated the ventrolateral aspect of the lateral septal nucleus and medial part of the nucleus accumbens, while stimulation of the dorsal hippocampal sites metabolically activated the dorsomedial aspect of the lateral septal nucleus (Watson et al., 1983b). Metabolic activation of the nucleus accumbens was achieved by stimulation of fibers arising in the entorhinal cortex which pass through the hippocampal formation, fornix and lateral septal nucleus (Krayniak et al., 1981).

Histochemical and autoradiographic analysis of the septal efferent pathways in both the rat (Meibach and Siegel, 1977b; Swanson and Cowan, 1979; Watson et al.,

1985), cat (Krayniak et al., 1978; Stoddard-Apter and MacDonnell, 1980; Brutus et al., 1984b), and other species (Krayniak and Siegel, 1978), confirm the presence of extensive projections from the lateral septal nucleus, which utilize the medial forebrain bundle and synapse in the regions of the lateral preoptico-hypothalamus and midbrain. The hippocampal regulation of hypothalamically-elicited attack probably occurs by means of a disynaptic pathway including precommissural fornix fibers and the septal component of the medial forebrain bundle or a trisynaptic pathway also including a synapse in the diagonal band of Broca.

Behavioral Implications. Therefore, facilitation of quiet attack behavior is likely to be associated with stimulation of the far lateral aspect of the lateral septal nucleus which receives ventral hippocampal projections and in turn projects to the lateral preoptico-hypothalamus. Suppression of attack is achieved during stimulation of the dorsal hippocampus which innervates the medial aspects of the lateral septal nucleus. The lateral septal nucleus in turn projects heavily to the nuclei of the diagonal band--which is known to suppress attack behavior (Bandler and Vergnes, 1979; Inselman and Flynn, 1972; Watson et al., 1985). Efferent fibers from the diagonal band of Broca travel through the medial forebrain bundle and supply the lateral hypothalamus (Watson, 1985).

The fornix system represents a major pathway for the interconnection of the septohippocampal complex with the

hypothalamus and midbrain. The reciprocal connections between the hippocampus and septum and the sensory, visceral and motor aspects of the hypothalamus and midbrain provide a significant contribution to the organization of hypothalamically elicited quiet attack behavior.

Stria medullaris

Cell bodies of the septal nuclei that give rise to fibers passing through the stria medullaris are located in the posterior one-third of the medial and lateral septal nuclei and they acquire a large number of fibers as they pass through the preoptic area of the hypothalamus. Fibers from the olfactory tubercle and anterior preoptic region intermingle with fibers of septal origin in the stria medullaris and then project to the lateral habenular nucleus and dorsomedial nucleus of the thalamus (Cragg, 1961, Marburg, 1944; Nauta and Haymaker, 1964; 1969). This fiber bundle connects the septal, hypothalamic and olfactory regions with the more posteriorly located nuclei of the thalamus and tegmentum (See Appendix III).

Medial Forebrain Bundle

The major sources of cell bodies contributing to the medial forebrain bundle (MFB) include the anterior olfactory nucleus, pyriform cortex, and amygdala, septal area, lateral hypothalamus and preoptic area. The major contribution to the descending portion of the MFB arises in the septohippo-

campal complex (See Appendix IV). Inputs from all these systems then finally converge at the level of the preoptic nucleus to form the MFB which then descends caudally synapsing in the lateral hypothalamus and then in the ventral tegmental area of the midbrain (Nauta, 1956; Chi and Flynn, 1971; Troiano and Siegel, 1975).

The medial forebrain bundle is the major site associated with quiet attack behavior as demonstrated by degeneration studies (Chi and Flynn, 1971a). In this study electrodes were implanted in hypothalamic sites of cats, from which quiet biting attack was elicited by electrical stimulation, and then lesions were made at these sites. The Fink-Heimer (1967) and Eager (1970) modifications of the Nauta reduced-silver method for impregnating degenerating axoplasm were used to reveal that degeneration resulting from quiet attack sites followed largely along the course of the medial forebrain bundle. Degeneration was found to ascend through the preoptic region and diagonal band of Broca into the septum and to descend into the midbrain reticular formation along the medial forebrain bundle and into the central gray through the descending periventricular system. Degeneration was also traced into the dorsal hypothalamic area and midline thalamus. The areas to which degeneration was traced coincided well with sites from which attack had been reported to be elicited during electrical stimulation.

The midbrain central gray and tegmental structures which form the main target structures of the descending components of the medial forebrain bundle also give rise to the major ascending components of this fiber bundle. These fibers project rostrally to the lateral hypothalamus, the lateral preoptic area, nuclei of the medial septum and the diagonal band (Nauta, 1956; Chi and Flynn, 1971a; Troiano and Siegel, 1975). Lesions placed in ventral tegmental sites associated with the modification of attack behavior can effectively abolish (or diminish) hypothalamically-elicited attack (Proshansky et al., 1974).

Stria Terminalis

This system arises in the amygdala and pyriform cortex and projects initially to the bed nucleus of the stria terminalis and then to the preoptic region and the medial hypothalamus (See Appendix V). The medial preoptic and anterior hypothalamic regions project to the diagonal band, lateral septum, and bed nucleus of the stria terminalis (Conrad and Pfaff, 1975; Conrad and Pfaff, 1976a; Conrad and Pfaff, 1976b). Fibers from this region of the hypothalamus travel rostrally through the stria terminalis to the amygdala and caudally to the ventromedial hypothalamus, the periventricular system of the hypothalamus, the lateral mammillary nucleus, ventral tegmental area and the midbrain reticular formation. Lesions placed in hypothalamic periventricular fibers producing degeneration of fibers pro-

jecting to the periaqueductal gray of the midbrain are associated with affective defense behavior (Chi and Flynn, 1971a).

Other Hypothalamic Fiber Systems

A brief account of monoaminergic pathways that pass through and synapse in this region will follow. Other neurotransmitter systems have not been included in this account. The noradrenergic nucleus locus coeruleus sends fibers through the dorsal noradrenergic (NE) bundle to the reticular formation, and through the MFB to the lateral hypothalamus and such limbic forebrain structures as the septal area, the amygdala and cingulate cortex (Ungerstedt, 1971; Pickel et al., 1974). The ventral NE bundle courses ventrally to innervate brain regions from the medulla to the diencephalon, including most of the hypochalamus. 5-Hyroxtryptaminergic (5-HT) cell bodies project fibers to the lateral hypothalamus, septum, amygdala and frontal cortex (Moore and Halaris, 1975; Conrad et al., 1974; Saavedra et al., 1974). Other 5-HT fibers project caudally from the raphe nuclei and synapse in the hippocampus and cingulate cortex. The ascending dopaminergic (DA) neurons project primarily through the nigro-striatal and mesolimbic pathways (Brownstein et al., 1976; Kruk and Pycock, 1983). Cell bodies of the nigrostriatal DA system project from the substantia nigra through the lateral hypothalamus to innervate the neo-striatum. The mesolimbic system cell bodies project

from the ventral tegmentum and terminate in the caudate nucleus, the nucleus accumbens, olfactory tubercle, and amygdaloid nuclei, the frontal and cingulate cortices.

Structures Modulating Aggressive Behavior Elicited From The Hypothalamus

In recent years an active research program in the laborary of A. Siegel has been carried out to understand the regulatory nature of limbic system structures in the control of hypothalamic aggression (See Appendix VI). Brain regions displaying suppression of attack elicited by hypothalamic stimulation include the basomedial amygdala (Block et al., 1980a), the prefrontal cortex (Siegel et al., 1977a; Siegel et al., 1975; Siegel et al., 1974a), the dorsal hippocampus (Watson et al., 1983b), the pyriform cortex (Siegel et al., 1972), the lateral septal nucleus (Brutus et al., 1984b), the lateral aspect of the substantia innominata (Block et al., 1980b) and the anterior cingulate gyrus (Siegel and Chabora, 1971). Sites producing facilitation of attack elicited by hypothalamic stimulation include the ventral hippocampus (Watson et al., 1983a), the far lateral aspect of the lateral septal nucleus (Brutus et al., 1984b), and the lateral amygdaloid nucleus (Block et al., 1980a). These limbic system structures provide a powerful regulatory control over aggressive behavior. It has been suggested that the medial forebrain bundle and stria terminalis allow those limbic structures which utilize these pathways to

modify hypothalamic function, while the bed nucleus of stria terminalis, the mediodorsal thalamic nucleus, diagonal band of Broca and substantia innominata provide important interneurons in the control of this aggressive behavior (Siegel and Edinger, 1981). Regulation of aggressive behavior is in part due to the modification of the sensory components of the aggressive response that are of trigeminal origin (Watson et al., 1983a; Block et al., 1980a, 1980b; Brutus et al., 1984b; Chi et al., 1976). For the purposes of this review, the limbic system can be divided into a hippocampal-septal system and a mediodorsal thalamic system, with each region serving as a focus for channeling the inhibitory and facilitory limbic inputs to the hypothalamic attack sites.

Hippocampal-Septal System

Septal Area

Behavioral Observations. The septal area plays a significant role in the regulation of emotional behavior and aggression. Lesions of the septum cause increases in irritability, emotional reactivity and aggressiveness (Brady and Nauta, 1953; King, 1958; Yutzey et al., 1967; Amhad and Harvey, 1968; Blanchard and Blanchard, 1968). Electrical stimulation studies generally complement the lesions studies. Stimulation of the lateral septal nucleus in general produces suppression of hypothalamically-elicited quiet biting attack (Siegel and Skog, 1970). In contrast, the far ventrolateral aspect of the lateral septal

area was found to facilitate hypothalamic quiet attack in cat (Brutus et al., 1984b). Suppression of attack can also be elicited by stimulation of the diagonal band of Broca (Inselman & Flynn, 1972). In the rat Bandler and Vergnes (1979) found that diagonal band lesions induced muricidal behavior. Stimulation of the medial aspect of the dorsal septum has been found to facilitate affective attack (intraspecific) and associated vocalization (MacDonnell and Stoddard-Apter, 1978).

Anatomical Connections. The nomenclature for the nuclei of the septal area is derived from the studies of Meibach and Siegel (1977b), Young (1936), Raisman (1966) and Swanson and Cowan (1979). The lateral septal nucleus can be divided into three regions; a dorsomedial quadrant, dorsolateral quadrant and a ventrolateral quadrant. (See Appendix VII). Another region, situated half way between the midline and the lateral ventricle referred to by Meibach and Siegel (1977b) as the "intermediolateral" region corresponds to Swanson and Cowan's "intermediate part of the lateral septal nucleus." The diagonal band of Broca contains a vertical limb, a crus and a horizontal limb. The medial septal nucleus is located along the midline immediately dorsal to the vertical limb of the diagonal band.

There exist two major pathways by which the septal area could modulate quiet biting attack (Krayniak et al., 1980; Meibach and Siegel, 1977b; Siegel and Tassoni, 1971; Watson et al., 1985; Brutus et al., 1984b). The lateral hypo-

thalamus and preoptic area are directly supplied by a massive projection from wide regions of the lateral septal nucleus. This projection may represent a second-order neuron linking the hippocampal formation with the lateral hypothalamus. An indirect route by which the septal region may effectively modify lateral hypothalamic responses may involve fibers arising from the lateral septal nucleus, synapse within the nuclei of the diagonal band which then in turn synapse in limbic system structures such as the lateral hypothalamus, hippocampal formation, medial amygdala, medial habenular nucleus, interpenduncular nucleus, anterior cingulate cortex, prefrontal cortex, olfactory bulbs and mammillary bodies (Domesick, 1976; Conrad and Pfaff, 1976a; 1976b; Meibach and Siegel, 1977a; Krayniak et al., 1980; Meibach and Siegel, 1977b; Siegel and Tassoni, 1971b; Watson et al., 1985).

Since most of these limbic system structures inhibit attack, it is possible that the diagonal band produces its effects upon attack behavior by activation of those structures inhibitory to attack. It is possible that the more indirect pathway from the lateral septal nucleus represents the route by which attack behavior is inhibited from the dorsal septum. In addition to suppression and facilitation of attack behavior by the septal area, separate regions of this area can both drive and inhibit independent populations of cells in the lateral hypothalamus (Driefuss and Murphy, 1986; Miller and Mogensen, 1971).

Cingulate Gyrus

The cingulate gyrus has been historically considered to be a cortical component of the limbic system. That it is intimately involved in the regulation of emotional behavior was first examined by Papez (1937) and MacLean (1949). In cats, dogs, monkeys and humans, it has been reported that lesions of the cingulate gyrus produce increases in aggressive behavior (Kennard, 1955; Pechtel et al., 1958; Brutkowski et al., 1961; Malamud, 1967). However, other researchers have reported reductions in aggressive behavior in humans and monkeys following such lesions (Glees et al., 1950; LeBeau, 1954; Livingston, 1953). In electrical stimulation studies, the anterior regions of the cingulate cortex have been found to suppress quiet biting attack behavior (Siegel and Chabora, 1971). In contrast, the more posterior levels of the cingulate cortex including the retrosplenial cortex appear to have no effect upon this response.

Anatomy. The anterior and posterior regions of the cingulate cortex project differentially to the thalamus (See Appendix VIII). Anterior cingulate gyrus fibers arising from cortical layers V and VI (Siegel et al., 1977b) project to the lateral segment of the mediodorsal thalamic nucleus. Fibers from the posterior cingulate gyrus are distributed to the anteroventral nucleus (Domesick, 1969; Siegel et al., 1973). It is therefore likely that cingulate gyrus modulation of hypothalamically elicited aggression is mediated indirectly via the mediodorsal nucleus and those inter-

neurons of the midline thalamus which synapse in the nucleus reuniens (Brutus et al., 1984a) and inter-anteromedial nucleus (Siegel et al., 1973b), which in turn directly project to the hypothalamus. The anterior cingulate cortex functionally and structurally resembles the prefrontal cortex. Both of these regions suppress quiet biting attack, and their axons which arise from cortical layers V and VI project to the lateral segment of the mediodorsal nucleus. It has been suggested that they are structurally continuous and it is likely that they form a functionally homogeneous limbic forebrain system which regulates aggressive responding and associated behaviors (Siegel and Edinger, 1981).

RATIONALE

It is now well established that the septal area plays an important role in the regulation of aggressive behaviors (Albert and Richmond, 1976; Albert and Wong, 1978; Amhad and Harvey, 1968; Bandler and Flynn, 1971; Bandler and Flynn, 1972; Bandler and Vergnes, 1979; Bawden and Racine, 1979; Blanchard and Blanchard, 1968; Block et al., 1980a; Brady and Nauta, 1953; Brayley and Albert, 1977a; Brayley and Albert, 1977b; Flynn et al., 1971; Gotsick and Marshall, 1972; Hernandez-Peon et al., 1963; Inselman and Flynn, 1972; King, 1958; Latham and Thorne, 1974; MacDonnell and Flynn, 1966a; MacDonnell and Flynn, 1966b; MacDonnell and Stoddard-Apter, 1978; Miczek and Grossman, 1972; Potegal et al., 1980; Raisman, 1966; Rubenstein and Delgado, 1963; Siegel and Skog, 1970; Sierra et al., 1972; Stoddard-Apter, 1980; Watson et al., 1983a; and Yutzey et al., 1967). Electrical stimulation of the septal nuclei and diagonal band of the cat appears to selectively suppress quiet biting attack (interspecific aggression) behavior (Bandler and Vergnes, 1979; Inselman and Flynn, 1972; Siegel and Skog, 1970), while stimulation of the same regions can facilitate affective defense behavior (intraspecific aggression) (MacDonnell and Stoddard-Apter, 1978; Siegel and Skog, 1970).

It is also well known that the quiet biting attack response is under the control of sensory processes insofar as visual, tactile and olfactory cues can facilitate the

occurrence of this response pattern in the cat (Bandler and Flynn, 1971; Bandler and Flynn, 1972; Flynn et al., 1971; MacDonnell and Flynn, 1966a; MacDonnell and Flynn, 1966b; MacDonnell and Stoddard-Apter, 1978). An intact trigeminal sensory input to the perioral region is essential for the occurrence of the attack response as well (MacDonnell, 1966b). Recently it has also been demonstrated that modulation of hypothalamically elicited quiet attack behavior by such limbic structures as the amygdala (Block, et al., 1980a) and hippocampal formation (Watson et al., 1980a) involves the modification of sensorimotor components of the trigeminal system.

A major goal of the present study was to extend this analysis to the septal area and adjacent regions such as the cingulate cortex in order to determine whether modulation of attack behavior by the septum or cingulate gyrus may result, in part, from the modification of the trigeminal sensorimotor components related to this response. A second goal of this study was to characterize, through the use of ^{14}C-2-deoxyglucose autoradiography, the pathways and structures metabolically activated by electrical stimulation of septal area sites previously shown to significantly modulate quiet biting attack behavior. The recently developed [^{14}C] deoxyglucose method (Sokoloff et al., 1977) measures the rate of glucose utilization in discrete structural and functional components of the central nervous system. These studies have demonstrated that a close correlation exists between

the levels of local functional activity and local glucose utilization. Experimentally induced alterations in functional activity (as during electrical brain stimulation) in specific sensory or motor systems will result in corresponding changes in glucose utilization in specific nuclei and fiber pathways of the brain. Combined with the autoradiographic technique, maps illustrating the functional activation of brain regions during microstimulation of the brain may be produced. The acquisition of the above information would further identify the functional anatomy and mechanisms underlying septal area regulation of quiet biting attack behavior.

METHODS

Nine female cats which did not spontaneously attack rats and which weighed between 2.5 and 3.5 kg. were used as subjects in this study. Before surgery and experimental testing, all cats were placed in a cage with an anesthetized rat for a half hour period of time and observed to see if they bit or attacked the rat naturally (without electrical stimulation). Those cats who attacked the rat were eliminated from the experiments. None of the cats were in estrous during experimental testing. They were maintained on an ad-libitum feeding (Purina Cat Chow) and drinking schedule throughout the duration of the experiments. The cats were individually housed in stainless steel wire cages (24"x36"x36") and also maintained on a 12 hour dark and 12 hour light cycle.

Surgery

Prior to experimental procedures, the cats were anesthetized with sodium pentobarbital (45 mg/kg of body weight, I.P.) and under surgically aseptic conditions, two 18 gauge steel guide tubes were mounted bilaterally on the surface of the skull for the subsequent implantation of four moveable cingulate and septal electrodes (AP 17.0 mm and 15.5 mm; L: 1.0 mm). Following this, 6 more 18 gauge stainless steel guide tubes were mounted bilaterally on the surface of the skull so as to accommodate the placement of the moveable hypothalamic electrodes (AP: 11.0 mm, 9.5 mm and

8.0 mm; L: 1.0 mm and 2.5 mm). All electrodes implanted through guide tubes were electrolytically-sharpened stainless steel stylets, which were insulated with oil base paint except for 0.5 mm of their tips. Three uninsulated stainless steel stylets which served as indifferent electrodes were also implanted in the skull. All stereotaxic coordinates were obtained from the atlas of Jasper and Ajmone-Marsan (1954).

One large steel bolt was then implanted rostral to the cannulae and electrode array and 2 plastic bolts were attached to the skull caudal to the cannulae-electrode complex. These bolts enabled us to attach the cat's head to a head restrainer so as to allow undisturbed measurement of the "effective sensory fields" of the lipline. Specific details of the head restraining apparatus have been described elsewhere (MacDonnell et al., 1971). Cats were allowed to recover for a least one week prior to hypothalamic electrode implantation and behavioral testing.

Behavioral Experiments.

Identification of Quiet Biting Attack Sites. All experiments were conducted in a test chamber constructed of wood (61 cm x 61 cm x 61 cm) with a clear plexiglas door. A pentobarbital anesthetized rat and food were always present within the test chamber.

The research protocol first required finding consistent quiet biting attack behavior by lowering calibrated

electrodes in 0.5 mm steps through the guide tubes and electrically stimulating the hypothalamus as the electrode was passed through the brain. When the behavior was consistently elicited on every trial, electrodes were cemented in place with dental acrylic. The mean latency to attack was defined as the time (in secs) from onset of electrical stimulation to the moment of contact of the cat's teeth with the nape of an anesthetized rat's neck. In addition to recording the latency to quiet attack, we also recorded the latency to initial movement which was defined as the initial transposition (one front paw moving past the other) of the forepaws of the cat following the onset of stimulation. Initial movement of the forepaws always preceded the quiet attack response. Therefore the former latencies were generally less than the later.

Electrical stimuli were generated by 2 independent Grass S-8 stimulators and channeled through stimulus isolation units (Grass SIU-4678) to the animals. Constant current conditions were approximated by pairs of 40,000 Ohm resistors placed in series with the cat. Stimulation and recording was possible through the same electrode by connecting pairs of leads through relays to both the input of a Grass Model 78 polygraph and to the electrode. Stimulation consisted of balanced biphasic pulses delivered at 62.5 Hz with a pulse width of 1 msec per half cycle duration. Peak-to-peak current was measured on Tektronix 5113 dual beam oscilloscope with differential inputs (Block et al., 1980a).

When two structures (septal area of cingulate gyrus and lateral hypothalamus) were concurrently stimulated, the onset of the stimulation of one structure followed the onset of stimulation of the other by 4 msec. This separation of stimulus pulses enables the limbic modulatory site to have inhibitory or excitatory influences on the hypothalamic neuronal substrate which organizes and generates attack behavior during stimulation. Stimulation onset of the septal or cingulate gyrus modulatory site always preceded hypothalamic stimulation onset. In order to elicit attack behavior within 20 sec, the intensity of current delivered to the hypothalamus ranged from 100 to 800 uA. At current intensities, lower than 100 uA it was not possible to elicit behavior. At current intensities higher than 800 uA, the latencies to attack were so rapid that it was more difficult to modulate behavior during concurrent stimulation. The septum or cingulate gyrus was stimulated at current intensities ranging from 140 to 300 uA.

Identification of sites capable of modulating quiet biting attack behavior. The first phase of these experiments was conducted to identify those sites within the septum and cingulate gyrus capable of significantly modulating the latency to quiet biting attack elicited by hypothalamic stimulation. Modulation was defined as the "increase" or "decrease" in the initial response or quiet attack latencies as a function of dual stimulation of the hypothalamus and the limbic structure (septal area or cingulate cortex), in

contrast to the latencies obtained for single stimulation of the hypothalamus alone. An A-B-B-A paradigm was employed for the sequence of 10 trials each of single and dual stimulation to eliminate any order effects as a possible confounding variable in the experiment. The intertrial intervals between single and dual stimulation trials were 2 minutes. Following both single and dual stimulation, the EEG was recorded and any trial in which afterdischarges were present was discarded from the statistical analysis of the data. Seizure activity, here should be considered a pathological (not physiological) influence upon aggressive behavior. Therefore seizure effects, whether absence-like or convulsive, would interfere with the measurement of attack latencies and would be inappropriate for data analysis here. A t-test for paired observations was utilized to test for the statistical significance of response latencies between trials of single and dual stimulation. In 8 out of 30 cases (7, 10, 14, 15, 20, 23, 25, 26), septal area or cingulate gyrus modulatory sites were contralateral to the hypothalamic attack eliciting sites. In all other cases (22 out of 30), the modulatory sites and hypothalamic sites eliciting quiet attack were ipsilateral to each other.

Sensory fields experiments: Effects of stimulation of the septal area and adjacent regions upon trigeminal sensorimotor fields.

After a site in the septal area or adjacent structures

was found to exert either a significant inhibitory or facilitatory effect upon hypothalamically-elicited quiet biting attack behavior, a series of experiments was conducted in order to investigate the effect of stimulation of these modulatory sites upon the "effective sensory fields" of the lipline established during hypothalamic stimulation. The "effective sensory fields" are defined as the lateral extent of the lipline that, when probed during stimulation of a hypothalamic attack site, produces a jaw-opening response (Block et al., 1980a; 1980b). While this definition of "effective sensory fields" has been utilized in the present study, it does not preclude the possibility that during the time when a jaw-opening response is elicited, involvement of motor systems may be operative as well. The term "effective sensory fields" was merely employed to describe the relationship between somatosensory stimulation along the lipline and the behavioral response of jaw-opening during hypothalamic and limbic stimulation. Neither stimulation of either the septal area or cingulate cortex alone resulted in a jaw-opening response.

In this experiment, the cat was placed in a head and body restrainer in order to facilitate measurement of the effective sensory fields. The body restraining sling (Alice King-Chatham, Los Angeles) allowed free limb movement, while the specially designed head restraining frame immobilized the head. Animals were habituated to the apparatus prior to

the initiation of this phase of the experiment. The habituation procedure was not painful and was used in order to eliminate effects of stress or other variables on experimental effects.

The paradigm and methods of probing the lipline were similar to those employed by Block et al. (1980a; 1980b). First, vertical lines were drawn on the lip at 1.0 cm intervals lateral to the midline. Prior to electrical stimulation of any site, the lipline was probed with an anesthesiometer (2000 mg) (Rowan Products Panorama City, CA) or a blunt probe at a constant pressure and rate from the lateral extent towards the midline. Control probing in the absence of hypothalamic stimulation did not elicit jaw opening or biting responses. Then, a similar probing procedure was conducted during stimulation of the hypothalamus alone and the position along the lipline at which the jaw opening response first occurred was recorded. Another control probe followed in which no stimulation was delivered. This trial was followed by "dual" stimulation of both the hypothalamus and septal area (or adjacent structures), and again, the distance from the midline at which the jaw opening response occurred was recorded. At least 2 minutes elapsed between trials of lipline probing and stimulation to avoid habituation or sensitization effects.

At least 5 paired trials of single and dual stimulation applied during probing along the lipline ipsilateral to the stimulating electrodes were followed by similar paired

trials of stimulation during lipline probing along the contralateral side. The order of presentation for paired trials of electrical brain stimulation again utilized an A-B-B-A design.

The current intensities applied to both the septal area, adjacent limbic structures, and hypothalamus in this phase of the study were identical to those which were used in the previous behavioral experiments to demonstrate significant modulation of hypothalamically-elicited attack behavior. T-tests for paired observations within cats were used to statistically compare the differences between the effects of single and dual stimulation upon the lateral extent of the lipline from which the jaw opening response was elicited.

Effects of stimulation of the septal area and adjacent regions upon jaw opening latencies.

The effect of single or dual stimulation upon the latency for the jaw opening response was tested by probing only a midline region of the lip. This area, within a boundary of approximately 0.5 cm lateral from the midline of the lip on either side, was found to elicit a jaw-opening response when probed, regardless of whether single or dual stimulation was delivered. Hence, significant alterations in the latency to jaw opening resulting from concurrent stimluation of the septal area or adjacent structures during probing of the midline of the lip would suggest that motor

components of the response were affected by such stimulation.

Again, trials in which afterdischarges were elicited were eliminated from statistical analysis of the data. Generally, no afterdischarges occurred because modulation currents for all aspects of these experiments was very low. Also no kindling occurred because the testing procedures were not similar to those utilized during kindling. A t-test for paired observations was used to compare differences in latencies to jaw-opening for paired trials of single and dual stimulation for experiments involving probing of the lip midline.

[^{14}C]2-Deoxyglucose Experiments: Autoradiography of the pathways activated following stimulation of septal modulatory sites.

Following the completion of all behavioral testing [^{14}C]2-deoxyglucose (2-DG) autoradiography was performed in order to investigate the neural pathways activated following electrical stimulation of sites in the septal area which significantly modulated attack behavior during the prior behavioral and sensory field experiments. Six cats were anesthetized with sodium pentobarbital (45 mg/kg) 1.5 to 3 hr prior to septal stimulation and 2-DG injection was attempted. Then a femoral vein was cannulated with PE-100 tubing. Rectal temperature was monitored continuously and

maintained between 37.5 and 38.0°C with a warming pad and radiant lamp.

Stimulation was applied through septal electrodes which previously had been demonstrated to significantly modulate quiet biting attack behavior. Hypothalamic sites eliciting attack behavior were not electrically stimulated during the 2-DG experiments. The paradigm involved 30 sec stimulation periods separated by an interstimulus interval of 30 sec. Stimulation was initiated 5 min prior to 2-DG injection. The total course of stimulation was 45 min.

Each cat received fifty uCi/kg body weight of 2-(U-^{14}C)-deoxyglucose (Amersham Searle, 267-283 mCi/mmole). Since the 2-DG was suspended in 3% ethanol, it was first transferred to a vial and evaporated to dryness with a gentle stream of ultrapure (99.9999%) gaseous nitrogen. The 2-DG was then reconstituted in 1.0 ml sterile saline and injected as a bolus through the venous cannula. Stimulating current intensities were set between 0.2 to 0.4 mA above those employed during behavioral experimentation in order to compensate for the suppressive effects of the anesthetic upon cellular metabolism. EEG activity was recorded (Grass Model 78) during the 30 sec interstimulus interval through the monopolar stimulating electrode. At no time during the course of stimulation were afterdischarges noted.

Following the 45 min. stimulation period, very small electrolytic lesions were placed at the tips of the electrodes within the septal area and all other sites pro-

ducing significant modulation or initiation of attack behavior in order to facilitate histological localization. Lesions can disrupt blood flow to brain regions and therefore may disrupt glucose utilization in these regions. However, since maximal absorption of 2-DG in whole brain occurs by 10 min after I.V. injection (Meibach et al., 1980), it is unlikely that a small lesion will effectively alter the picture of 2-DG, or more precisely, 2-deoxyglucose-6-phosphate trapped within cells after a 45 min period of stimulation. This has been found to be the case for 2-DG experiments involving stimulation of thalamic and cortical sites in the rat (Brutus et al., 1984a). The cat was then perfused transcardially with 0.9% NaCl and 5% formalin. The brain was removed, blocked, frozen in Freon (dichlorodifluoromethane), chilled to -55°C with liquid nitrogen and embedded in Tissue-Tek O.C.T. compound. The tissue was stored in a Revco freezer at -70°C until it was sectioned. Blocks of tissue were cut at a thickness of 20 um in a Slee (New York) cryostat maintained at 22°C. Every 7th and 8th section was taken for autoradiography and correlative histological analysis, respectively. Sections prepared for histological examination were stained with cresyl violet. Standard procedures were utilized for the preparation and analysis of sections for 2-DG autoradiography (Watson et al., 1983b; Watson et al., 1983c).

Analysis of 2-DG Autoradiographs. Sections were prepared for 2-DG autoradiography in the following manner. Tissue sections were mounted on cover slips and allowed to dry for 30-60 minutes on a hot plate (55°C). Then, cover slips were glued to heavy cardboard in a sequential order. X-ray films (Kodak SB-5, Rochester, NY) were placed over each cardboard array of sections with the emulsion side opposed to the tissue and sealed in light tight cases. Kodak SB-5 X-ray film was then exposed for 28 days to both the brain sections mounted on cover slips and the autoradiographic standards (^{14}C, Amersham, Searle). Proper contact between the tissue and the X-ray film was assured by placing the cases under lead bricks. The film was developed by immersion in Kodak liquid X-ray developer for 5 minutes at 70°F followed by a water rinse and immersion in Kodak Rapid Fixer with Hardener for 7 min.

After the X-rays were developed and areas of differential 2-DG uptake established maps delineating labeled nuclear structures and pathways were drawn from the cresyl violet sections. The autoradiographic images of labeled brain sections from the X-rays were then enlarged and superimposed upon line drawings. Areas on these autoradiographs showing significantly increased optical densities as a function of stimulation were then portrayed on the line drawings by stippled gradients conforming with the optical densities on the original autoradiographs. Analysis of autoradiographs was performed by a student who was blind

to the behavioral data. Ineffective sites were used as controls.

RESULTS

Single Stimulation of the Hypothalamus

Quiet biting attack behavior was obtained when electrical stimluation applied to the lateral and posterior hypothalamus and supramammillary region, at minimal current intensities, produced a consistent response within 20 sec. A map of attack sites in the hypothalamus is shown in Fig. 6. The response is characterized by an initial crouching followed by stalking of the prey, culminating in a vigorous bite to the neck of the rat. Overt sympathetic signs are generally not visible with the exception of some pupillary dilation. The mean latency for this response ranged between 2.0 to 12.0 sec for hypothalamic stimulation alone. The mean latency to initial movement of the cat's forepaws varied between 1.0 and 8.0 sec.

Limbic Sites Modulating Attack Behavior: Dual stimulation of the septal area, adjacent regions and the hypothalamus

Electrical stimulation of sites in the septal area, bed nucleus of the stria terminalis and cingulate gyrus (Figs. 7 & 8), in general, significantly suppressed quiet biting attack behavior. Stimulation of septal area sites alone elicited no overt behaviors or alerting responses. This inhibitory effect was seen in cases where the modulatory site was both ipsilateral (cases 1-6, 8, 9, 11-13, 16-19, 21, 22, 24, 27-30) and contralateral (cases 7, 10, 14, 15, 20, 23, 25, 26) to the hypothalamic stimulating electrode (Fig. 8;

Fig. 6. Maps of hypothalamic sites (electrode placements) from which quiet biting attack behavior was elicited by electrical stimulation (filled circles). Sections are taken from the atlas of Jasper and Ajmone-Marsan (1954). Abbreviations: aHd, dorsal hypothalamus; HL, lateral hypothalamus; Hp, posterior hyothalamus; SMx, supramammillary region.

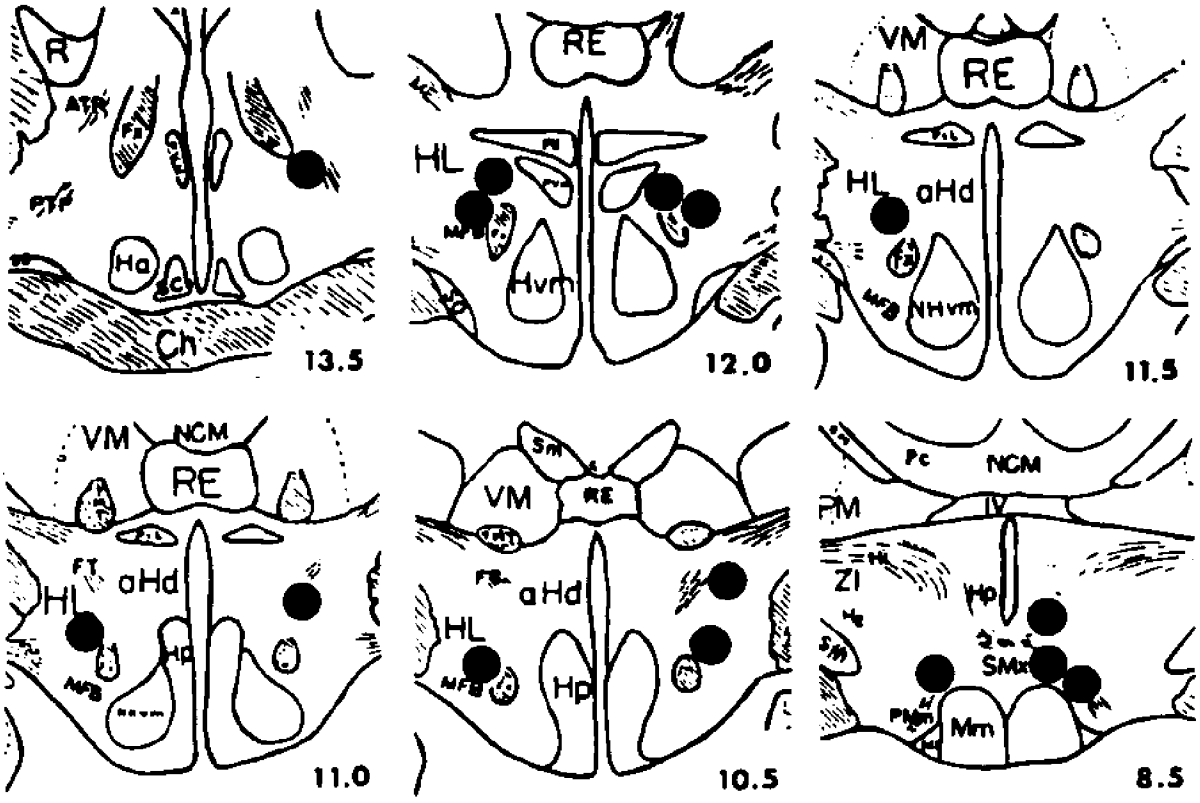

R
Ha
Ch
13.5
RE
HL
Hvm
12.0
VM
RE
HL
aHd
NHvm
11.5
VM
NCM
RE
HL
aHd
Hp
11.0
SM
VM
RE
aHd
HL
Hp
10.5
Pc
NCM
PM
ZI
Hp
SMx
Mm
8.5

Fig. 6.

Fig. 7. Electrode placements in the septal area and adjacent regions that modulated hypothalamically-elicited quiet biting attack. Triangles facing down: suppression of quiet biting attack; triangles facing up: facilitation of quiet biting attack; open circles: no effect upon quiet biting attack.

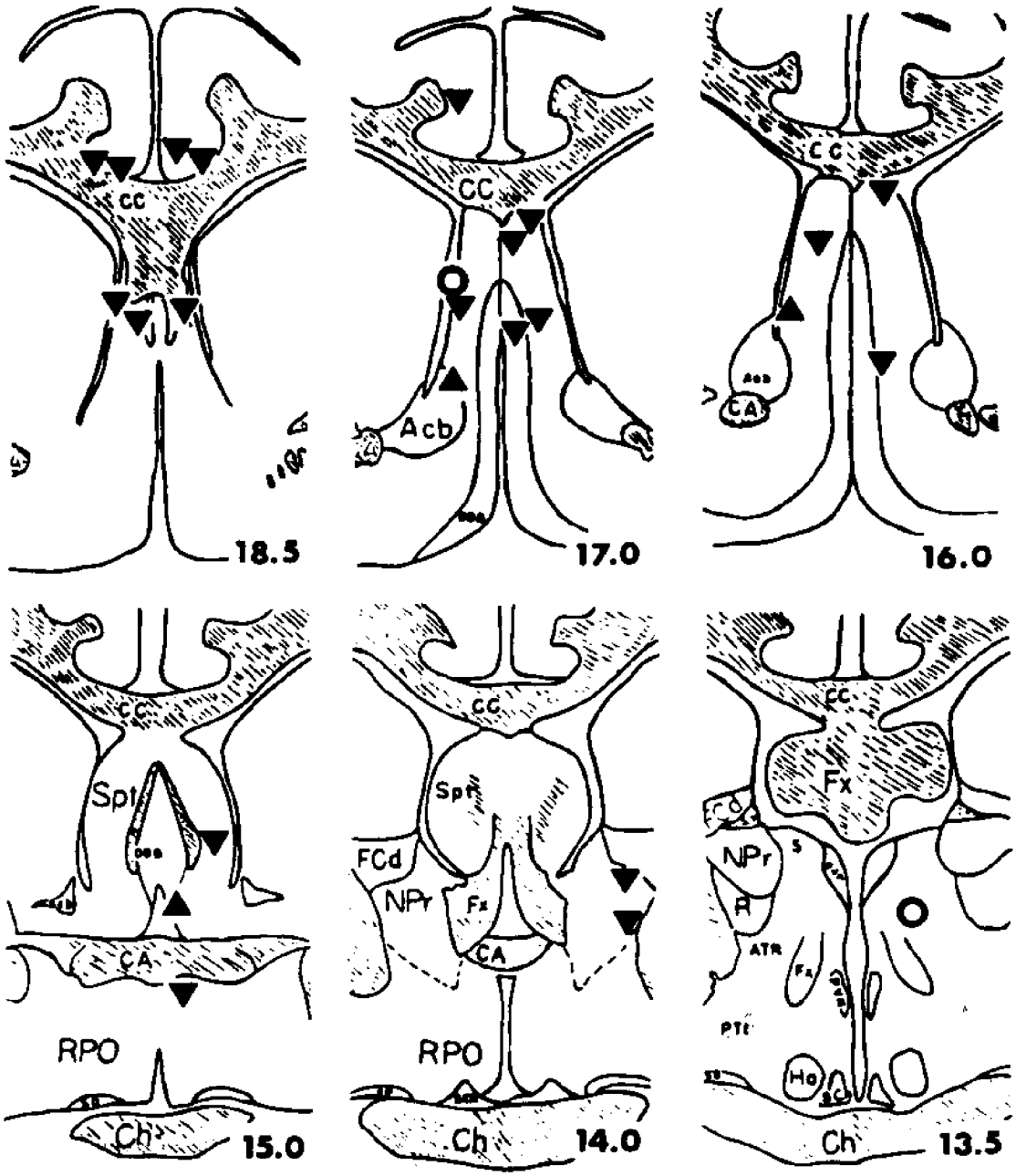

cc
18.5
Acb
17.0
CA
16.0
Spl
RPO
Ch
15.0
FCd
NPr
Fx
14.0
R
ATR
PTE
Ho
13.5

Fig. 7.

Fig. 8. Bar graphs indicate that concurrent stimulation of the hypothalamus with the septal area, bed nucleus of the stria terminalis or cingulate gyrus alters the latency to attack (open histograms), whereas this stimulation has no effect upon latencies to initial movement of the forepaws (crosshatched histograms). For each pair of histograms, the first bar corresponds to the mean attack latency for stimulation of the hypothalamus alone; the second bar represents the mean attack latency for dual stimulation. Numbers centered below pairs of bar graphs identify case numbers in Table I. The "C" superscripts indicate that during concurrent stimulation, the modulatory site was contralateral to the hypothalamic attack site; in all other cases the modulatory site was ipsilateral to the attack site; the three sites in the rostral thalamus depicted in Fig. 2 (AP-13.5) which had no effect upon attack behavior are not represented in this figure; BNST represents the bed nucleus of the stria terminalis; +$p<0.10$; *$p<0.05$; **$p<0.02$.

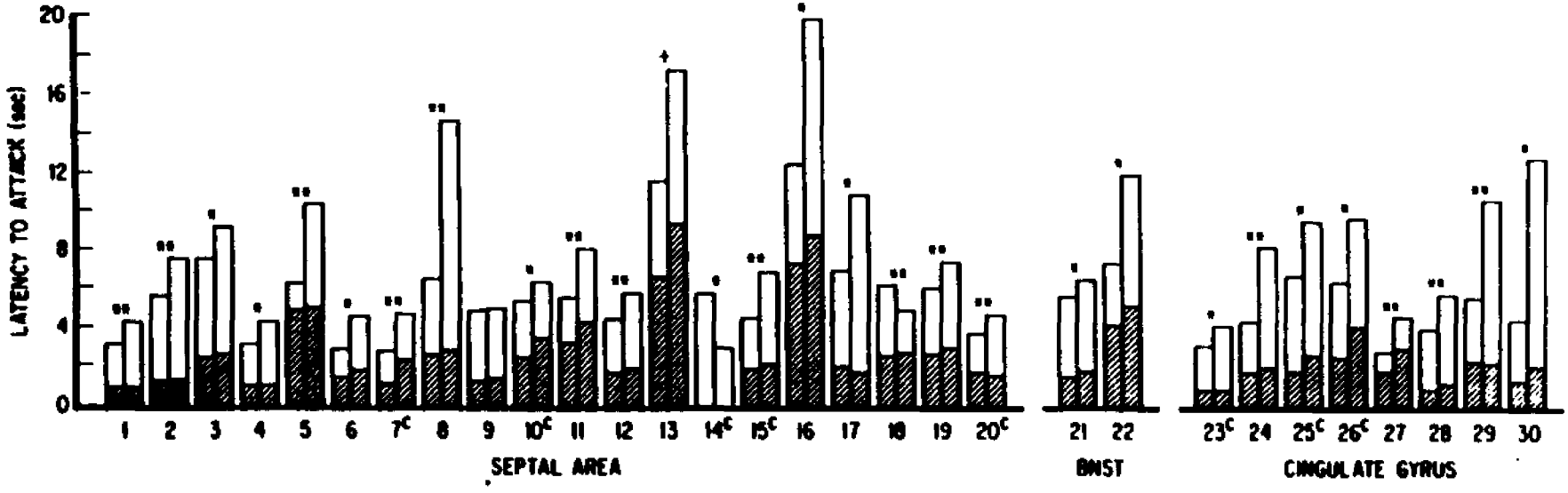

LATENCY TO ATTACK (sec)
20
16
12
8
4
0
1 2 3 4 5 6 7C 8 9 10C 11 12 13 14C 15C 16 17 18 19 20C
SEPTAL AREA
21 22
BNST
23C 24 25C 26C 27 28 29 30
CINGULATE GYRUS

Fig. 8.

Table I). Additionally, certain individual septal or cingulate electrodes (cases 2 and 17; 12 and 20; 15, 18 and 19; 24, 29 and 30; and 25 and 26) were found to modulate attack behavior elicited from several sites along the hypothalamic continuum within the same animal. Initial movement latencies during dual stimulation of septal area or cingulate gyrus and the hypothalamus ranged between 1.0 to 9.0 sec, while mean latencies for attack occurred between 2.5 to 18.0 sec.

While the overall behavioral pattern observed during concurrent stimulation of sites suppressing attack and the hypothalamus was similar to the attack sequence initiated by hypothalamic stimulation alone, the following differences were noted. During dual stimulation, the cat would either fail to attack following its initial facial sensory contact with the rat or it would, instead, circle the rat another time or just hesitate before biting the prey. This observation supports the view that following stimulation of sites suppressing attack, initial sensory input to the cat's lipline had become ineffective for triggering the biting response (Block et al., 1980a).

Suppression of attack behavior.

Septal area. Stimulation at 12 sites in the lateral septal nucleus (cases 1-6, 8, 11-13, 17, 20) produced statistically significant suppression of quiet biting attack behavior elicited from the hypothalamus ($p<0.05$). In

TABLE I

EFFECTS OF CONCURRENT SEPTAL OR CINGULATE GYRUS STIMULATION UPON INITIAL MOVEMENT AND ATTACK LATENCIES ELICITED FROM THE HYPOTHALAMUS

Case	Modulating Electrode Site:Frontal Plane	Number Of Paired Trials	Initial Movement Latency	Mean Differences In Attack Latencies (sec) $\bar{X}_s - \bar{X}_D / S_{\bar{D}}$	Effect
	Septal Area:				
1	18.5	11	NS	-1.05/0.30	I**
2	18.5	9	NS	-1.90/0.48	I**
3	18.5	10	NS	-1.68/0.57	I*
4	17.0	9	NS	-1.08/0.43	I*
5	17.0	11	NS	-4.15/0.41	I**
6	17.0	5	NS	-1.52/0.64	I*
7	17.0	10	I**	-1.86/0.45	I**
8	17.0	13	NS	-8.14/1.98	I**
9	17.0	12	NS	-0.32/0.42	NS
10	17.0	17	NS	-0.90/0.36	I*
11	16.0	8	NS	-2.25/0.31	I**
12	16.0	17	NS	-1.23/0.31	I**
13	16.0	6	NS	-7.00/2.83	NS
14	16.0	6	--	2.57/0.73	F*
15	16.0	10	NS	-2.00/0.57	I**
16	15.5	5	NS	-9.37/3.33	I*
17	18.5	10	NS	-3.90/1.57	I*
18	16.0	7	NS	1.20/0.19	F**

19	16.0	21	NS	-1.24/0.28	I**
20	16.0	12	NS	-0.95/0.16	I**
21	17.0	13	NS	-0.79/0.34	I*
22	14.0	15	I*	-4.55/1.58	I*
23	18.5	11	NS	-1.80/0.39	I*
24	18.5	6	NS	-3.95/0.86	I**
25	18.5	7	I*	-2.51/ .82	I*
26	18.5	10	I*	-3.26/1.08	I*
27	18.5	6	NS	-1.80/0.39	I**
28	17.0	12	I**	-1.68/0.40	I**
29	18.5	11	NS	-5.24/1.07	I**
30	18.5	5	NS	-8.61/2.34	I*

$\bar{X}_S$ refers to the mean value of attack latencies resulting from stimulation of the hypothalamus alone: $\bar{X}_D$ refers to the mean value of attack latencies resulting from dual stimulation of the hypothalamus and septal area or cingulate cortex; $S_{\bar{D}}$ refers to the standard error of the mean of the distribution of difference scores of paired trials of single and dual stimulation. F refers to facilitation of the attack response; and I refers to inhibition of the attack response; NS refers to a nonsignificant effect. $^*p < 0.05$; $^{**}p < 0.02$.

one additional case, stimulation of the lateral septal nucleus (case 13) resulted in suppression of attack that approached statistical significance.

Concerning adjacent regions, stimulation of the medial septal nucleus (case 7), dorsal border of the nucleus accumbens (case 10), bed nucleus of the stria terminalis (cases 21 and 22) and bed nucleus of the anterior commissure (cases 15 and 19) also produced significant suppression of attack behavior ($p<0.02$ and $p<0.05$). An analysis of the effects of dual stimulation upon latencies to initial movement revealed that significant modulation was found in only 2 of 22 cases tested (cases 7 and 22).

Cingulate gyrus. Stimulation of all 5 sites in the anterior cingulate gyrus significantly suppressed attack behavior elicited from the hypothalamus ($p<0.05$). In 3 of 5 cases tested (cases 25, 26, 28) dual stimulation resulted in significant increases in latencies for initial movement of the forepaws ($p<0.05$).

Facilitation of Attack Behavior

Facilitation of attack behavior was noted from only 2 sites tested ($p<0.05$). One electrode tip was located in the far ventrolateral aspect of the lateral septal nucleus (case 14), a region which receives a major input from the ventral hippocampus (Meibach and Siegel, 1977a) and is known to facilitate quiet biting attack behavior. The other electrode tip was situated in the posterior aspect of the septal

area, adjacent to the bed nucleus of the anterior commissure and triangular septal nucleus (case 18).

Individual sites in the septal area or anterior cingulate gyrus which modulated attack behavior elicited from separate regions of the hypothalamus

This aspect of the study determined whether stimulation induced modulation was limited to selective regions of the hypothalamus or whether stimulation uniformly modulated attack behavior elicited from widely different regions of the hypothalamus. These findings suggest that stimulation produced a relatively uniform effect upon attack behavior elicited over a wide region of the hypothalamus.

One site in the dorsolateral septum significantly ($p<0.02$ or $p<0.05$) modulated one quiet biting attack site in the ipsilateral anterior perifornical lateral hypothalamus (case 2) and another quiet biting attack site in the posterior hypothalamus (case 17). A second site located in the "intermediolateral" septum was found to modulate attack behavior elicited from both ipsilateral (case 12) and contralateral (case 20) supramammillary region. Stimulation at a third electrode tip in the ventrolateral septum, bordering the diagonal band of Broca was found to modulate attack elicited from the contralateral perifornical lateral hypothalamus (case 15) as well as from the ipsi- (case 18) and contralateral (case 19) supramammillary regions. Stimulation of another site located in the dorsomedial preoptico-

hypothalamus, significantly modulated attack elicited from the contralateral hypothalamus (case 15) and from the ipsilateral suprammillary region (case 19).

With regard to anterior cingulate gyrus modulation of attack, one site in this region modulated 3 different hypothalamic sites producing attack. One of these electrodes was located in the ipsilateral perifornical lateral hypothalamus (case 24), a second was situated in the posterior hypothalamus (case 29) and a third was located in the supramammillary region (case 30). Finally, we observed that an anterior cingulate gyrus site modulated attack elicited from both the contralateral perifornical hypothalamus (case 25) and posterior hypothalamus (case 26).

Effects of hypothalamic stimulation upon trigeminal sensory fields

MacDonnell and Flynn (1966a) established that the jaw opening response that could be elicited during hypothalamic stimulation and lipline probing in the cat, was a function of the current intensity delivered to that hypothalamic site. It was observed that if either the ipsilateral or the contralateral lipline was probed during single stimulation of the hypothalamus and if the procedure was coupled with increasing current intensities delivered to that site, the extent of the lipline from which jaw opening was elicited during probing, expanded laterally from midline. Following

the procedure of Block et al., (1980a), the lateral extent of the lipline from which probing can elicit a jaw opening response during hypothalamic stimulation has been defined as the "effective sensory field."

Effects of stimulation of septal area and cingulate gyrus upon hypothalamically elicited "effective sensory fields"

The effects upon the effective sensory fields, following stimulation of septal area and cingulate gyrus sites which clearly modulated quiet biting attack elicited by hypothalamic stimulation are described in Fig. 9 and Table II. The results indicate that modulating sites in both the septal area and cingulate gyrus generally constricted the "effective sensory fields." A greater number of significant effects were obtained on the side contralateral to the hypothalamic electrode. This indicates a differential excitation of each side of the body, with the receptive field for the reflex on the contralateral side affected more than the other side.

Inhibitory sites. Those septal or cingulate sites that produced significant suppression of attack during dual electrical stimulation of the hypothalamus also produced a statistically significant constriction ($p<0.05$) of the "effective sensory fields" along the lipline (Fig. 9 and Table II). In 11 cases (1, 4-6, 8, 10-13, 15, 16) of septal area stimulation and 2 cases (23, 28) of cingulate gyrus stimulation, the contralateral extent of the lipline was significantly ($p<0.05$) constricted following stimulation of

Fig. 9. Bar graphs depict the alteration of the size of the "effective sensory fields" following concomitant stimulation of the hypothalamus with the septal area, bed nucleus of the stria terminalis or cingulate gyrus (crosshatched histograms) and following stimulation of the hypothalamus alone (open histograms). Numbers centered below pairs of histograms identify cases described in Table II. *$p<0.05$; **$p<0.02$.

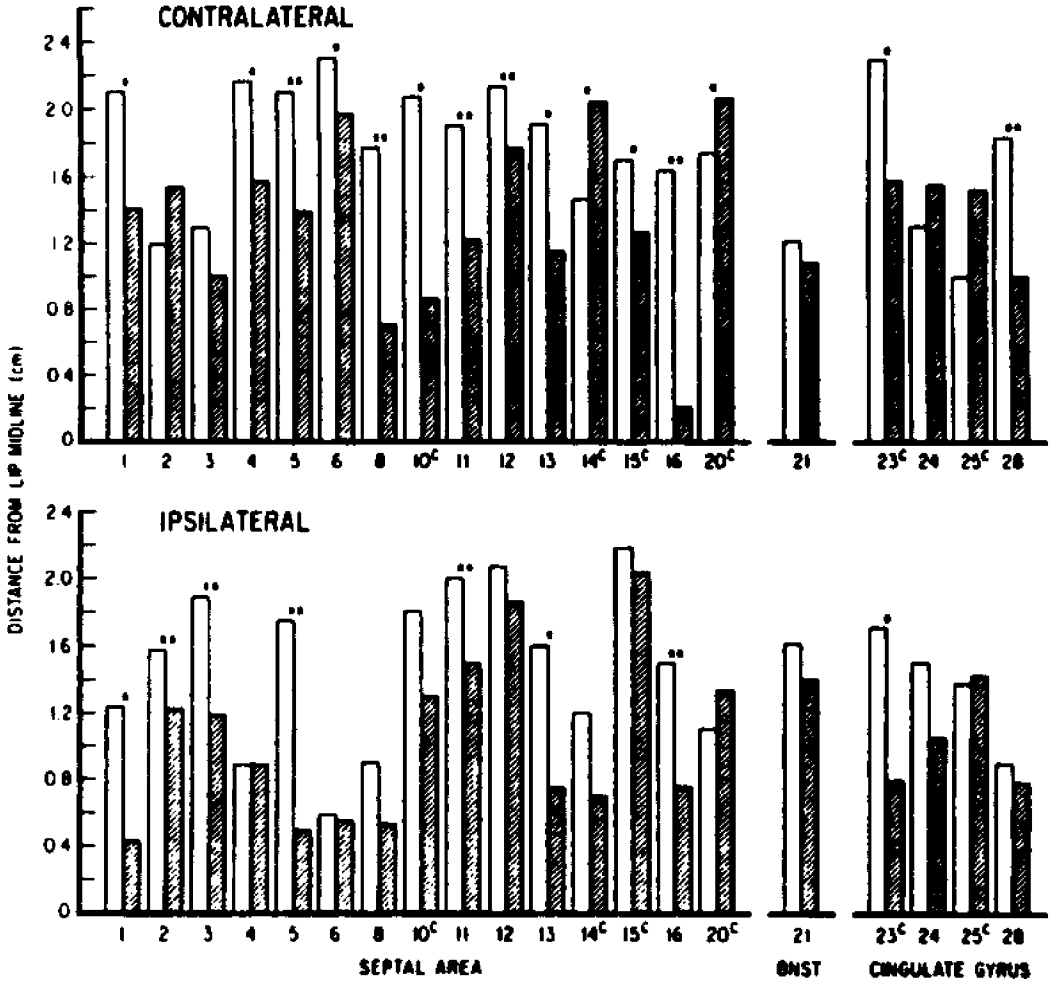

CONTRALATERAL
IPSILATERAL
DISTANCE FROM LIP MIDLINE (cm)
SEPTAL AREA
BNST
CINGULATE GYRUS

Fig. 9.

TABLE II

EFFECTS OF CONCURRENT SEPTAL OR CINGULATE GYRUS STIMULATION
UPON THE IPSILATERAL AND CONTRALATERAL EXTENT OF THE "EFFECTIVE SENSORY FIELDS"
AND UPON THE LATENCY TO JAW OPENING DURING LIPLINE PROBING

		Sensory effects				Motor effects	
		Ipsilateral Lipline		Contralateral Lipline		Mid-Lipline	
Case	Modulating Electrode Site: Frontal Plane	Number of Paired Trials	Effect	Number of Paired Trials	Effect	Number of Paired Trials	Effect
	Septal area:						
1	18.5	5	C*	10	C*	5	NS
2	18.5	8	C**	5	NS	5	NS
3	18.5	8	C**	5	NS	--	--
4	17.0	5	NS	6	C*	5	NS
5	17.0	5	C**	11	C**	5	NS
6	17.0	5	C*	9	NS	9	NS
7	17.0	--	--	--	--	--	--
8	17.0	5	NS	8	C**	5	NS
9	17.0	--	--	--	--	--	--
10	17.0	5	NS	6	C*	5	F*
11	16.0	5	C**	11	C**	5	NS
12	16.0	7	C**	8	NS	5	NS

13	16.0	6	C*	7	C*	5	F*
14	16.0	5	NS	8	E*	--	--
15	16.0	6	NS	6	C*	--	--
16	15.5	5	C**	5	C**	7	NS
17	18.5	--	--	--	--	--	--
18	16.0	--	--	--	--	--	--
19	16.0	--	--	--	--	--	--
20	16.0	5	NS	6	E*	5	NS
21	17.0	7	NS	7	NS	--	--
22	14.0	--	--	--	--	--	--
	Anterior Cingulate Gyrus:						
23	18.5	5	C*	7	C*	5	NS
24	18.5	5	NS	11	NS	5	NS
25	18.5	6	NS	5	NS	--	--
26	18.5	--	--	--	--	--	--
27	18.5	--	--	--	--	--	--
28	17.0	5	NS	7	C*	5	NS
29	18.5	--	--	--	--	--	--
30	18.5	--	--	--	--	--	--

C refers to constriction of the sensory fields of the lipline; E refers to expansion of the sensory fields of the lipline; F refers to facilitation of the jaw opening response; NS refers to a nonsignificant effect. *$p < 0.05$; **$p < 0.05$.

sites previously shown to suppress attack. In 7 cases (1-3, 5, 11, 13, 16) of septal stimulation and 1 case (23) of cingulate gyrus stimulation a significant constriction of the ipsilateral sensory field was also noted ($p<0.05$).

Facilitatory sites. Of 2 septal sites that produced facilitation of the attack response (cases 14, 18) only one site (case 14) displayed a significant expansion of "effective sensory fields" during stimulation. The modulating electrode tip in this case was located in the far ventrolateral septal area. In case 18, sensory field testing was not carried out. In case 20, in which the modulatory electrode tip was situated in the central aspect of the lateral septal nucleus, a significant inhibition of the attack response was coupled with a significant expansion of the contralateral "effective sensory field." In this animal, septal stimulation had no effect upon the ipsilateral "effective sensory fields" of the lipline.

Effect of dual stimulation upon the latency for the jaw opening response

In the following experiment, a constant sensory field was generated when probing occurred along the region of the midline of the lip during both conditions of single and dual stimulation. This aspect of the study was carried out in order to assess the effects of dual stimulation upon the motor component of this response. In general, stimulation

from modulating sites had little or no effect upon jaw opening latencies.

Inhibitory sites. Stimulation of 13 of 15 septal area and cingulate gyrus sites which significantly suppressed attack behavior produced no changes in the latencies for the occurrence of jaw opening response (as indicated in Fig. 10 and Table II). The latencies for the occurrence of this response during either single or dual stimulation ranged from 2.0 to 10.0 sec. Only 2 electrode sites situated in the septal area produced, upon stimulation, a significant suppression of jaw opening latencies. See Fig. 11 for a summary of the typical effects of stimulation of the septal area.

[^{14}C]2-deoxyglucose autoradiography

Following behavioral testing, a [^{14}C]2-DG metabolic mapping experiment was performed in order to identify the specific pathways and structures metabolically activated by electrical stimulation of select septal area sites from which modulation of attack was obtained. The results from two successful inhibitory sites will be described below.

The first stimulating electrode from which inhibition of attack was obtained (case 8), was located in the ventral aspect of the lateral septal nucleus (Fig. 12, 13a and 13b). At the level of the stimulating electrode, the 2-DG autoradiographs revealed an intense zone of activation about the electrode tip, which could be followed dorsally into the

Fig. 10. Bar graphs indicating that concomitant stimulation of the hypothalamus and septal area has little effect upon the latency to jaw opening during probing of the midline region of the lip. For each pair of histograms, the first bar indicates the mean latency to jaw opening resulting from stimulation of the hypothalamus alone, while the second bar indicates the mean latency to jaw opening resulting from concurrent stimulation of the hypothalamus and septal area or cingulate gyrus. *$p<0.05$.

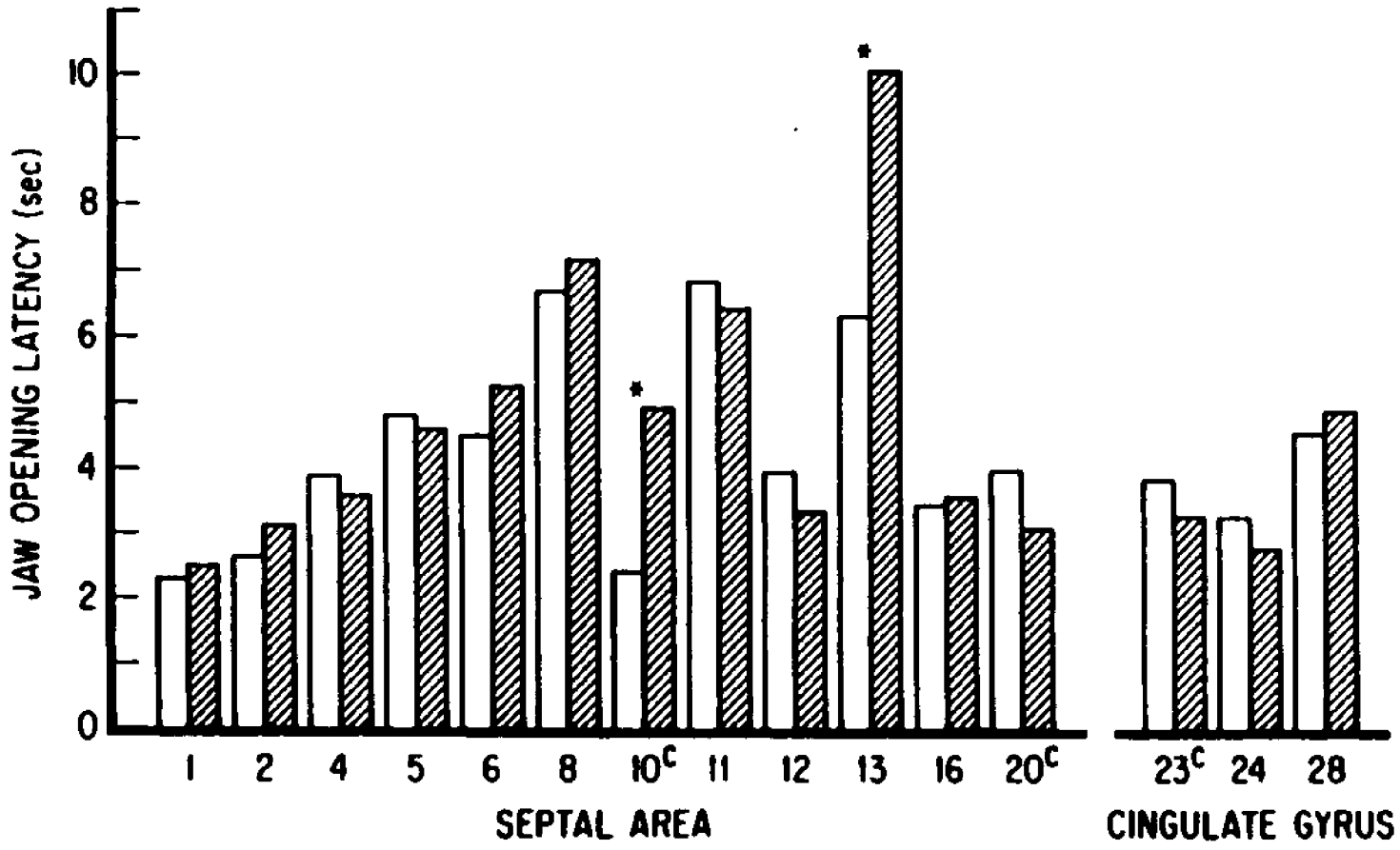

JAW OPENING LATENCY (sec)
0
2
4
6
8
10
*
*
1
2
4
5
6
8
10C
11
12
13
16
20C
23C
24
28
SEPTAL AREA
CINGULATE GYRUS

fig. 10.

Fig. 11. Histograms illustrating typical effects of stimulation of the septal area upon: (A) latency to initial movement of the forepaws; (B) latency to quiet biting attack; (C) the ipsilateral and contralateral "effective sensory fields"; and (D) the latency to jaw opening. Open histograms, stimulation of the hypothalamus alone; cross-hatched histograms, dual stimulation of the hypothalamus and the septal area (case 8). **$p<0.02$.

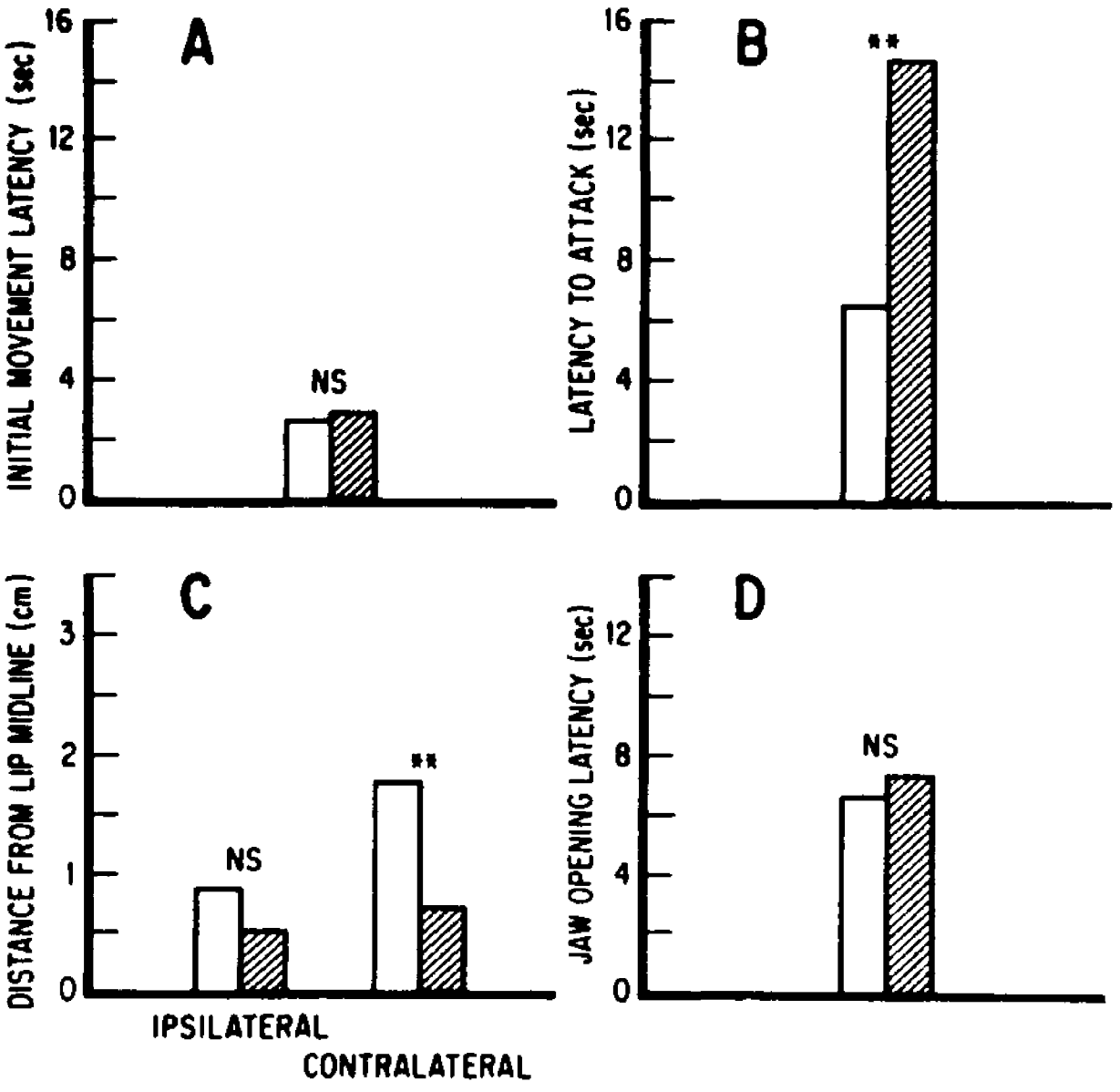

A
INITIAL MOVEMENT LATENCY (sec)
16
12
8
4
0
NS
B
LATENCY TO ATTACK (sec)
16
12
8
4
0
**
C
DISTANCE FROM LIP MIDLINE (cm)
3
2
1
0
NS
**
IPSILATERAL
CONTRALATERAL
D
JAW OPENING LATENCY (sec)
12
8
4
0
NS

Fig. 11

Fig. 12. [^{14}C]2-Deoxyglucose autoradiographs demonstrating the regions metabolically activated following electrical stimulation of a site in the ventral aspect of the lateral septal nucleus (case 8), which was shown previously to suppress hypothalamically-elicited quiet biting attack and to constrict the contralateral "effective sensory fields." The white dot depicts the position of the stimulating electrode tip. Note uptake of label in the diagonal band of Broca (level c) and anterior lateral hypothalamus (level e). For a detailed description of brain sites activated, see Fig. 13a and 13b.

Fig. 12

Fig. 13a and 13b. Line diagrams demonstrating the structures metabolically activated as determined from the autoradiographs displayed in Fig. 12 (case 8). The location of the stimulating electrode in the lateral septal nucleus is depicted by the closed circle in level c. At the level of the stimulating electrode (level c), an intense zone of activation could be seen about the electrode tip. Label could be followed into the entire lateral septal area (levels c and b). Rostrally, label could be followed through the anterior aspect of this nucleus into the medial part of the nucleus accumbens (level b) and prelimbic cortex (level a). No activation was seen on the side of the brain contralateral to the stimulating electrode. Activation could be followed medially into the medial septal nucleus (level c) and ventrally into both the vertical and horizontal limbs of the diagonal band of Broca (levels c and d). Additional label was followed into the lateral preoptic (level e) and anterior perifornical lateral hypothalamus (level f and g). Some label was also seen at rostral levels of the periventricular thalamus (level f). Caudally, label could be followed from the lateral septal area through the fornix (levels d-h) into the dorsal and ventral hippocampus where label was most pronounced over the CA fields and subicular cortex. Abbreviations: ACB, nucleus accumbens; CA, anterior commissure; CA1, hippocampal field CA1; CA3, hippocampal field CA3; Cd, caudate nucleus; Dbb, diagonal band of Broca; E, entorhinal cortex; Fx, fornix; HL, lateral

hypothalamus; PL, prelimbic cortex; Pre, presubiculum; RPO, preoptic area; S, subicular cortex; Spt, septal area.

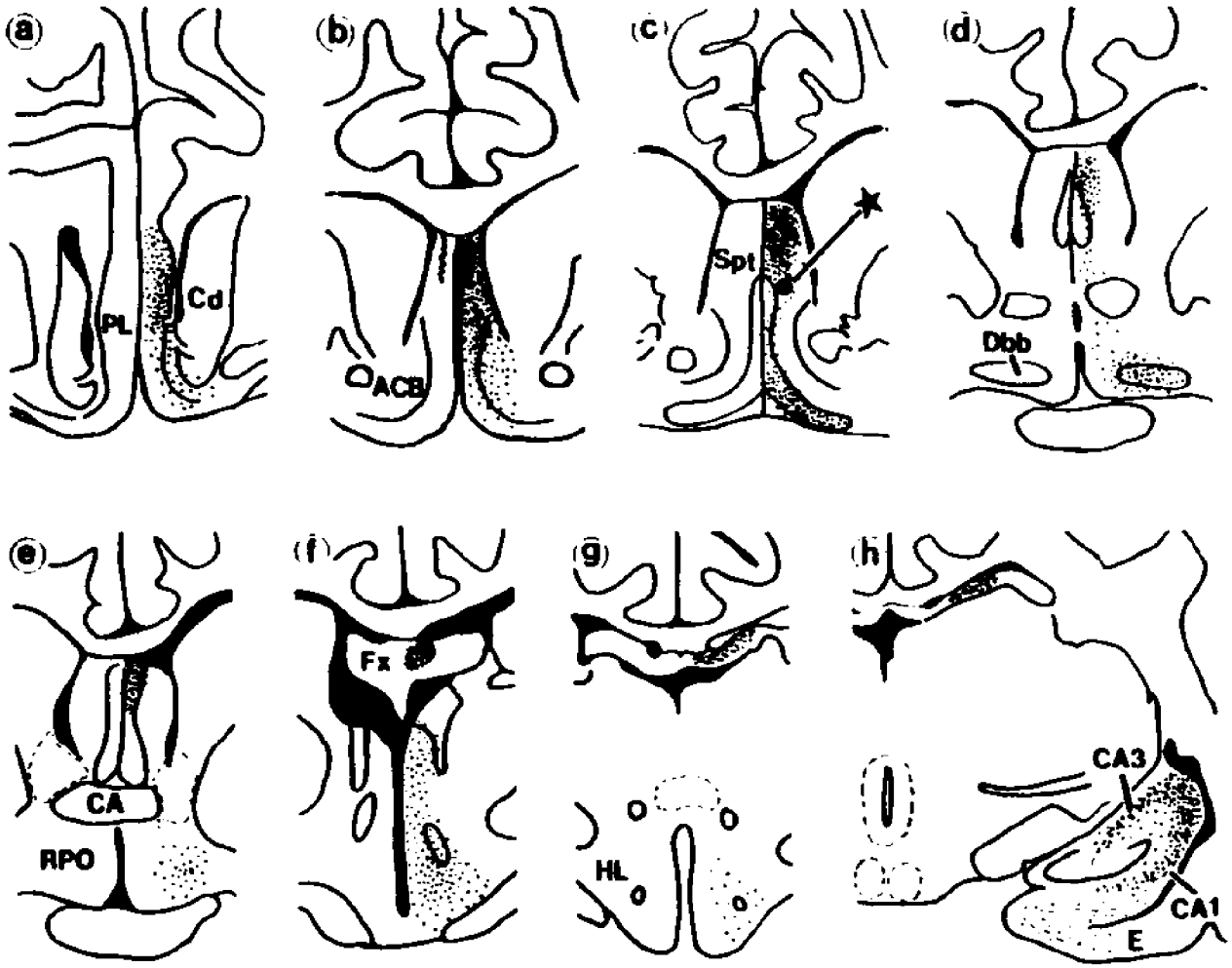


Fig. 13a.

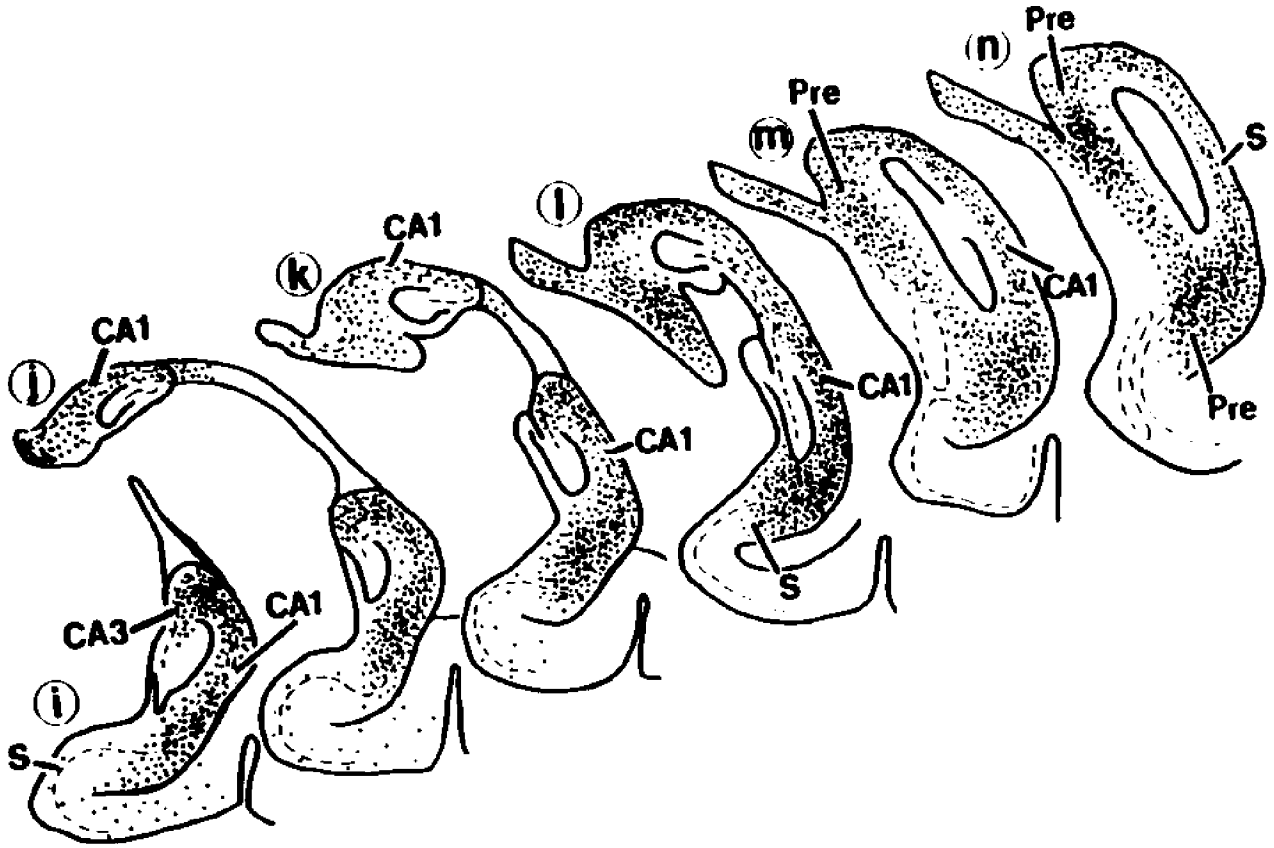


Fig. 13b.

entire lateral septal area. Rostrally, label could be followed through the anterior aspect of this nucleus into the medial part of the nucleus accumbens and prelimbic cortex. No activation was seen on the side of the brain contralateral to the stimulating electrode. Activation could be followed medially into the medial septal nucleus and ventrally into the both vertical and horizontal limbs of the diagonal band of Broca. Additional label was followed into the lateral preoptic and anterior perifornical lateral hypothalamus. Some label was also seen at rostral levels of the periventricular thalamus.

Caudally, label could be followed from the lateral septal area through the fornix into the dorsal and ventral hippocampus where label was most pronounced over the CA fields and subicular cortex.

In the second case (5), in which inhibition of attack was also obtained, the stimulating electrode tip was located in the dorsomedial quadrant of the lateral septal nucleus (Fig. 14a & 14b). Activation could be followed rostrally into the prelimbic cortex but not into the nucleus accumbens. At the level of the stimulating electrode tip, activation could also be followed into the ipsilateral medial septal nucleus, both vertical and horizontal limbs of the diagonal band of Broca and the lateral preoptic region. The intensity of label in these structures was generally not as intense as that observed in case 8. Label could also be traced from the dorsomedial septum into the dorsal fornix

Fig. 14a and 14b. Line diagrams depicting the structures metabolically activated following electrical stimulation of the dorsomedial aspect of the lateral septal nucleus (case 5). The location of the stimulating electrode is depicted by the closed circle in level d. Note the uptake of label in the diagonal band of Broca. See Fig. 13 for abbreviations.

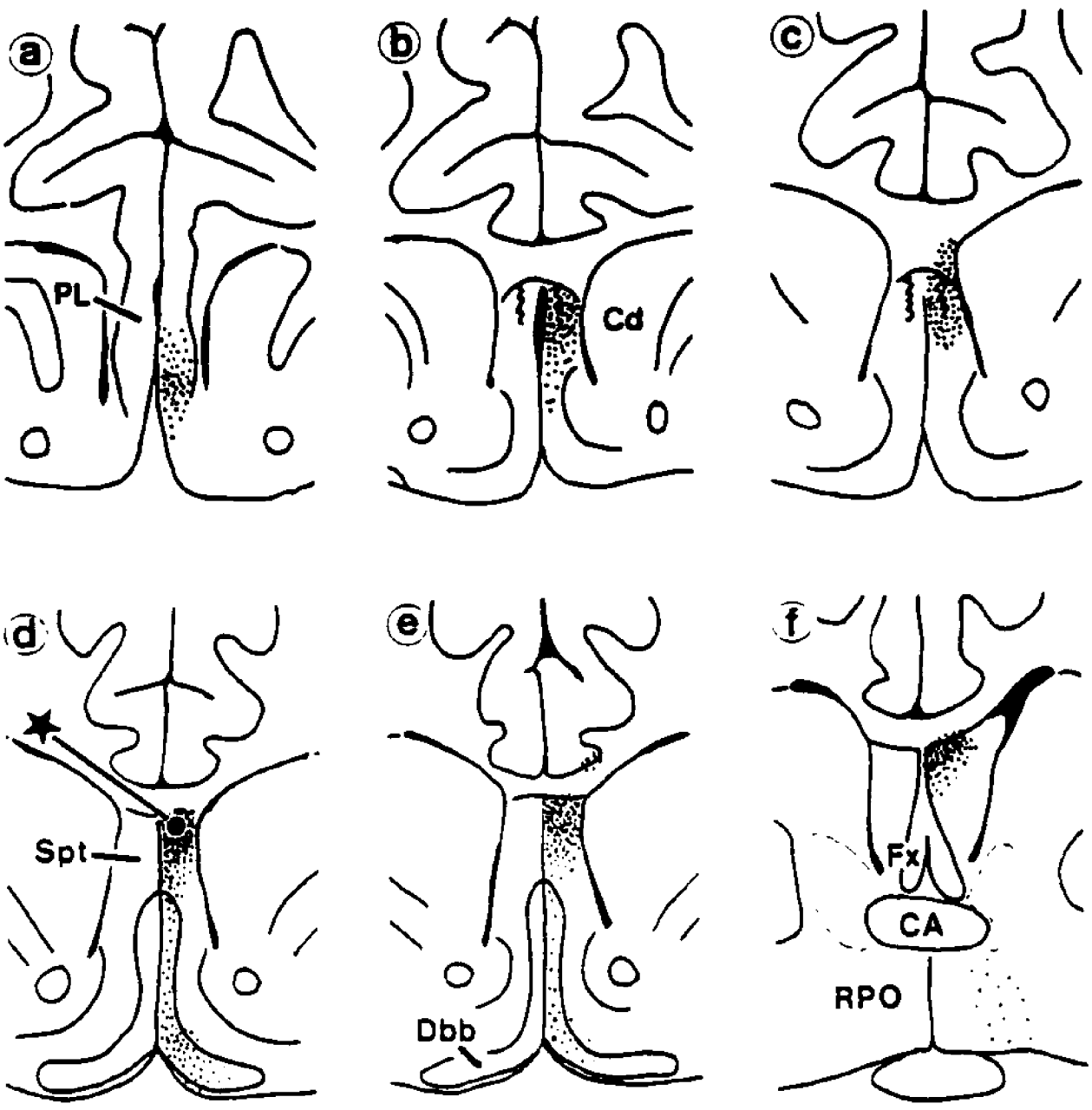


Fig. 14a.

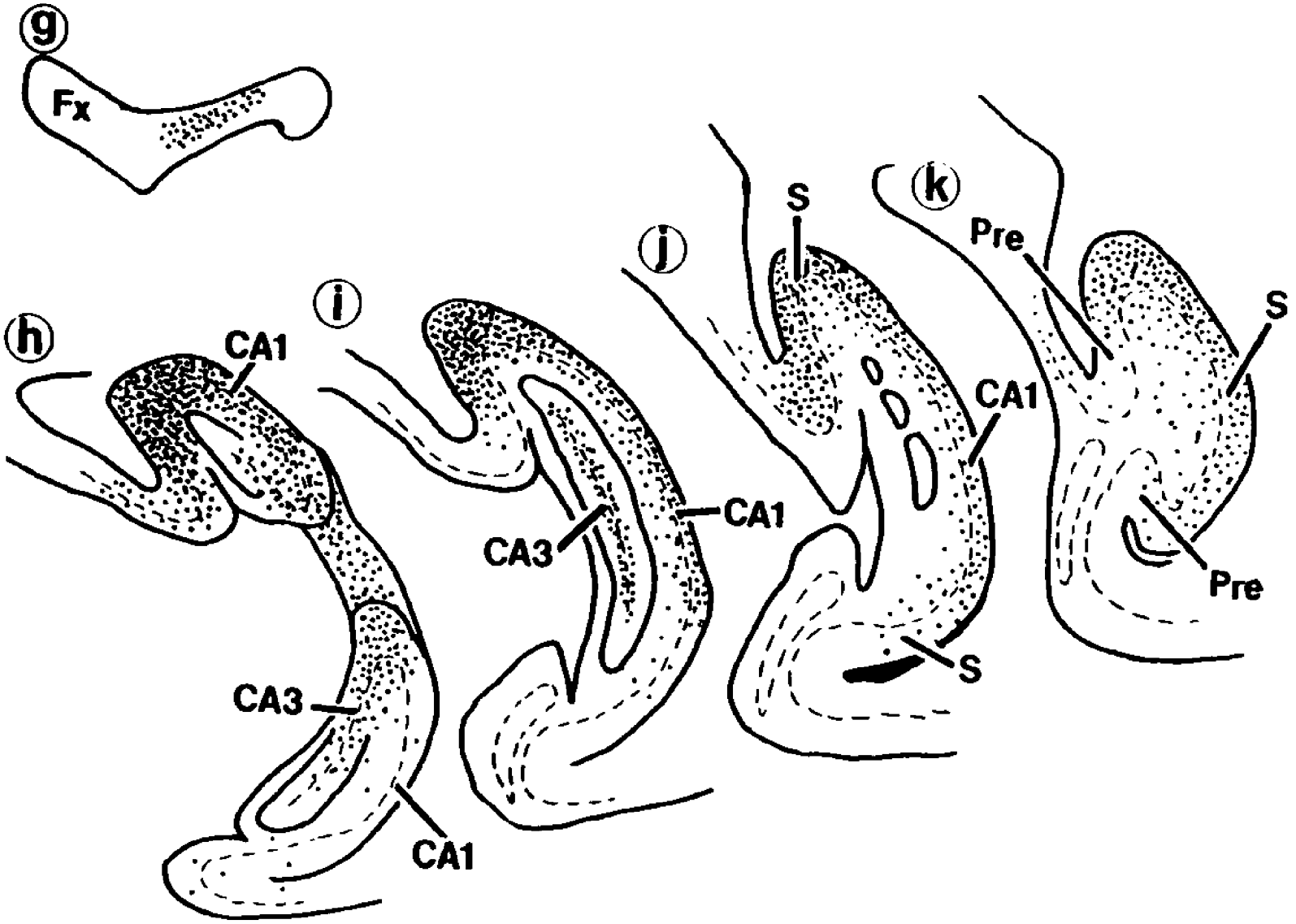


Fig. 14b.

and dorsal hippocampus, with somewhat less intense activation visible in the dorsal aspects of the ventral hippocampus and subicular cortex.

DISCUSSION

Septal suppression of attack

The results of this study replicate and extend the earlier findings of Siegel and Skog (1970) and Siegel and Chabora (1971). It is clear from the present study that an extensive inhibitory network is present for the control of quiet biting attack behavior which includes much of the ipsilateral and contralateral septal area and anterior cingulate gyrus. The findings further indicate that stimulation of sites in the septal area which suppress quiet attack also significantly constrict the "effective sensory fields" of the lipline (Block et al., 1980a; Block et al., 1980b) established during stimulation of sites eliciting quiet biting attack behavior. Accordingly, it is reasonable to conclude that the suppressive effects of septal area stimulation on quiet biting attack behavior are achieved in part, by the influence this region exerts upon the sensory (behavioral) component of the jaw-opening response, which is present during the occurrence of the attack response (MacDonnell and Flynn, 1966).

It is important to note that while septal stimulation had potent effects upon the effective sensory fields of the lipline, there was little or no effect upon motor components of this response. This is evidenced by the fact that: (1) latencies to initial movement following stimulation of the hypothalamus and (2) latencies for the jaw opening response during probing of the midline of the lip

were both unaffected by septal stimulation and (3) stimulation of the septal area did not result in the initiation of any motor components of the attack response nor of any other motor responses unrelated to the attack sequence. Inasmuch as stimulation of most regions of the septal area appears to suppress quiet attack in part by regulating the "effective sensory fields" along the lip, the mechanisms operative during septal modulation of attack appear to parallel those previously ascribed to several other portions of the limbic forebrain for the suppression of attack behavior, such as the amygdala (with the exception of its lateral and central nuclei) (Block et al., 1980a) and lateral aspect of the substantia innominata (Block et al., 1980b) stimulation.

Although earlier evidence that the septum (Ranson et al., 1935; Mogenson, 1976) primarily regulates behavioral and physiological responses in an inhibitory manner, there is a growing body of evidence which indicates that it also has facilitatory effects (Malmo, 1961; Stuart et al., 1961; Sibole et al., 1971; Covian, 1967; Miller and Mogenson, 1971, 1972; Calaresu and Mogenson, 1972; Covian et al., 1964; Covian and Timo-Iaria, 1966; Stoddard-Apter and MacDonnell, 1980; Siegel and Edinger, 1976; Mogenson, 1976). It has been reported that septal stimulation can increase the rate of respiration, heart rate and blood pressure as well as decreasing these responses (Calaresu and Mogenson, 1972; Covian et al., 1964; Covian et al., 1966; Malmo, 1961). Septal sitmulation has been shown to both increase

and decrease drinking elicited by lateral hypothalamic stimulation (Sibole et al., 1971). Tachycardia and bradycardia can be elicited by stimulating the same septal site (Stuart et al., 1961). It has been suggested that the septum exerts either facilitatory or inhibitory effects upon hypothalamic and midbrain systems, so as to modulate a variety of responses organized within these regions (Covian, 1967; Sibole et al., 1971; Miller and Mogenson, 1971; 1972).

With regard to aggression, it has also been found that the septal region is not exclusively inhibitory to aggressive behavior. This study and others indicate that the lateral septal nucleus inhibits hypothalamically elicited attack behavior (Brutus et al., 1984b; Siegel and Edinger, 1976; Siegel and Skog; 1971), while the far ventrolateral aspects of this region are facilitatory to quiet attack behavior (Brutus et al., 1984b; Siegel and Edinger, 1976; Siegel and Skog, 1970). Therefore, a functional differentiation exists within the septum with regard to quiet attack behavior. In addition, electrical stimulation of much of the septum has been found to be facilitatory to another form of hypothalamically elicited aggressive behavior, intraspecific aggression and associated hissing (affective defense) (Siegel and Edinger, 1976; Stoddard-Apter and MacDonnell, 1980) and also to flight behavior (Edinger and Siegel, 1976) in the cat. It is important to note that septal area modulation of affective defense is opposite to that for quiet attack and this can therefore serve as a

control for any generalized effects produced by electrical stimulation. These findings indicate that septal inhibition of quiet attack behavior cannot be interpreted in terms of a general inhibition of all motor responses.

2-DG findings

Methodological considerations of [^{14}C]2-DG functional mapping following electrical brain stimulation of septal region. [^{14}C]-2-deoxyglucose autoradiography was undertaken in concert with electrical stimulation of sites in the septal area from which modulation could be achieved in order to gain further insight into the nature of the pathways and structures activated during electrical stimulation. This approach represents an improvement over other techniques and can provide significant new information concerning the functional output of the septal area. Classical neuroanatomical methods such as silver impregnation procedures for staining of degenerating axons, tritiated amino acid radioautography, and HRP provide only indirect evidence concerning anatomically related structures. Electrophysiological approaches also provide only a sampling of the affected brain regions following activation of a given brain site. In contrast, the 2-DG method permits visualization of the entire brain, thus allowing one to determine the overall changes that occur in metabolic activity in a variety of brain pathways. Another advantage of this technique is that it can provide a basis for comparing the relative strength

of effects upon different target regions following stimulation of a given site. These effects can be visualized as relative difference in optical densities on the X-rays. Relative differences in optical densities (which have been assumed to be correlated with metabolic activity) can be quantified by the use of densitometry.

This procedure has been applied successfully in this study and a series of previous studies in order to identify similar functional pathways of limbic structures in both cat (Watson et al., 1983a) and rat (Watson et al., 1983b; Watson et al., 1985; Watson et al., 1983c; Fuchs et al., 1981; Fuchs and Siegel, 1984). In this procedure it is assumed that stimulation will activate both the cell bodies of origin as well as the fibers of passage in proximity to the stimulating electrode. Increases in the uptake of isotope in these regions are expressed as labeled or optically dense areas on the brain section autoradiographs. That a functional relationship exists between 2-DG labeling of tissue and functional activity within the brains has already been established (Hubel et al., 1978; Plum et al., 1976; Roberts, 1980; Schwartz et al., 1979; Sokoloff et al., 1977). Increases in 2-DG uptake within discrete regions following electrical stimulation of various brain sites are suggestive of functional activation of these regions (Roberts, 1980; Watson et al., 1983a; Watson et al., 1983b; Watson et al., 1985; Watson et al., 1983c). The pathways labeled by this procedure will most likely be the ones which

serve as the anatomical substrate over which septal modulation of attack is achieved.

A working hypothesis has been that 2-DG labeling reflects the functional activation of the most prominent pathways which may be essential for the functional regulation subserved by the stimulated region in question. Several conclusions regarding how brain tissue is labeled following electrical stimulation can therefore be made. It can be noted that functional brain activation of distal structures utilizing electrical brain stimulation coupled with 2-DG autoradiography, appears to be limited to monosynaptic labeling of neural tissue in both the awake and anesthetized rat (Brutus et al., 1984a; Roberts, 1980) and cat (Brutus et al., 1984b; Fuchs et al., 1981). In the absence of elicited seizure activity, the labeling of first-order projection systems for widespread regions of the limbic system and now the septal area has been demonstrated (Watson et al., 1985). Another conclusion drawn from this study and the overwhelming majority of other studies is that the labeling observed subsequent to stimulation of fiber pathways, their axon terminals or nuclear groups, appears to be orthodromic in nature, although the possibility of antidromic activation may not be entirely ruled out for all cases. This is based primarily upon the fact that the regions activated following electrical stimulation of the septal nucleus closely resemble the patterns of labeling derived from such anterograde anatomical techniques as ^{3}H-

amino acid radioautography and experimental degeneration. Additional support for this view comes from a study by Fuchs et al., 1981, in which they found that distribution patterns of label within forebrain and brainstem sites following ^{3}H-amino acid injections into the medial hypothalamus, matched those following systemic 2-DG injections coupled with electrical brain stimulation of equivalent hypothalamic sites. An additional issue relates to the number of pathways activated from stimulation of a given structure. When stimulation is applied to a given site in the limbic system, the regional patterns of increased 2-DG uptake do not always reflect the total number of target structures known to receive fibers arising or passing through the stimulated region. From previous studies (Watson et al., 1985; Watson et al., 1983a, b, c), it has been concluded that this procedure most likely yields positive visualization of those fiber bundles and their axon terminals which are large in number, relatively compact and of small diameter. The surface area to volume ratio of the activated cellular element is presumably a critical factor in determining the extent of labeling that can be identified on the X-ray autoradiographs (Matta et al., 1980; Schwartz et al., 1979). Consequently, the principal elements labeled by this method would most likely be small diameter axons, dendrites and synaptic terminals rather than cell bodies (Divac and Diemer, 1980; Savaki et al., 1983), although cell bodies are also labeled. Accordingly, another working hypothesis has been that 2-DG

activation reflects the functional activation of the most prominent pathways essential for the functional regulation subserved by the stimulated region in question.

Anatomy. Anatomical studies (Krayniak et al., 1980; Meibach and Siegel, 1977; Raisman, 1966; Siegel and Tassoni, 1971; Watson et al., 1985) have indicated that the major projection targets of the septal area include the lateral hypothalamus, hippocampal formation and habenular complex. In the present study, we noted marked [^{14}C]2-DG uptake in both dorsal and ventral hippocampal formation and diagonal band nuclei, with lesser quantities of label present within hypothalamus. Accordingly, from these observations, the following possible anatomical mechanisms may account for our results. One view is that inhibition from the septal area is mediated monosynaptically, from the septal area to the lateral hypothalamus. The anatomical basis for such a projection is well known (Krayniak et al., 1980; Meibach and Siegel, 1977; Siegel and Tassoni, 1971; Watson et al., 1985). Related 2-DG studies in the rat show a similar activation pattern in the nuclei of the diagonal band and the lateral hypothalamus (Watson et al., 1985). This suggests that the functional pathways activated during electrical stimulation of the septal area are basically similar in the cat and rat.

A second possibility is that septal suppression of attack is mediated either indirectly as a feedback pathway by activating the inhibitory components of the dorsal hippo-

campal formation or by suppressing the facilitatory components of the ventral hippocampal formation (Siegel and Flynn, 1968; Watson et al., 1983a) or by serving as a more direct relay for dorsal hippocampal modulation of attack. This hypothesis seems somewhat less likely since one would have to predict that both dorsal hippocampal as well as septal inhibition of attack would involve similar functional mechanisms upon this behavior or that septal stimulation would selectively inhibit neuronal activity within the ventral hippocampal formation. In fact, dorsal hippocampal stimulation has little or no effect upon the "effective sensory fields" (Watson et al., 1983a), while significant effects upon the sensory fields of the lipline were reported from stimulation of the septal area in the present study. For the same reason, the dissimilarity in modulating effects between dorsal hippocampus and septal area would appear to rule out the likelihood that the inhibitory portions of the septal area merely form a final relay link for the suppression of attack from the dorsal hippocampus. Further, it is not likely that inhibition from the septal area is the result of inhibition of the facilitatory influence upon the ventral hippocampal formation, since fimbria-fornix stimulation is known to produce primary excitation in pyramidal neurons (Spencer and Kandel, 1961; Spencer and Kandel, 1968). That septal stimulation produced activation of the hippocampal formation indicated that, in this instance, only fibers of passage were activated, because the sole origin of

the septo- hippocampal pathway is restricted to the diagonal band nuclei and to a lesser extent, the adjoining medial septal nucleus (Krayniak et al., 1980; Meibach and Siegel, 1977). Therefore, for this reason as well, it is somewhat unlikely that the lateral septal nucleus could exert a direct influence upon the hippocampal formation.

A more attractive hypothesis is that the inhibitory components of the septal area produced their modulation of attack behavior by initially acting upon the nuclei of the diagonal band. The region receives a major input from parts of the lateral septal area (Krayniak et al., 1980; Meibach and Siegel, 1977), and is known to exert a powerful inhibitory effect upon a quiet attack in the cat (Inselman and Flynn, 1972) and muricidal behavior in the rat (Bandler and Vergnes, 1979). The diagonal band is known to project extensively to the hypothalamus as demonstrated by both classical autoradiographic approaches (Krayniak et al., 1980; Meibach and Siegel, 1977) as well as by functional 2-DG autoradiography (Watson et al., 1985).

It should also be pointed out that in the present study two sites producing suppression of attack behavior were located in the bed nucleus of the stria terminalis. In these instances, the pathways mediating suppression of attack could appear to be different, involving instead the amygdaloid projection system. Specifically, those portions of the amygdala from which suppression of quiet attack can be obtained (Block et al., 1980a; Egger and Flynn, 1963)

project heavily via the stria terminalis to its bed nucleus (DeOlmos and Ingram, 1972; Krettek and Price, 1978). Stimulation of these amygdaloid nuclei can also intensely activate the bed nucleus (Watson et al., 1983c). Since stimulation of the bed nucleus can produce activation within the perifornical hypothalamus, a region from which quiet attack can be initiated upon stimulation, it is reasonable to suggest that suppression of quiet attack from the bed nucleus of the stria terminalis is monosynaptically mediated and that it constitutes part of an overall system involving inhibitory regions of the amygdala.

Septal Facilitation of Attack

Septal facilitation of quiet attack was only observed in several instances in the present study. Electrode sites were noted mainly in the far ventrolateral aspect of the lateral septal nucleus. It should be noted that facilitation of attack was also noted from this region of the septum in an earlier study (Siegel and Skog, 1970).

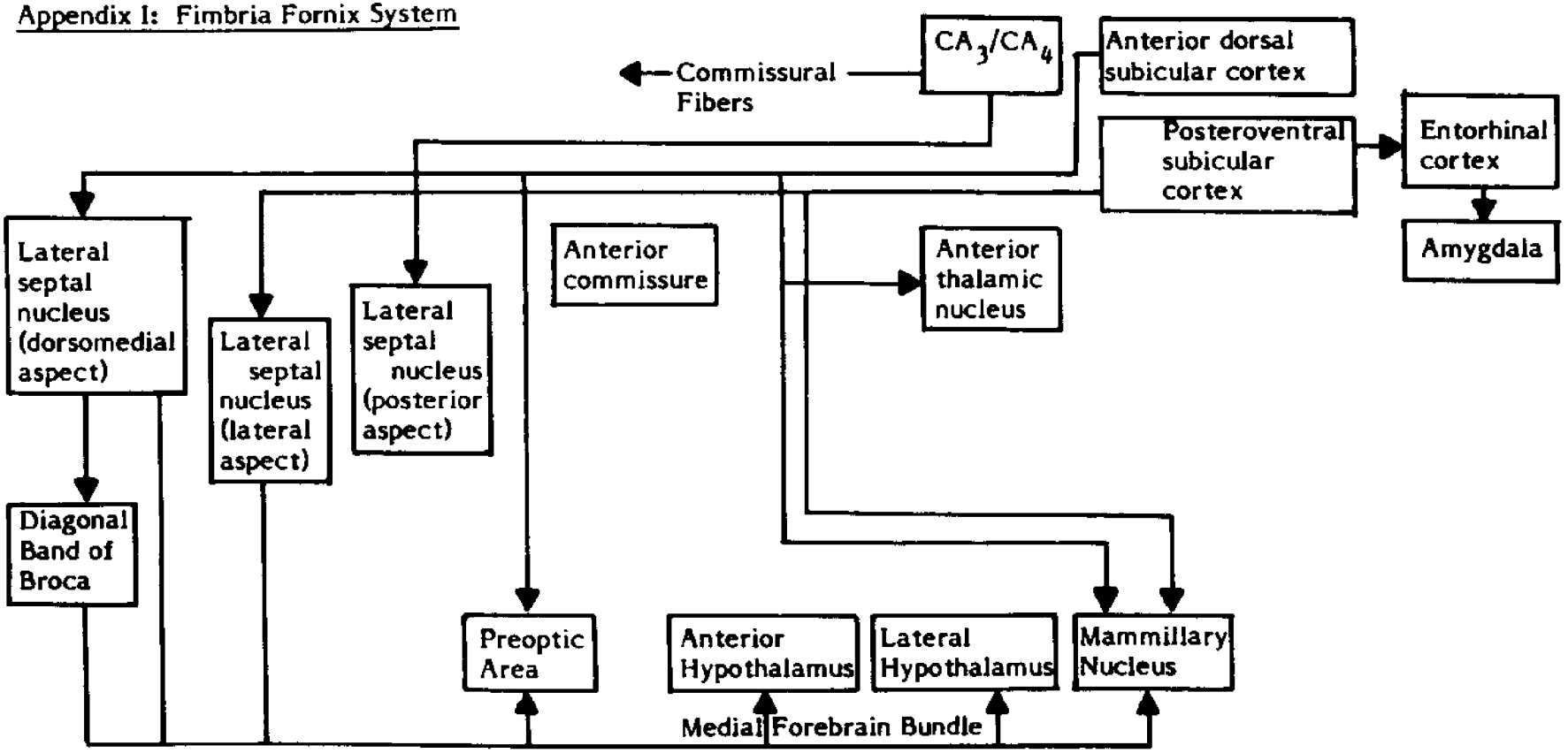
With regard to facilitation of attack, as noted above in the Results Section, this region of the lateral septum receives a major input from the ventral hippocampal formation. This portion of the hippocampal formation is known to exert a powerful facilitatory effect upon quiet attack behavior, in part by modulation of the "effective sensory fields" of the lipline (Watson et al., 1983a). Therefore, it is suggested that the ventrolateral aspect of the lateral

septal area which is also known to project to the lateral hypothalamus (Krayniak et al., 1980; Meibach and Siegel, 1977; Watson et al., 1983c), may serve as a relay mechanism from the ventral hippocampal formation for the facilitation of quiet attack behavior.

Cingulate Gyrus

In the present study, an attempt was also made to determine whether the mechanism for cingulate gyrus suppression of attack behavior involved regulation of the "effective sensory fields" active during the attack sequence. In the first phase of this experiment, replication of an earlier study by Siegel and Chabora (1971) demonstrated that suppression of hypothalamically elicited attack could be observed from stimulation of the ipsilateral anterior cingulate cortex in 5 cases and from the contralateral cortex in 3 additional instances. Of these 8 cases, sensory field testing was done for 4. Here, stimulation yielded significant results only for two of the points, and had no effect upon the latency for jaw-opening or upon initial movement latencies in most cases. These results suggest that anterior cingulate cortex suppression of quiet attack behavior may involve mechanisms other than those associated with the regulation of the "effective sensory fields" or the motor component of the attack response.

Appendix I: Fimbria Fornix System



The fimbria-fornix system reciprocally connects the hippocampal formation, septum, hypothalamus, thalamus, entorhinal cortex and midbrain. Descending fiber pathways are shown here.

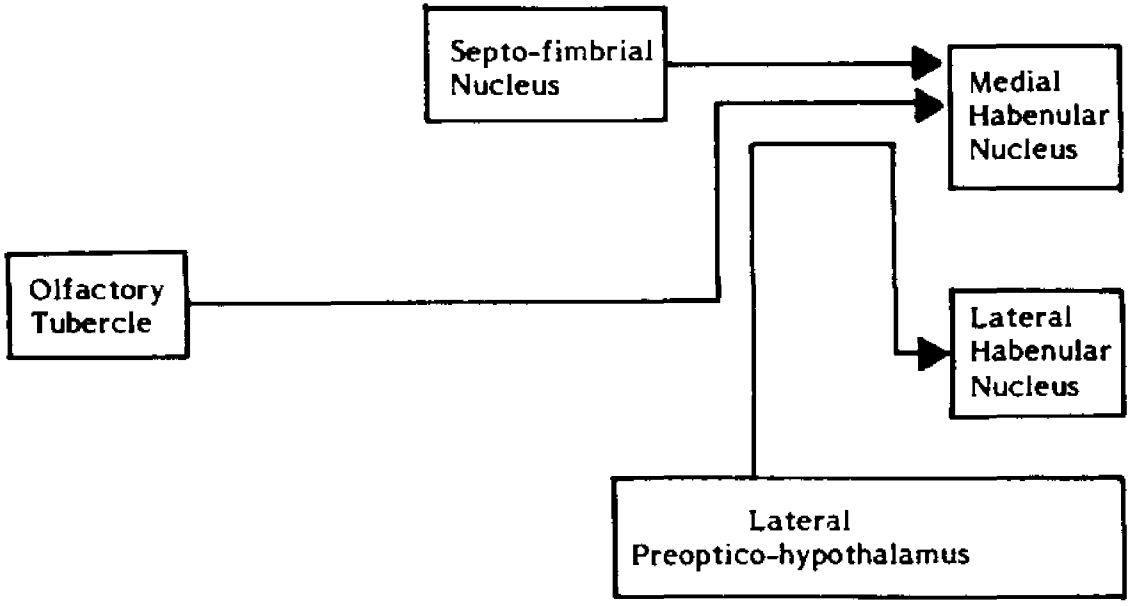
Appendix II. [^{14}C]-2-Deoxyglucose Metabolism.

Oxygen utilization by tissue is the most direct measure of energy metabolism. However, the radioactive isotopes of oxygen have a very short physical half-life and oxygen is too volatile to allow for the measurement of brain oxidative metabolism by the autoradiographic technique. In the majority of cases, glucose is almost the only substrate for cerebral oxidative metabolism and its utilization is correlated with oxygen consumption (Kety, 1957; Sokoloff, 1976). Radioactive glucose, like oxygen, is also not satisfactory because its labeled products also have a very short biological half-life. They are lost much too rapidly from cerebral tissues. An analogue of glucose, 2-deoxy-D-[^{14}C]glucose has several biochemical properties which make it excellent for tracing glucose metabolism and measuring local rates of cerebral glucose utilization by the autoradiographic technique. 2-Deoxyglucose (2-DG) is transported in both directions between blood and brain by the same carrier that transports glucose across the blood-brain barrier (Bidder, 1968; Bachelard, 1971; Oldendorf, 1971). In the brain, 2-DG is phosphorylated by hexokinase to 2-deoxyglucose-6-phosphate (Sols and Crane, 1954). Both 2-DG and glucose are competitive substrates for both blood-brain transport and hexokinase-catalyzed phosphorylation. Deoxy-glucose-6-phosphate, however, cannot be further metabolized to fructose-6-phosphate, whereas glucose-6-phosphate can and is eventually further metabolized to CO_2

and water (Sols & Crane, 1954). There is very little glucose-6-phosphatase activity in the brain (Hers, 1957) and even less deoxyglucose-6-phosphatase activity (Sokoloff, et al., 1977). ^{14}C-labeled deoxyglucose-6-phosphate is essentially trapped in brain tissue (within neuronal perikarya or fibers) to allow for its experimental measurement. The half-life of [^{14}C]-deoxyglucose 6-phosphate in brain has been estimated by Sokoloff et al. (1977) to be 7.7 hours for gray matter and 9.7 hours in white matter in mammals. If the duration of the experiment is kept short enough, for about 1 hour, there will be negligible loss of [^{14}C]deoxyglucose 6-phosphate from cerebral tissue.

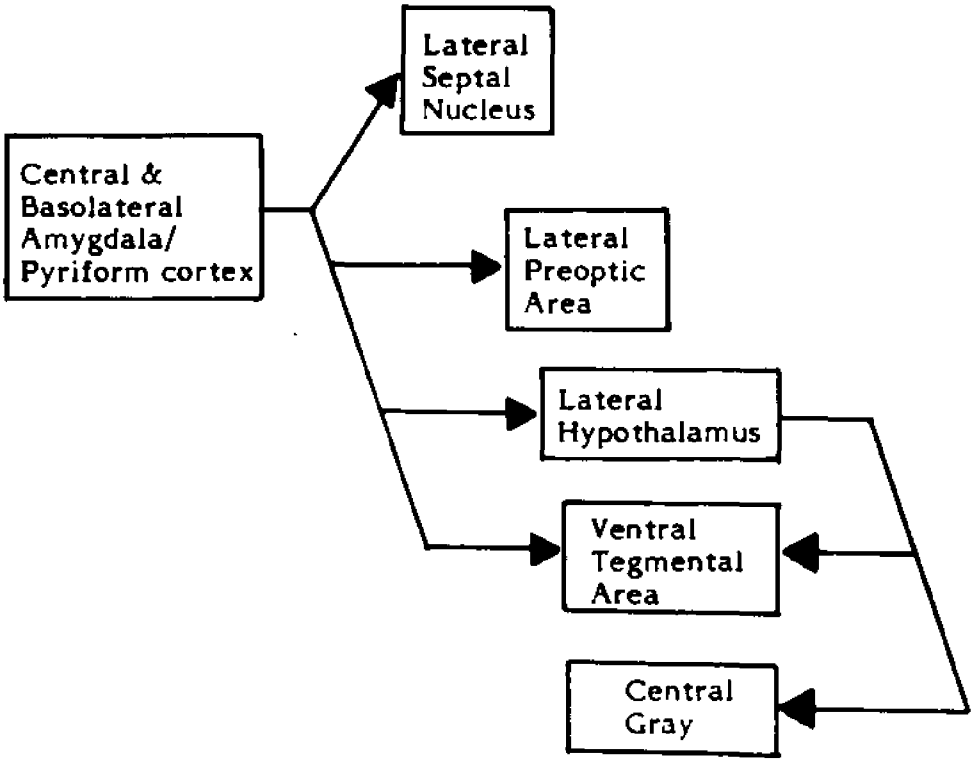
Glucose uptake is increased in active neurons, as during normal functional activity or electrical stimulation of brain loci. If radioactive 2-DG is substituted for glucose, it will cross the blood brain barrier and will be taken up like glucose by those cerebral tissues which are more metabolically active, but it will not be metabolized like glucose. Therefore the uptake of radioactive 2-DG by those brain regions which are metabolically or functionally more active, can be used to map the activity of neurons simultaneously in all the macroscopically visible structures of the brain. The optical densities in the autoradiographs then represent the concentrations of [^{14}C]-deoxyglucose-6-phosphate trapped within cells and therefore directly reflects the relative rates of glucose utilization in various brain structures (Sokoloff, 1977).

Appendix III: Stria Medullaris System



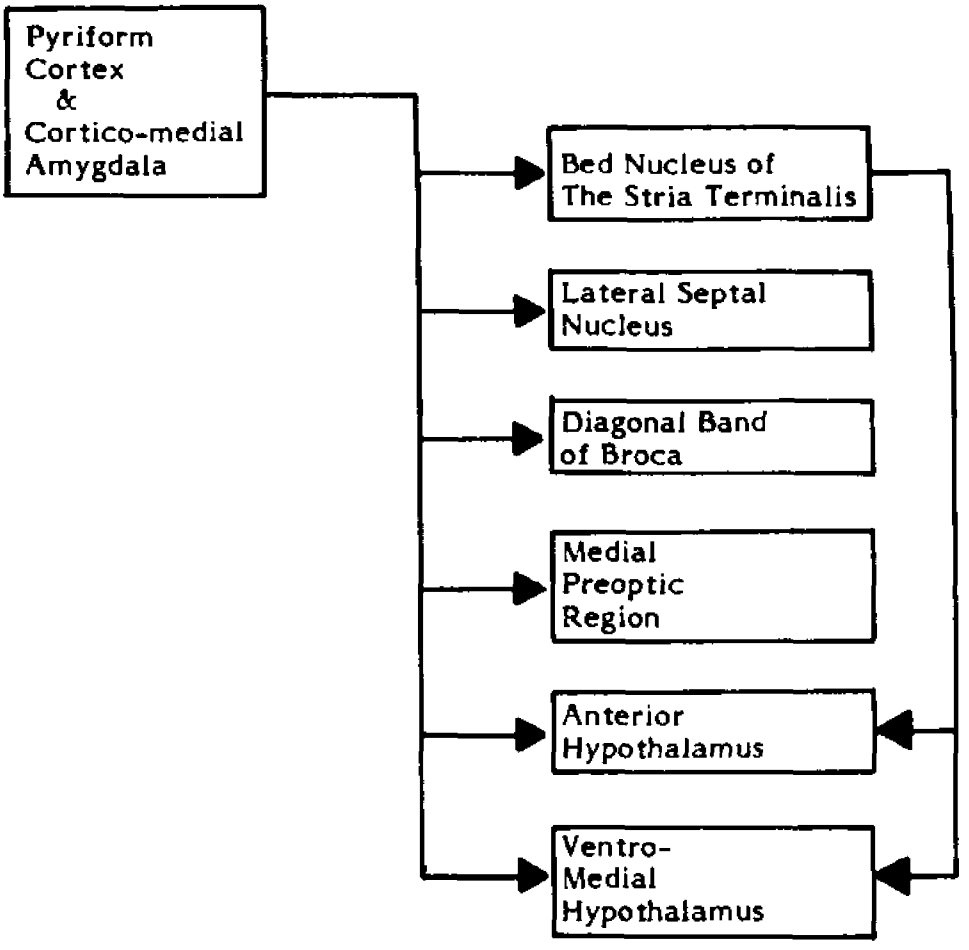
Appendix IV: Medial Forebrain Bundle System

Descending portion of the medial forebrain bundle.



The midbrain central gray and tegmental structures which form the main target structures of the descending components of the medial forebrain bundle also give rise to the major ascending components of this fiber bundle.

Appendix V: Stria Terminalis System

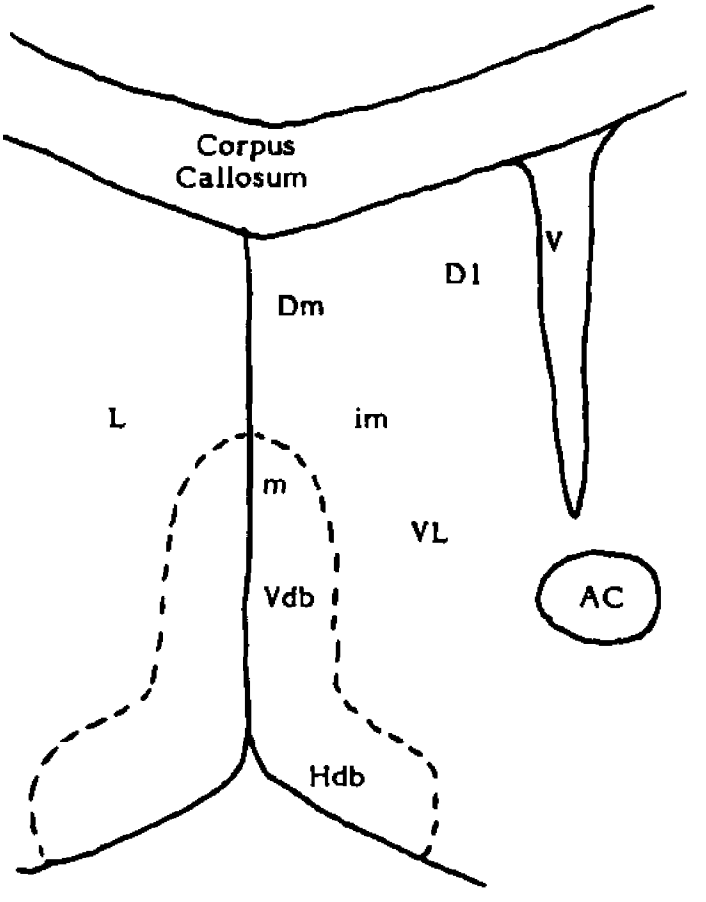


Appendix VI: Structures Modulating Quiet Biting Attack Behavior

EFFECTS OF STIMULATION OF LIMBIC SYSTEM STRUCTURES UPON ATTACK BEHAVIOR AND THE ASSOCIATED ANATOMICAL PATHWAYS UNDERLYING MODULATION (Siegel and Edinger, 1983).

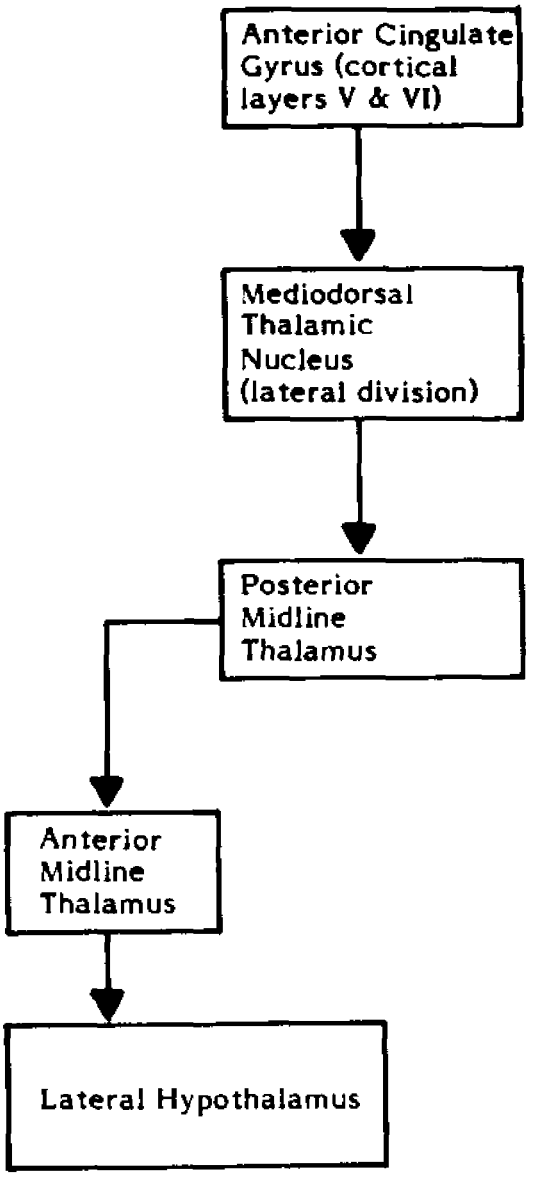
Structure	Effect	Interneuron	Final Common Pathway
ventral hippocampus	facilitation	lateral septal nucleus	medial forebrain bundle
dorsal hippocampus	suppression	lateral septal nucleus and diagonal band nuclei	medial forebrain bundle
lateral septal nucleus	suppression	diagonal band nuclei	medial forebrain bundle
lateral septal nucleus (far lateral aspect)	facilitation	--	medial forebrain bundle
basomedial amygdala and pyriform cortex	suppression	direct fibers or via the bed nucleus of stria terminalis	stria terminalis/bed nucleus-hypothalamic fibers
lateral amygdaloid nucleus	facilitation	substantia innominata	medial forebrain bundle
substantia innominata (lateral aspect)	suppression	feedback to amygdala	stria terminalis/bed nucleus-hypothalamic fibers
substantia innominata (medial aspect)	facilitation	--	medial forebrain bundle
prefrontal cortex	suppression	mediodorsal nucleus and midline thalamus	thalamo-hypothalamic fibers
anterior cingulate gyrus	suppression	mediodorsal nucleus and midline thalamus	thalamo-hypothalamic fibers

Appendix VII: Lateral Septal Area Anatomy



This coronal section through the septum identifies the subdivisions of this region (Meibach and Siegel, 1977a). DM, dorsomedial quadrant; Dl, dorsolateral quadrant; Vl, ventrolateral quadrant; im, intermediolateral septum; M, medial septal nucleus; Vdb, vertical limb of the diagonal band of Broca; Hdb, horizontal limb of the diagonal band of Broca; AC, anterior commissure; V, ventricle.

Appendix VIII: Pathways by which the cingulate gyrus can modulate quiet attack.



(from Siegel et al., 1973b)

REFERENCES

Adams, D., & Flynn, J.P. (1966). Transfer of an escape response from tail shock to brain stimulated attack behavior. J. exp. anal. Behav., 8, 401-408.

Ahmad, S.S., & Harvey, J.A. (1968). Long-term effects of septal lesions and social experience on shock elicited fighting in rats. J. comp. physiol. Psychol., 66, 596-602.

Albert, D.J., & Richmond, S.E. (1976). Hyperreactivity and aggressiveness following infusion of local anesthetic into the lateral septum or surrounding structures. Behav. Biol., 18, 211-226.

Albert, D.J., & Wong, R.C.K. (1978). Hyperreactivity, muricide and intraspecific aggression in the rat produced by infusion of local anesthetic into the lateral septum and surrounding areas. J. comp. physiol. Psychol., 92, 1962-1073.

Andy, O.J., Webster, C.L., Mukawa, J., & Bann, P.(1964). Electrophysiological comparisons of the dorsal and ventral hippocampus. In P. Passovant (Ed.), Physiologie de D'Hippocampe (pp. 411-427). Paris: C.N.R.S.

Azrin, N.H., Hutchinson, R.R., & Sallery, R.D. (1964). Pain aggression toward inanimate objects. J. exp. analysis Behav., 7, 223-228.

Bachelard, H.S. (1971). Specificity and kinetic properties of monosaccharide uptake into guinea pig cerebral cortex in vitro. J. Neurochem., 18, 213-222.

Bandler, R.J. (1969). Facilitation of aggressive behavior in the rat by direct cholinergic stimulation of the hypothalamus. Nature, 224, 1035-1036.

Bandler, R.J., Chi, C.C., & Flynn, J.P. (1972). Biting attack elicited by stimulation of the ventral midbrain tegmentum of cats. Science, 177, 364-366.

Bandler, R.J., & Flynn, J.P. (1971). Visual patterned reflex present during hypothalamic elicited attack. Science, 171, 817-818.

Bandler, R.J., & Flynn, J.P. (1972). Control of somatosensory fields for striking during hypothalamically elicited attack. Brain Res., 38, 197-201.

Bandler, R.J., & Flynn, J.P. (1974). Neural pathways from

thalamus associated with regulation of aggressive behavior. Science, 183, 96-99.

Bandler, R.J., & Vergnes, M. (1979). Interspecies aggression in the rat: The role of the diagonal band of Broca. Brain Res., 175, 327-333.

Bard, P. (1928). A diencephalic mechanism for the expression of rage with special reference to the sympathetic nervous system. Amer. J. Physiol., 84, 490-513.

Barnett, S.A. (1963). A study in Behavior. London, Methein.

Bateson, G., III. (1941). The frustration aggression hypothesis and culture. Psychol. Rev., 48, 350-355.

Bawden, H.N., & Racine, R.J. (1979). Effects of bilateral kindling or bilateral sub-threshold stimulation of the amygdala or septum on muricide, ranacide, intraspecific aggression and passive avoidance in the rat. Physiol. Behav., 22, 115-123.

Bazett, H.C., Oxon, M.D., & Eng, F.R.C. (1922). A study of the sherrington decerebrate animal in the chronic as well as the actue animal. Brain, 45, 185-221.

Berkowitz, L. (1962). Aggression: A social psychological analysis. New York: McGraw-Hill.

Berkowitz, L. (1969). Roots of aggression. New York: Atherton Press.

Berntson, G.G. (1972). Blockade and release of hypothalamically and naturally elicited aggressive behaviors in cats following midbrain lesions. J. comp. physiol. Psychol., 81, 541-554.

Berntson, G.G. (1973). Attack, grooming, and threat elicited by stimulation of the pontine tegmentum in cats. Physiol. Behav., 11, 81-87.

Berntson, G.G., Hughes, H.C., & Beattie, M.S. (1976). A comparison of hypothalamically induced biting attack with natural predatory behavior in the cat. J. comp. physiol. Psychol., 90, 167-178.

Bevan, W., Daves, W.F., Levy, G.W., et al. (1960). The relation of castration, androgen therapy and pretest fighting experience to competitive aggression in male C57, BL/10 mice. Animal Behav., 8, 6-12.

Bidder, T.G. (1968). Hexose translocation across the blood-brain interface: configurational aspects. J. Neurochem., 15, 867-874.

Bignall, K.E., & Schramm, L. (1974). Behavior of chronically decerebrate kittens. Exp. Neurol., 42, 519-531.

Blanchard, R.J., & Blanchard, D.C. (1968). Limbic lesions and reflexive fighting. J. comp. physiol. Psychol., 66, 604-605.

Block, C.H., Siegel, A., & Edinger, H.M. (1980a). Effects of electrical stimulation of the amygdala upon trigeminal sensory fields established during hypothalamically elicited quiet biting attack in the cat. Brain Res., 197, 39-55.

Block, C.H., Siegel, A., & Edinger, H.M. (1980b). Effects of stimulation of the substantia innominata upon attack behavior elicited from the hypothalamus in the cat. Brain Res., 197, 57-74.

Bodnar, R.J. (1985). Environmental triggers of endogenous pain-inhibitory systems. Ann. NY Acad. Sci. In press.

Brady, J.V., & Nauta, W.J.H. (1953). Subcortical mechanisms in emotional behavior: Affective changes following septal forebrain lesions in the albino rat. J. comp. physiol. Psychol., 46, 339-346.

Brain, P.F. (1972). Effects of isolation grouping on endocrine function and fighting behavior in male and female golden-hamsters (Mesocricetus auratus waterhouse), Behav. Biol., 7, 349-357.

Brayley, K.N., & Albert, D.J. (1977a). Suppression of VMH-lesion induced reactivity and aggressiveness in the rat by stimulation of the lateral septum, but not medial septum or cingulate cortex. J. comp. physiol. Psychol., 91, 290-299.

Brayley, K.N., & Albert, D.J. (1977b). Suppression of VMH-lesion induced reactivity and aggressiveness by electrical stimulation ventral to anterior septum in the rat. Physiol. Behav., 18, 567-571.

Brownstein, M., Saavedra, J.M., & Palkovitz, M. (1974). Norepinephrine and dopamine in the limbic system of the rat. Brain Res., 79, 431-436.

Brutus, M., Shaikh, M.B., Weiner, S., Siegel, H.E., & Siegel, A. (1984a). A [^{14}C]-2-deoxyglucose analysis of the functional neural pathways of the limbic forebrain in the rat. IV. A pathway from the prefrontal cortical-medial thalamic system to the hypothalamus. Brain Res., 310, 279-293.

Brutus, M., Shaikh, M., Siegel, H.E., & Siegel, A. (1984b). An analysis of the mechanisms underlying septal area control of hypothalamically elicited aggression in the cat. Brain Res., 310, 235-248.

Brutkowski, S., Fonberg, E., & Mempel, E. (1961). Angry behavior in dogs following bilateral lesions in the general portion of the rostral cingulate gyrus. Acta Biol. Exp. (Warsaw), 21, 199-205.

Bugbee, N.M., & Eichelman, B.S. (1972). Sensory alterations and aggressive behavior in the rat. Physiol. Behav., 8, 981-985.

Buss, A. (1961). The psychology of aggression. New York: Wiley.

Calaresu, F.R., & Mogenson, G.J. (1972). Cardiovascular responses to electrical stimulation of the septum in the rat. Amer. J. Physiol., 223, 777-782.

Cannon, W.B., & Britton, S.W. (1925). Studies on the conditions of activity in endocrine glands. XV. Pseudoaffective medullary-adrenal secretion. Am. J. Physiol., 22, 283-294.

Chi, C.C., Bandler, R.J., & Flynn, J.P. (1976). Neuroanatomic projections related to biting attack elicited from ventral midbrain in cats. Brain Behav. Evol., 13, 91-110.

Chi, C.C., & Flynn, J.P. (1971a). Neuroanatomic projections related to biting attack elicited from the hypothalamus in cats. Brain Res., 35, 49-66.

Chi, C.C., & Flynn, J.P. (1971b). Neural pathways associated with hypothalamically elicited attack behavior in cats. Science, 171, 703-706.

Clemente, C.D., & Chase, M.H. (1973). Neurological substrates of aggressive behavior. Ann. Rev. Physiol., 50, 329-356.

Conrad, L.A., Leonard, C.M., & Pfaff, D.W. (1974). Connections of the median and dorsal raphe nuclei in the rat: An autoradiographic and degeneration study. J. comp. Neurol., 156, 179-206.

Conrad, L.A., & Pfaff, D.W. (1975). Axonal projections of medial preoptic and anterior hypothalamic neurons. Science, 190, 1112-1114.

Conrad, L.A., & Pfaff, D.W. (1976a). Efferents from medial basal forebrain and hypothalamus in the rat. I. An

autoradiographic study of the medial preoptic area. J. comp. Neurol., 169, 185-220.

Conrad, L.A., & Pfaff, D.W. (1976b). Efferents from medial basal forebrain and hypothalamus in the rat. II. An autoradiographic study of the anterior hypothalamus. J. comp. Neurol., 169, 221-246.

Coote, J.H., Hilton, S.M., & Zbrozyna, A.W. (1973). The pontomedullary area integrating the defense reaction in the cat and its influence on muscle blood flow. J. Physiol., 229, 257-274.

Covian, M.R. (1969). Studies on the neurovegetative and behavioral functions of the brain septal area. In W.R. Adey, & T. Tokizane (Eds.), Progress in Brain Research: Structure and Function of the Limbic System (pp. 189-217). Amsterdam: Elsevier.

Covian, M.R., Antunes-Rodrigues, J., & O'Flaherty, J.J. (1964). Effects of stimulation of the septal area upon blood pressure and respiration in the cat. J. Neurophysiol., 27, 394-407.

Covian, M.R., Lico, M.C., & Antunes-Rodrigues, J. (1966). Blood pressure and respiratory changes by stimulation of brain septal area in rats. Acta Physiol., Latino Amer., 16, 99-105.

Covian, M.R., & Timo-Iaria, C. (1966). Decreased blood pressure due to brain septal stimulation: parameters of stimulation, bradycardia, baroreceptor reflex. Physiol. Behav., 1, 37-43.

Cragg, B.C. (1961). The connections of the habenula in the rabbit. Exp. Neurol., 3, 388-409.

DeMolina, A., & Hunsperger, R.W. (1959). Central representation of affective reactions in forebrain and brainstem: Electrical stimulation of amygdala, stria terminalis and adjacent structures. J. Physiol. (London), 145, 251-265.

DeMolina, F., & Hunsperger, R.W. (1962). Organization of the subcortical system governing defense and flight reactions in the cat. J. Physiol. (London), 160, 200-213.

DeOlmos, J.S., & Ingram, W.R. (1972). The projection field of the stria terminalis in the rat brain. An Experimental study. J. comp. Neurol., 146, 303-334.

Divac, I., & Diemer, N.H. (1980). Prefrontal system in the rat visualized by means of labeled deoxyglucose. Fur-

ther evidence for functional heterogeneity of the neostriatum. J. comp. Neurol., 190, 1-13.

Dollard, J.L., Doob, L.W., Miller, N.E., Mowrer, O.H., & Sears, R.R. (1939). Frustration and aggression. New Haven: Yale University Press.

Domesick, V.B. (1969). Projections from the cingulate cortex in the rat. Brain Res., 12, 296-320.

Domesick, V.B. (1976). Projections of the nucleus of the diagonal band of Broca in the rat. Anat. Rec., 184, 391-392.

Dreifuss, J.J., & Murphy, J.T. (1968). Convergence of impulses upon single hypothalamic neurons. Brain Res., 8, 167-176.

Eager, R.P. (1970). Selective staining of degenerating axons in the central nervous system by a simplified silver method: spinal cord projections to external cuneate and inferior olivary nuclei in the cat. Brain Res., 22, 137-141.

Edinger, H., Kramer, S., & Siegel, A. (1977). Effect of hypothalamic stimulation on mesencephalic neurona. Exp. Neurol., 54, 91-103.

Edinger, H.M., Kramer, S.Z., Weiner, S., Krayniak, P., & Siegel, A. (1979). The subicular cortex of the cat: an anatomical and electrophysiological study. Exp. Neurol., 63, 504-526.

Edinger, H., Siegel, A., & Troiano, R. (1973). Single unit analysis of the hippocampal projections to the septum in the cat. Exp. Neurol., 41, 569-583.

Egger, M.D., & Flynn, J.P. (1963). Effects of electrical stimulation of the amygdala on hypothalamically elicited attack behavior in cats. J. Neurophysiol., 26, 705-720.

Eibl-Eikesbeldt, I. (1961). The fighting behavior of animals. Scientific American, 205, 112-122.

Ellison, G.D., & Flynn, J.P. (1968). Organized aggressive behavior in cats after surgical isolation of the hypothalamus. Archives Italiennes de Biologie, 106, 1-20.

Elul, R. (1964). Regional differences in the hippocampus of the cat. Electroencephalogr. Clin. Neurophysiol., 16, 470-502.

Fink, R.P., & Heimer, L. (1967). Two methods for selective silver impregnation of degenerating axons in their synaptic endings in the central nervous system. Brain Res., 4, 369-374.

Flory, R.K., & Ulrich, R.E. (1965). The effects of visual impairment on aggressive behavior. Psychol. Rec., 15, 185-190.

Flynn, J.P. (1967). The neural basis of aggression in cats. In D.C. Glass (Ed.), Neurophysiology and Emotion (pp. 40-60). New York: Rockefellar Univ. Press and Russell Sage Foundation.

Flynn, J.P. (1976). Neural basis of threat and attack. In R.G. Grenall, & S. Gabay (Eds.), Biological Foundation of Psychiatry (pp. 273-295). New York: Raven Press.

Flynn, J.P. (1972). Patterning mechanisms, patterned reflexes and attack behavior in cats. In J.K. Cole, & D.D. Jansen (Eds.), Nebraska Symposium on Motivation (pp. 125-153). Lincoln, Neb: Univ. of Nebraska Press.

Flynn, J.P., Edwards, S.B., & Bandler, R.J. (1971). Changes in sensory and motor systems during centrally elicited attack. Behav. Sci., 16, 1-19.

Flynn, J.P., Vanegas, H., Foote, W., & Edwards, S. (1970). Neural mechanisms involved in a cat's attack on a rat. In: R. Whalen (Ed.), The Neural Control of Behavior (pp. 135-173). New York: Academic Press.

Fuchs, S.A.G., Dalsass, M., Siegel, H.E., & Siegel, A. (1981). The neural pathways mediating quiet biting attack behavior from the hypothalamus in the cat: A functional autoradiographic study. Aggressive Behavior, 7, 51-67.

Fuchs, S.A.G., & Siegel, A. (1984). Neural Pathways mediating hypothalamically elicited flight behavior in the cat. Brain Res., 306, 263-281.

Gage, F., & Thompson, R. (1980). Differential distribution of norepinephrine and serotonin along the dorsal-ventral axis of the hippocampal formation. Brain Res. Bull., 5, 711-773.

Gage, F., & Thompson, R. (1980). Differential distribution of norepinephrine and serotonin along the dorsal-ventral axis of the hippocampal formation. Brain Res. Bull., 5, 711-773.

Glees, P., Cole, J., Whitty, C.W.M., & Cairns, H. (1950). The effects of lesions in the cingular gyrus and ad-

jacent areas in monkeys. J. Neurol. Neurosurg. Psychiat., 13, 178-190.

Glusman, M. (1954). The hypothalamic "savage" syndrome. Res. Publ. Assoc. Nerv. Ment. Dis., 152, 52-90.

Glusman, M., & Roizin, L. (1960). Role of the hypothalamus in the organization of agonistic behavior in the cat. Transactions of the American Neurological Assoc., 177-179.

Goltz, R. (1892). Der Hund ohne grosshirn. Pflugers Arch. Ges. Physiol. Menschen Tiere, 51, 570-614.

Gotsick, J.E., & Marshall, R.C. (1972). Time course of the septal rage syndrome. Physiol. Behav., 9, 685-687.

Harlow, H.F., & Harlow, M.K. (1962). Social deprivation in monkeys. Scientific American, 207, 137-146.

Hatch, A., Wiberg, G.S., Balzas, T., & Grice, H.C. (1963). Long-term isolation in rats. Science, 142, 507.

Hekmatpanah, J. (1961). Organization of tactile dermatomes, C_1 through L_4, in cat. J. Neurophysiol., 24, 129-140.

Hernandez-Peon, R., Chevez-Ibarra, G., Morgane, P.J., & Timo-Iaria, C. (1963). Limbic cholinergic pathways involved in sleep and emotional behavior. Exp. Neurol., 8, 93-111.

Hers, II, G. (1957). Le Metabolisme du Fructose. Bruxelles: Editions Arscia.

Hess, W.R., & Brugger, M. (1943). Das subkortikale Zentrum der affecktiven Abruehrreaktion. Helv. Physiol. Pharm. Acta, 1, 35-52.

Hubel, D.H., Wiesel, T.N., & Stryker, M.P. (1978). Anatomical demonstration of orientation columns in macaque monkey. J. comp. Neurol., 177, 361-380.

Hughes, K.R. (1965). Dorsal and ventral hippocampal lesions and maze learning influence of preoperative environment. Can. J. Psychol., 19, 325-332.

Hunsperger, R.W. (1956). Affektreaktionen auf elektrische Reizung in Hirnstamm der Katz. Helv. Physiol. Acta, 14, 70-92.

Hunsperger, R.W., & Bucher, V.M. (1967). Affective behavior produced by electrical stimulation in the forebrain and brain stem of the cat. Progress in Brain Research, 27, 103-127.

Hutchinson, R.R., Renfrew, J.W. (1966). Stalking attack and eating behaviors elicited from the same sites in the hypothalamus. J. comp. Physiol. Psychol., 61, 360-367.

Ingram, W.R., Barris, R.W., & Ranson, S.W. (1936). Catalepsy: An experimental study. Arch. of Neurol. and Psychiat., 35, 1175-1197.

Inselman, B.R., & Flynn, J.P. (1972). Modulatory effects of preoptic stimulation on hypothalamically elicited attack in cats. Brain Res., 42, 73-87.

Jasper, H.H., & Ajmone-Marsan, C. (1954). A Stereotaxic Atlas of the Diencephalon of the Cat. Ottawa: National Res. Council of Canada.

Johnson, R.N., DeSisto, M.J., & Koenig, A.B. (1972). Social and developmental experience and interspecific aggression in rats. J. comp. physiol. Psych., 79, 237-242.

Karli, P. (1956). The Norway rat's killing response to the white mouse. Behavior, 10, 81-103.

Karli, P., & Vergnes, M. (1963). Role du rhinencephale dans le controle du comportiment d'aggression interspecifique du rat. J. de Physiologie, 55, 272-273.

Karli, P., Vergnes, M., & Didiergeorges, F. (1969). Rat-mouse interspecific aggressive behavior and its manipulation by brain ablation and by brain stimulation. In S. Garattini, & E.B. Sigg (Eds.), Aggressive Behavior (pp. 47-55). Amsterdam: Excerpta Medica Foundation.

Keller, A. (1932). Studies of rage and midbrain stimulation or lesions. Am. J. Physiol., 100.

Keller, A. (1932). Autonomic discharges elicited by physiological stimuli in midbrain preparations. Am. J. Physiol., 100, 576-586.

Kennard, M.A. (1955). Effect of bilateral ablation of cingulate area on behavior of cats. J. Neurophysiol., 18, 159-169.

Kety, S.S. (1957). The general metabolism of the brain. In Richter, D. (Ed.), Metabolism of the nervous system (pp. 221-237). London: Pergamon Press.

King, F.A. (1958). Effects of septal and amygdaloid lesions on emotional behavior and conditioned avoidance responses in the rat. J. Neurol. Ment. Dis., 126, 57-63.

Korn, J.H., & Moyer, K.E. (1968) Behavioral effects of isolation in the rat: The role of sex and time of isolation.

Krayniak, P.F., Meibach, R.C., & Siegel, A. (1981). A projection from the entorhinal cortex of the nucleus accumbens in the rat. Brain Res., 209, 427-431.

Krayniak, P.F., & Siegel, A. (1978). Efferent connections of the septal region in the pidgeon. Brain Behav. Evol., 15, 389-404.

Krayniak, P.F., Weiner, S., & Siegel, A. (1980). An analysis of the efferent connections of the septal area in the cat. Brain Res., 189, 15-29.

Krayniak, P.F., Weiner, S., & Siegel, A. (1980). An analysis of the efferent connections of the septal area in the cat. Brain Res., 189, 15-29.

Krettek, J.E., & Price, J.L. (1978). Amygdaloid projections to subcortical structures within the basal forebrain and brainstem in the rat and cat. J. comp. Neurol., 178, 225-254.

Kruk, Z.L., & Pycock, C.J. (1983). Neurotransmitters and Drugs (pp. 84-85). Baltimore: University Park Press.

Kuo, Z.Y. (1967). The dynamics of behavior development: An epigenetic View. New York: Random House.

Landau, W.M., Freygang, W.H., Jr., Rowland, L.P., Sokoloff, L., & Kety, S.S. (1955). The local circulation of the living brain: values in unanesthetized cat. Trans. Am. Neurol. Assoc., 80, 125-129.

Largerspetz, K., & Nurmi, R. (1964). An experiment on the frustration-aggression hypothesis. (Reports No. 10 (pp. 1-8) from the Institute of Psychology) Turku: University of Turku.

Latham, E.E., & Thorne, M.B. (1974). Septal damage and muricide. Effects of strain and handling. Physiol. Behav., 12, 521-526.

LeBeau, J. (1954). Anterior cingulectomy in man. J. Neurosurg., 2, 268-276.

Levinson, P.K., Flynn, J.P. (1965). The objects attacked by cats during stimulation of the hypothalamus. Animal Behavior, 13, 217-220.

Livingston, K.E. (1953). Cingulate cortex isolation for

treatment of psychoses and psychoneuroses. Res. Publ. Assoc. Nerv. Men. Dis., 31, 374-378.

Malamud, N. (1967). Psychiatric disorders with intracranial tumors of limbic system. Arch. Neurol., 17, 113-123.

MacDonnell, M.F., Fessock, L., & Brown, S.H. (1971). Ethanol and the neural substrate for affective defense in the cat. Quart. J. Stud. Alcohol, 32, 406-419.

MacDonnell, M., & Flynn, J.P. (1966a). Sensory control of hypothalamic attack. Animal Behavior, 14, 399-405.

MacDonnell, M., & Flynn, J.P. (1966b). Control of sensory fields by stimulation of hypothalamus. Science, 152, 1406-1408.

MacDonnell, M.F., & Stoddard-Apter, S. (1978). Effects of medial septal stimulation on hypothalamically-elicited intraspecific attack and associated hissing in cats. Physiol. Behav., 211. 679-683.

MacLean, P. (1949). Psychosomatic disease and the visceral brain. Recent developments bearing on the Papez theory of emotion. Psychosom. Med., 11, 338-353.

Magoun, H.W., Atlas, D., Ingersole, E.H., & Ranson, S.W. (1937). Associated facial, vocal and respiratory components of emotional expression: an experimental study. J. Neurol. Psychopath., 17, 241-255.

Malmo, R.B. (1961). Slowing of heart rate after septal self-stimulation in rats. Science, 133, 1128-1130.

Marburg, O. (1944). The structure and fiber connections of the human habenula. J. comp. Neurol., 80, 211-233.

Masserman, J.H. (1938). Destruction of the hypothalamus in cats. Effects on activity of CNS and its reaction to sodium amytal. Arch. Neurol. Psychiat., 39, 1250-1268.

Matta, M., Fink, D.J., Gainer, H., Smith, C.B., Davidsen, L., Savaki, H., Schwartz, W.J., & Sokoloff, L. (1980). Activity dependent energy metabolism in rat posterior pituitary primarily reflects sodium pump activity. J. Neuro. Chem., 34, 213-215.

Meibach, R.C., Glick, S.D., Ross, D.A., Cox, D., & Maayani, S. (1980). Intraperitoneal administration and other modifications of the 2-deoxy-D-glucose technique. Brain Res., 199, 167-176.

Meibach, R.C., & Siegel, A. (1977a). Efferent connections of the septal area in the rat: An analysis utilizing

retrograde and anterograde transport methods. Brain Res., 119, 1-20.

Meibach, R.C., & Siegel, A. (1977b). Efferent connections of the hippocampal formation in the rat. Brain Res., 124, 197-224.

Miczek, K.A., & Grossman, S.P. (1972). Effects of septal lesions on inter- and intraspecies aggression in rats. J. comp. physiol. Psychol., 79, 37-45.

Miller, N.E. (1941). The frustration-aggression hypothesis. Psychol. Rev., 48, 337-342.

Miller, J.J., & Mogenson, G.J. (1972). Projections of the septum to the lateral hypothalamus. Exp. Neurol., 34, 229-243.

Miller, J.J., & Mogenson, G.J. (1971). Modulatory influences of the septum on lateral hypothalamic self-stimulation. Exp. Neurol., 33, 671-683.

Mogenson, G.J. (1976). Septal-hypothalamic relationships. In J.F. Defrance (Ed.), The septal nuclei (pp. 149-184). New York: Plenum Press.

Moyer, K.E. (1976). The psychobiology of aggression. New York: Harper and Row.

Moore, R., & Halaris, A.E. (1975). Hippocampal innervation by serotonin neurons in the midbrain raphe in the rat. J. comp. Neurol., 164, 171-184.

Myer, J.F., & White, R.I. (1965). Aggressive motivation in the rat. Animal Behav., 13, 430-433.

Nakao, H. (1958). Emotional behavior produced by hypothalamic stimulation. Am. J. Physiol., 194, 414-418.

Nauta, W.J.H. (1956). An experimental study of the fornix in the rat. J. comp. Neurol., 104, 247-272.

Nauta, W.J.H. (1958). Hippocampal projections and related neural pathways in the midbrain in the cat. Brain, 81, 319-340.

Nauta, W.J.H., & Haymaker, W. (1969). Hypothalamic nuclei and fiber connections. In W. Haymaker, E. Anderson, & W.J.H. Nauta (Eds.), The Hypothalamus (pp. 136-209). Springfield: C.C. Thomas.

Numan, R. (1978). Cortical limbic mechanisms and response control: A theoretical review. Physiol. Psych., 6, 445-470.

Oldendorf, W.H. (1971). Brain uptake of radiolabelled amino acids, amines and hexopea after arterial injection. Am. J. Physiol., 2219, 1629-1638.

Panksepp, J. (1971). Aggression elicited by electrical stimulation of the hypothalamus in albino rat. Physiol. Behav., 6, 321-329.

Panksepp, J., & Trovill, J. (1969). Electrically induced affective attack from the hypothalamus of the albino rat. Psychonom. Sci., 16, 118-119.

Papez, J.W. (1937). A proposed mechanism of emotion. AMA Arch. Neurol. Psychiat., 38, 725-743.

Paul, L. (1972). Predatory attack by rats: Its relationship to feeding the type of prey. J. comp. physiol. Psychol., 78, 69-76.

Pechtel, C., McAvoy, T., Levitt, M., Kling, A., & Masserman, J.H. (1958). The cingulates and behavior. J. Neurol. Ment. Dis., 126, 148-152.

Pickel, V.M., Segal, M., & Bloom, F.E. (1974). A radioautographic study of the efferent pathways of the nucleus locus coeruleus. J. comp. Neurol., 155, 15-42.

Platt, J.J., Sutkin, L.W., & James, W.T. (1967). Social facilitation of eating behavior in young oppossums: The effects of social isolation. Paper presented at Society for Philosophy and Psychology, Roanoke, VA.

Plum, F., Gjedde, A., & Samson, F.E. (1976). Neuroanatomical mapping by the radioactive 2-deoxy-D-glucose method. Neurosci. Res. Prog. Bull., 14, 457-518.

Potegal, M., Gibbons, J.L., & Glusman, M. (1980). Inhibition of muricide by septal stimulation in rats. Physiol. Behav., 24, 863-867.

Proshansky, E., Bandler, R.J., & Flynn, J.P. (1974). Elimination of hypothalamically elicited biting attack by unilateral lesion of ventral midbrain tegmentum of cats. Brain Res., 77, 309-313.

Proshansky, E., & Bandler, R.J. (1975). Midbrain-hypothalamic interrelationship in the control of aggressive behavior. Aggressive Behavior, 1, 135-155.

Rabin, B.M. (1968). Effect of lesions of the ventromedial hypothalamus on the electrical activity of the ventrolateral hypothalamus. Electroenceph. Clin. Neurophysiol., 25, 344-350.

Raisman, G. (1966). The connections of the septum. Brain, 89, 317-348.

Ranson, S.W., Kabat, H., & Magoun, H.W. (1935). Autonomic responses to electrical stimulation of the hypothalamus, preoptic region and septum. Arch. Neurol. Psychiat., 33, 467-477.

Ranson, S.W. (1934). The hypothalamus: Its significance for visceral innervation and emotional expression. The Weir Mitchell Oration, Transactions of the College of Physicians of Philadelphia, Series IV, 2, pp. 222-243.

Ranson, S.W. (1936-1937). Some functions of the hypothalamus, The Harvey Lecture Series XXXII, 92-121.

Reeves, A.G., & Plum, F. (1969). Hyperphagia, rage and dementia accompanying a ventromedial hypothalamic neoplasm. Arch. Neurol., 20, 616-624.

Reivich, M., Jehle, J., Sokoloff, L., & Kety, S.S. (1969). Measurement of regional cerebral blood flow with antipyrine-^{14}C in awake cats. J. Appl. Physiol., 27, 296-300.

Reynolds, R.W. (1963). Ventromedial hypothalamic lesions without hyperphagia. Amer. J. Physiol., 204, 60-62.

Roberts, W.W. (1980). [^{14}C] Deoxyglucose mapping of first order projections activated by stimulation of lateral hypothalamic sites eliciting gnawing, eating and drinking in rats. J. comp. Neurol., 194, 617-638.

Roberts, W.W., Steinberg, M.L., & Means, L.W. (1967). Hypothalamic mechanisms for sexual, aggressive and other motivational behaviors in the oppossum, Didelphis virginiana. J. comp. physiol. Psychol., 64, 1-15.

Rubenstein, E.H., & Delgado, J.M.R. (1963). Inhibition induced by forebrain stimulation in the monkey. Amer. J. Physiol., 205, 941-948.

Saavedra, J.M., Brownstein, M., & Palkovitz, M. (1974). Serotonin distribution in the limbic system of the rat. Brain Res., 79, 437-441.

Savaki, H.E., Desban, M., Glowinski, J., & Besson, M.-J. (1983). Local cerebral glucose consumption in the rat. II. Effects of unilateral substantia nigra stimulation in conscious and in halothane-anesthetized animals. J. comp. Neurol., 213, 46-55.

Schwartz, W.J., Smith, C.B., Davidson, L., Savaki, H., Sokoloff, L., Matta, M., Fink, D.J., & Gainer, H.

(1979). Metabolic mapping of functional activity in the hypothalamo-neurohypophysial system of the rat. Science, 205, 723-725.

Scott, J.P., & Fredericson, E. (1951). The causes of fighting in mice and rats. Physiological Zoology, 24, 273-309.

Scott, J.P. (1944). Social behavior, range and territoriality in domestic mice. Proceedings of the Indiana Academy of Science, 53, 188-195.

Shaikh, M.B., Brutus, M., Siegel, H.E., & Siegel, A. (1984). Differential control of aggression by the midbrain. Exp. Neurol., 83, 436-442.

Sheard, M., & Flynn, J.P. (1967). Facilitation of attack by stimulation of the midbrain of cats. Brain Res., 27, 165-182.

Sibole, W., Miller, J.J., & Mogenson, G.J. (1971). Effects of septal stimulation on drinking elicited by electrical stimulation of the lateral hypothalamus. Exp. Neurol., 32, 466-477.

Siegel, A. (1982). On the nature of specific hard-wired brain circuits. In J. Panksepp (Ed.), Behavior & Brain Sciences: Vol. 3. Toward a General Psychobiological Theory of Emotions (pp. 443-444).

Siegel, A., & Chabora, J. (1971). Effects of electrical stimulation of the cingulate gyrus upon attack behavior elicited from the hypothalamus in the cat. Brain Res., 32, 169-177.

Siegel, A., Chabora, J., & Troiano, R. (1972). Effects of electrical stimulation of pyriform cortex upon hypothalamically elicited aggression in the cat. Brain Res., 47, 497-500.

Siegel, A.S., & Edinger, H. (1976). Organization of the Hippocampal-Septal Axis. In J.F. Defrance (Ed.), The Septal Nuclei (pp. 79-113). New York: Plenum Press.

Siegel, A., & Edinger, H.M. (1981). Neural Control of Aggression and Rage Behavior. In P. Morgane, & J. Panksepp (Eds.), Handbook of the Hypothalamus, Vol. 3 (pp. 203-240). New York: M. Dekker.

Siegel, A., & Edinger, H.M. (1983). Role of the Limbic System in hypothalamically elicited attack behavior. Neurosci. & Biobehav. Revs., 7, 395-407.

Siegel, A., Edinger, H., & Dotto, M. (1975). Effects of electrical stimulation of the lateral aspect of the prefrontal cortex upon attack behavior in cats. Brain Res., 93, 473-484.

Siegel, A., Edinger, H., & Koo, A. (1977a). Suppression of attack behavior in the cat by the prefrontal cortex: Role of the mediodorsal thalamic nucleus. Brain Res., 127, 185-190.

Siegel, A., Edinger, H., & Lowenthal, H. (1974a). Effects of electrical stimulation of medial aspect of the prefrontal cortex upon attack behavior in cats. Brain Res., 66, 467-479.

Siegel, A., Edinger, H., & Ohgami, S. (1974b). The topographical organization of the hippocampal projection to the septal area: A comparative neuroanatomical analysis in the gerbil, rat, rabbit and cat. J. comp. Neurol., 157, 359-378.

Siegel, A., & Flynn, J.P. (1968). Differential effects of electrical stimulation and lesions of the hippocampus and adjacent regions upon attack behavior in cats. Brain Res., 7, 252-267.

Siegel, A., Fukushima, T., Meibach, R., Burke, L., Edinger, H., & Weiner, S. (1977b). The origin of the afferent supply to the mediodorsal thalamic nucleus: Enhancement of HRP transport by selective lesions. Brain Res., 135, 11-23.

Siegel, A., Ohgami, S., & Edinger, H. (1975). Projections of the hippocampus to the septal area in the squirrel monkey. Brain Res., 99, 247-260.

Siegel, A., & Skog, D. (1970). Effects of electrical stimulation of the septum upon attack behavior elicited from the hypothalamus in the cat. Brain Res., 23, 371-380.

Siegel, A., & Tassoni, J.P. (1971a). Differential efferent projections from the ventral and dorsal hippocampus of the cat. Brain Behav. Evol., 4, 185-200.

Siegel, A., & Tassoni, J.P. (1971b). Differential efferent projections of the lateral and medial septal nuclei to the hippocampus in the cat. Brain Behav. Evol., 4, 201-219.

Siegel, A., Troiano, R., & Edinger, H. (1973a). The pathway from the mediodorsal nucleus to the hypothalamus in the cat. Exp. Neurol., 38, 202-217.

Siegel, A., Troiano, R., Royce, A. (1973b). Differential efferent projections of the anterior and posterior cingulate gyrus to the thalamus in the cat. Exp. Neurol., 38, 192-201.

Sierra, G., Acuna, C., Otero, J., & Dominquez, R. (1972). Simultaneous stimulation of limbic system structures. Brain Res., 47, 113-125.

Skultety, F.M. (1963). Stimulation of the Periaqueductal gray and hypothalamus. Archives of Neurol., 8, 608-620.

Smith, D.A. (1972). Increased perioral responsiveness: A possible explanation for the switching of behavior observed during lateral hypothalamic stimulation. Physiol. Behav., 8, 617-621.

Sokoloff, L. (1977). Relation between physiological function and energy metabolism in the central nervous system. J. Neurochem., 29, 13-26.

Sokoloff, L. (1976). Circulation and energy metabolism of the brain. In G.J., Siegel, R.W., Albers, R., Katzman, & B.W., Agranoff (Eds.), Basic Neurochemistry (pp. 388-413). Boston: Little, Brown and Co.

Sokoloff, L., Reivich, M., Kennedy, C., DesRosiers, M.H., Patlak, C.S., Pettigrew, K.D., Sakurada, O., & Shinohara, M. (1977). The [^{14}C] deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. J. Neurochem., 28, 897-916.

Sols, L., & Crane, R.K. (1954). Substrate specificity of brain hexokinase. J. Biol. Chem., 210, 581-595.

Spencer, W.A., & Kandel, E.R. (1961). Electrophysiology of hippocampal neurons. IV. Fast prepotentials. J. Neurophysiol., 24, 272-285.

Spencer, W.A., & Kandel, E.R. (1968). Cellular and integrative properties of the hippocampal pyramidal cell and the comparative electrophysiology of cortical neurons. Int. J. Neurol., 6, 266-296.

Stoddard-Apter, S.L., & MacDonnell, M.F. (1980). Septal and amygdalar efferents to the hypothalamus which facilitate hypothalamically elicited intraspecific aggression and associated hissing in the cat, An autoradiographic study. Brain Res., 193, 19-32.

Sutin, J., McBride, R.L., Thalmann, R.H., & Van Atta, E.L. (1975). Organization of some brainstem and limbic connections of the hypothalamus. Pharmacol. Biochem. Behav., 3, Suppl. 1, 49-59.

Sutin, J., McBride, R.L. Thalmann, R.H., & Van Atta, E.L. (1975). Organization of some brainstem and limbic connections of the hypothalamus. Pharmacol. Biochem. Behav., 3, Suppl. 1, 49-59.

Swanson, L.C. (1981). A direct projection from Ammon's horn to prefrontal cortex in the rat. Brain Res., 217, 150-154.

Swanson, L.C., & Cowan, W.M. (1975). Hippocampo-hypothalamic connections: origin in subicular cortex, not ammon's horn. Science, 189, 303-304.

Swanson, L.C., & Cowan, W.M., An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. J. comp. Neurol., 172, 49-84.

Swanson, L.C., & Cowan, W.M. (1979). The connections of the septal region in the rat. J. comp. Neurol., 186, 621-656.

Terman, G.W., Shavit, Y., Lewis, J.W., Cannon, J.T., & Liebeskind, J.C. (1984). Intrinsic mechanisms of pain inhibition: Activation by stress. Science, 226, 1270-1277.

Thor, D.H., & Ghiselli, W.B. (1973). Prolonged suppression of irritable aggression in rats by facial anesthesia. Psychol. Report., 33, 815-820.

Thor, D.H., Ghiselli, W.B., & Lambelet, D. (1974). Sensory control of shock elicited fighting in rats. Physiol. Behav., 13, 683-686.

Troiano, R., & Siegel, A. (1975). Ascending and descending connections on the hypothalamus in the cat. Exp. Neurol., 49, 161-173.

Ulrich, R.E. (1967). Unconditioned and conditioned aggression and its relation to pain. Activities Nervosa Superior, 9, 80-91.

Ulrich, R.E., Hutchinson, K.K., & Azrin, N.M. (1965). Pain-elicited aggression. The Psychol. Rec., 15, 111-126.

Ungerstedt, V. (1971). Stereotaxic mapping of monoamine pathways in the rat brain. Acta. Physiol. Scand. Suppl., 367, 1-48.

Valzelli, L. (1967). Drugs and aggressiveness. Advances in Pharmacology, 5, 79-108.

Valzelli, L. (1969). Aggressive behaviour induced by isolation. In S. Garattini, & E.B. Sigg (Eds.), Aggressive Behaviour (pp. 70-76). New York: Wiley.

Valenstein, E.S., Cox, V.C., & Kakolewski, J.W. (1968). Modification of motivated behavior elicited by electrical stimulation of the hypothalamus. Science, 159, 1119-1121.

Valenstein, E., & Nauta, W.J.A. (1959). A comparison of the distribution of the fornix system in the rat, guinea pig and monkey. J. comp. Neurol., 113, 337-363.

Wasman, M., & Flynn, J.P. (1962). Directed attack elicited from hypothalamus. Arch. Neurol., 6, 220-227.

Watson, Jr., R.E., Edinger, H., & Siegel, A. (1983a). An analysis of the mechanisms underlying hippocampal control of hypothalamically-elicited aggression in the cat. Brain Res., 269, 327-345.

Watson, Jr., R.E., Edinger, H.M., & Siegel, A. (1983b). A [^{14}C]-2-deoxyglucose analysis of the functional neural pathways of the limbic forebrain in the rat. III. The hippocampal formation. Brain Res. Rev., 5, 133-176.

Watson, Jr., R.E., Troiano, R., Poulakos, J.J., Weiner, S., Block, C.H., & Siegel, A. (1983c). A [^{14}C]-2-deoxyglucose analysis of the functional neural pathways of the limbic forebrain in the rat. I. The amygdala. Brain Res. Rev., 5, 1-44.

Watson, Jr., R.E., Siegel, H.E., & Siegel, A. (1985). A [^{14}C]-2-deoxyglucose analysis of the functional neural pathways of the limbic forebrain in the rat. V. The Septal Area. Brain Res., In press.

Watson, Jr., R.E., Siegel, A., Poulakos, J.J., Troiano, R., & Weiner, S. (1982). A [^{25}C]2-deoxyglucose analysis of the functional neural pathways of the limbic forebrain in the rat. II. The hypothalamus. Brain Res. Bull., 8, 459-476.

Wheatley, M.D. (1944). The hypothalamus and affective behavior in cats: A study of the effects of experimental lesions with anatomic correlations. Arch. Neurol. Psychiat., 52, 296-316.

Woods, J.W. (1964). Behavior of chronic decerebrate rats. J. Neurophysiol., 27, 635-644.

Woodworth, R.S., & Sherrington, C.S. (1964). A pseudoaffective reflex and its spinal path. J. Physiol., 31, 234-243.

Young, M.W. (1936). The nuclear pattern and fiber connections of the non-cortical centers of the telencephalon of the rabbit (Lepus cuniculus). J.C.N., 65, 295-401.

Yutzey, D.A., Meyer, D.R., & Meyer, P.M. (1967). Effects of simultaneous septal and neo- or limbic- cortical lesions upon emotionality in the rat. Brain Res., 5, 452-458.