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An Anatomical Mapping Study Of Brain Stimulation Reward In The Anterior Medial Forebrain Bundle

Adina Blander

A Thesis

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ABSTRACT

AN ANATOMICAL MAPPING STUDY OF BRAIN STIMULATION REWARD IN THE ANTERIOR MEDIAL FOREBRAIN BUNDLE

Adina Blander

Several levels of the anterior medial forebrain bundle were mapped for brain stimulation reward using a dorsal-ventral moveable electrode. Rate of lever-pressing was tested at several current intensities. Positive sites for self-stimulation were found from 1.0 - 2.8 mm anterior to Bregma. Stimulation was rewarding at sites in the stria medullaris, lateral preoptic area, diagonal band of Broca, medial and lateral septal areas and the amygdala. Stimulation was not rewarding at sites in the anterior hypothalamic area, arcuate nucleus and fornix. The medial-lateral dispersion of positive sites was wider at the more rostral levels than at the more caudal levels. The data suggest that the medial forebrain bundle brain stimulation reward fibers do not arise from a single group of nuclei in the anterior medial forebrain bundle. There are at least two distinct anatomical contributions to the medial forebrain bundle brain stimulation reward mechanism, including the stria medullaris, diagonal band of Broca-lateral preoptic area and the amygdala.

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Rats will learn to perform arbitrary responses rewarded by the delivery of electrical stimulation to specific regions of their brains (Olds & Milner, 1954). Given appropriate sites and stimulation parameters, rats will press a lever for stimulation at very high rates and to the exclusion of other behaviors. The behavioral phenomenon of working for electrical brain stimulation is referred to as self-stimulation and the stimulation that supports such behavior is referred to as brain stimulation reward. Brain-behavior scientists have hypothesized that the mechanisms that mediate brain stimulation reward are also important in the mediation of the effects of natural rewards.

Stimulation of a variety of brain regions has been found to be rewarding. Particularly effective stimulation sites are found along the course of the medial forebrain bundle, a central longitudinal fiber pathway that connects the midbrain with the forebrain. The medial forebrain bundle has been a major focus of attention in attempts to trace the neural circuitry of brain stimulation reward (Olds, 1962).

There are some 50 fiber pathways within the medial forebrain bundle; each pathway comprises many fibers (Nieuwenhuys, Geeraedts, & Veening, 1982). These fibers are, for the most part, either lightly myelinated or unmyelinated (Nieuwenhuys et al., 1982). The medial forebrain bundle pathways may be divided

into three classes. First, there are pathways originating in the forebrain and limbic region that extend caudally to join the medial forebrain bundle. These fibers originate from such regions as the olfactory tubercle, septal nuclei, nucleus of the diagonal band of Broca, interstitial nucleus of the stria terminalis and the nucleus accumbens septi. A great majority of these fibers funnel through the lateral hypothalamic area, a region which is largely co-extensive with the medial forebrain bundle over the central portion of its range.

The second class of pathways has origins in the midbrain and ascends rostrally; the fibers within these pathways are interpolated with the descending fibers of the bundle. The ascending pathways originate from such midbrain areas as the ventral tegmental area of Tsai, substantia nigra, locus coeruleus, nucleus raphe magnus and pontis, nucleus of solitary tract and other nuclei in the brainstem.

The third class of pathways has origin within or near the central region of the bundle. The cell bodies of most of these pathways are found in the lateral hypothalamic area, the anterior hypothalamic nucleus, posterior hypothalamic nucleus and lateral and medial preoptic area. Some of the fibers originating from these areas course in a rostro-caudal direction and others course in a caudo-rostral direction. There are also fibers originating from the medial hypothalamus that enter the medial forebrain

bundle and terminate in the lateral hypothalamic area (Van Cuc, Leranth, & Palkovits, 1979).

The physiological psychologist has been confronted with two tasks in attempting to characterize the various elements that make up the brain stimulation reward mechanism. The first task is to identify the fibers that are directly activated at the tip of the stimulating electrode. The concept of "directly activated" identifies the fibers that are depolarized by the stimulating current itself, at the tip of the electrode. Since there are at least 50 fiber pathways that make up the medial forebrain bundle, several will be directly activated by the current at the tip of the electrode. Some of these directly activated fibers will, in turn, activate other fibers. The concept of "directly activated" distinguishes the fibers activated immediately at the electrode tip, from the fibers that are trans-synaptically activated.

The second task is to identify which of the fibers in the medial forebrain bundle are relevant to the reward mechanism. The concept of "reward-relevance" implies that only some of the fibers that are activated by the electrical stimulation are critical to the reward process. Reward-relevant fibers may be directly activated or indirectly (trans-synaptically) activated; the fibers are reward-relevant as long as they are involved in the mechanism of medial forebrain bundle brain stimulation

reward. It is assumed that only a small fraction of the 50 pathways in the bundle plays a role in brain stimulation reward.

The fibers that are both directly activated and reward-relevant are of particular interest to brain stimulation reward specialists. A convention has been established to refer to these neurons as the first-stage neurons of brain stimulation reward (Gallistel, Shizgal, & Yeomans, 1981). The fibers that are indirectly (trans-synaptically) activated by the first-stage neurons and reward-relevant, are termed the second-stage neurons. The number of stages in the mechanism for brain stimulation reward is at present unknown. The present thesis deals only with the first-stage neurons.

Considerable attention has been given to the conceptualization of the first-stage neurons. It must be emphasized, however, that the first-stage neurons for brain stimulation reward are not necessarily the first-stage neurons for any other phenomenon. It may be that the neural circuitry underlying brain stimulation reward shares common elements with that of food reward; however, this does not mean that the first-stage neurons of these respective systems are the same. The first-stage neurons for brain stimulation reward originate in the depths of the brain, whereas the first-stage neurons for food reward originate in the periphery and are activated by the taste of food. The first-stage neurons for food reward are quite a

distance, in terms of the pathways that nerve impulses follow, from the first-stage neurons of brain stimulation reward. It is possible that the third-stage or the fourth-stage or even the fifth-stage neurons of food reward correspond to the first-stage neurons of brain stimulation reward. Thus the various "stages" of reward circuitry must be identified with respect to the respective rewarding event. For the purposes of the present thesis, the first-stage neurons of primary interest are those of medial forebrain bundle brain stimulation reward.

Several different approaches have been taken to understand which elements comprise the mechanism involved in brain stimulation reward. These approaches include methods used in pharmacology, anatomy and electrophysiology. The degree to which these methods have been useful in distinguishing between the various elements that comprise the mechanism of brain stimulation reward has varied. Some of these methods have in their capacity the ability to specifically characterize the first-stage neurons, whereas other approaches or methods only have in their capacity the ability to suggest a global involvement of some element in the mechanism of brain stimulation reward.

A pharmacological approach has been used to determine which neurochemical systems are involved in medial forebrain bundle brain stimulation reward. The medial forebrain bundle includes

fibers that contain such neurochemicals as dopamine and noradrenaline (Nieuwenhuys et al., 1982). Should any of these chemicals be intrinsically involved in medial forebrain bundle brain stimulation reward, then its potentiation or attenuation should result in increases and decreases in the rewarding impact of brain stimulation reward, respectively.

The first major theoretical framework within which specific neurotransmitters were linked to the mechanism of brain stimulation reward comprised the various catecholamine theories (Stein, 1964; Dreese, 1966; Crow, 1972a; Lippa, Antelman, Fisher, & Canfield, 1973; German & Bowden, 1974). Early studies demonstrated that drugs which impair the functioning of catecholamine-containing neurons (dopamine and noradrenaline) generally disrupt self-stimulation, whereas drugs which enhance the functioning of these neurons enhance self-stimulation (Olds & Travis, 1960; Stein, 1962; Stein, 1964; Poschel & Ninteman, 1966). The drugs that were used in these studies did not act selectively on either dopaminergic or noradrenergic neurons and thus did not indicate which class of neuron was involved in brain stimulation reward. The development of drugs that acted more selectively on either dopaminergic or noradrenergic neurons and the discovery that both noradrenergic and dopaminergic neurons are found within the medial forebrain bundle led to two variants of the catecholamine theory--the

noradrenergic hypothesis and the dopaminergic hypothesis.

The noradrenergic hypothesis suggested that the first-stage neurons involved in brain stimulation reward contained noradrenaline as their transmitter (Stein, 1962). Various investigators examined the effects on self-stimulation of drugs that selectively interfered with the synthesis of noradrenaline. Noradrenaline synthesis is inhibited by drugs that block the enzyme, dopamine-beta-hydroxylase, which converts dopamine into noradrenaline. Two such dopamine-beta-hydroxylase inhibitors (disulfirum, diethyldithiocarbamate) were shown to decrease responding for brain stimulation in rats (Wise & Stein, 1969; Wise & Stein, 1970). This decrease in responding was reversed when l-noradrenaline was infused into the lateral ventricles of these rats (Wise & Stein, 1969).

Interpretation of the effects of noradrenaline synthesis inhibitors on brain stimulation reward was not clear, however. Some investigators maintained that the decrease in responding for brain stimulation reflected a decrease in the rewarding impact of the electrical stimulation (Wise & Stein, 1969), but, the only response measure used in these studies was rate of lever pressing. Rate of lever-pressing can be altered by a variety of drug effects, including motor incapacitation, illness, sedation, or epileptic seizures. This being the case, many drugs are likely to decrease the rat's rate of lever pressing without

necessarily altering the rewarding value of the stimulation. Roll (1970) has argued for such an interpretation of the effects on brain stimulation of noradrenaline synthesis inhibitors. In support of this argument, Roll reported that disulfiram-treated rats increased the frequency and duration of pauses between periods of active lever pressing for brain stimulation. During these pauses, she observed the rats to be sedated or asleep. If, after a certain period of time, rats did not continue responding, Roll picked them up and placed them back at the bar; they generally resumed responding for a short period of time, at a rate that was comparable to that of non-drugged rats. The fact that response rates could resume to normal if the rats were aroused suggests that noradrenaline synthesis inhibition merely sedated the rats but did not alter the rewarding impact of the stimulation. More recently, additional drugs (FLA 63 and U-14,625) have been developed which interfere with the synthesis of dopamine-beta-hydroxylase. These drugs do not decrease responding for brain stimulation reward (Lippa et al., 1973; Cooper, Cott, & Breese, 1974). Thus these drugs neither affect the rat's performance capacity nor the rewarding impact of brain stimulation. The lack of response decrement following FLA 63 and U-14,625 treatment on the one hand is inconsistent with the presence of response decrements produced by disulfiram on the other. All of these drugs are dopamine-beta-hydroxylase inhibitors; yet only disulfiram has been shown to decrease responding for brain stimulation. The discrepancy between the

findings of Roll (1970) on the one hand and Lippa et al. (1973) and Cooper et al. (1974) on the other makes it difficult to summarize the effects of noradrenaline synthesis inhibition on lever pressing performance, but it seems safe to conclude that this inhibition does not, by itself, significantly alter the rewarding impact of the stimulation (Roll, 1970; Lippa et al., 1973; Cooper et al., 1974).

Another class of drugs that has been used to assess the involvement of noradrenaline in brain stimulation reward is the class of noradrenergic receptor blockers. Selective blockade of central beta-noradrenergic receptors with propranolol has no effect on self-stimulation (Hastings & Stutz, 1973). In contrast, drugs that selectively block alpha-noradrenergic receptors (phentolamine, phenoxybenzamine) do decrease responding for brain stimulation (Hastings & Stutz, 1973; Rolls, Kelly, & Shaw, 1974; Zarevics, Weidley, & Setler, 1977; Fouriezos, Hansson, & Wise, 1978), however, these response decrements appear to reflect sedative effects or performance deficits (Fouriezos et al., 1978). Fouriezos et al. (1978) examined rats that were treated with varying doses of phenoxybenzamine and observed signs of general malaise; rats exhibited symptoms such as ptosis, bradycardia, piloerection, and hypotonia.

It can be seen that the response decrements observed following alpha-noradrenergic receptor blockade or following

disulfiram treatment are similarly due to performance deficits resulting from non-specific side effects of these drugs. The decreased responding for brain stimulation is not due to a specific inhibition of reward. The work by Lippa et al. (1973) and Cooper et al. (1974) lends supports to this conclusion in that there were no performance deficits nor reward deficits observed following treatment with more selective noradrenaline synthesis inhibitors, suggesting that more selective inhibition of noradrenaline has no effect on medial forebrain bundle brain stimulation reward.

The dopaminergic hypothesis suggests that the first-stage neurons of brain stimulation reward contain dopamine as their transmitter. Several investigators examined the effects on brain stimulation reward of drugs that selectively block dopamine receptors. These drugs have been commonly referred to as neuroleptics. Treatment with neuroleptics has been shown to decrease responding for brain stimulation reward (see Wauquier, 1976 for review). Several neuroleptics have been tested, including pimozide (Fouriezos & Wise, 1976; Franklin & McCoy, 1979), spiroperidol (Rolls et al., 1974), haloperidol (Phillips, Brooke, & Fibiger, 1975; Fibiger, Carter, & Phillips, 1976; Gallistel & Davis, 1983), butaclamol (Fouriezos et al., 1978) and clozapine (Gallistel & Davis, 1983). In general, the effectiveness of these drugs in decreasing responding for brain stimulation is proportional to their affinities for dopamine

receptors of the D-2 type (Gallistel & Davis, 1983).

While the work with neuroleptics strongly supports a dopaminergic role in the brain stimulation reward mechanism, the nature of this role has been seriously questioned. Since dopaminergic neurons play a role in motoric output of behavior, the question has been raised as to whether response decrements following neuroleptic administration result from motoric impairments imposed upon the rat or from reward decrements. There are several investigators who have shown that neuroleptic treated rats are not motorically incapacitated as to preclude the normal output necessary to respond for brain stimulation. Fouriezos and Wise (1976) showed that neuroleptic treated rats decrease their responding for brain stimulation in an extinction-like pattern, where responding is normal at the beginning of the session and decreases or ceases as the session progresses. Once the rats ceased to respond, they were removed from the test box for a ten-minute period. Upon being replaced in the test box, the rats showed spontaneous recovery of responding. The fact that these rats showed spontaneous recovery of responding at different intervals throughout the session confirms that the neuroleptic treatment given does not motorically incapacitate the rat. Other work has shown that neuroleptic treated rats will reinitiate responding for brain stimulation only upon presentation of a light that was paired with the availability of brain stimulation reward but not upon

presentation of another light that held no association with reward (Franklin & McCoy, 1979). Using a wider range of neuroleptic dosages and stimulation intensities, Zarevics and Setler (1979) showed that the normal output of responding could be maintained after neuroleptic administration if the current intensity of stimulation was raised. The higher the neuroleptic dosage given, the more current was needed in order to maintain normal responding. If the rats had been motorically incapacitated, a decrease in responding should have been observed regardless of the stimulation intensity given. However, normal response capability after neuroleptic-induced cessation of responding was observed upon increasing the current intensity. Other demonstrations of normal response capability are based on studies showing task-specific extinction. In these studies, rats respond for brain stimulation in two different paradigms. Different tasks are learned in each of these paradigms. The rats are tested in both tasks following neuroleptic administration. After rats cease to respond for brain stimulation reward in the first task, they are removed from the apparatus and tested in the second task. Responding is normal at the beginning of this second test session even though these rats ceased to respond in the first task. Thus the response decrements observed following neuroleptic treatment appear to be specific to the response being carried out but do not generalize to other responses (Beninger & Freedman, 1982; Gallistel, Boytim, Gomita, & Klebanoff, 1982).

It appears safe to conclude that neuroleptics do not necessarily impair the performance capacity of rats. The studies described show that neuroleptic treatment results in response decrements that are suggestive of reward deficits. The evidence is strong in support of dopaminergic involvement in brain stimulation reward. Pharmacological studies of this sort, however, give us no indication whether dopaminergic neurons are part of the first-stage neurons of the brain stimulation reward mechanism.

Another major approach that has been used to determine the various elements involved in the mechanism of brain stimulation reward is the examination of the effects of various brain lesions. Lesion can be made in several ways including fiber damage, cell body damage and nerve terminal damage. Several investigators have used the lesion approach to further determine the nature of the involvement of catecholamines in brain stimulation reward.

Those investigators who were particularly interested in the noradrenergic hypothesis selectively destroyed the dorsal or the ventral noradrenergic systems. Neither ipsilateral nor bilateral destruction of the noradrenaline-containing cell bodies in the locus coeruleus attenuates self-stimulation when electrode tips are in the dorsal noradrenergic bundle (Clavier & Routtenberg,

1976). Lesion to the dorsal noradrenergic bundle had no effect on responding for stimulation in the locus coeruleus. This was assessed in two studies. One study examined the effects of bilateral dorsal noradrenergic bundle infusions of 6-hydroxydopamine (6-OHDA), in doses that cause selective destruction of catecholamine-containing neurons, on responding for stimulation in the locus coeruleus. The lesion had no effect on locus coeruleus self-stimulation despite resultant cortical norepinephrine depletions of 97% (Clavier, Fibiger, & Phillips, 1976). The fact that cortical norepinephrine was depleted to 97%, confirms that the dorsal noradrenergic fibers were destroyed; all cortical norepinephrine is thought to derive from the terminals of the dorsal noradrenergic fibers (Ungerstedt, 1971). In a second study, electrolytic lesions of the dorsal noradrenergic bundle resulted in no change in locus coeruleus reward (Corbett, Skelton, & Wise, 1977). The ventral noradrenergic system was also assessed for its possible involvement in medial forebrain bundle brain stimulation reward. Lesion to the ventral noradrenergic bundle failed to disrupt responding for stimulation in the dorsal tegmental bundle (Clavier & Routtenberg, 1976).

In summary, lesions to the noradrenergic cell bodies in the locus coeruleus do not disrupt medial forebrain bundle self-stimulation; lesions to the ventral noradrenergic fibers do not disrupt medial forebrain bundle self-stimulation; and lesions

to the dorsal noradrenergic fibers do not disrupt self-stimulation when electrodes are implanted in the locus coeruleus. Thus noradrenergic neurons do not appear to play a necessary role in medial forebrain bundle reward. These findings are consistent with the pharmacological studies already discussed that have also failed to reveal any role for noradrenaline in medial forebrain bundle brain stimulation reward.

In contrast, several workers have shown that lesion to the dopaminergic systems has a disruptive effect on self-stimulation in the medial forebrain bundle. There are two groups of dopamine neurons in the midbrain that course rostrally to join the fibers of the medial forebrain bundle. One group, the nigrostriatal bundle, originates from the substantia nigra and ascends rostrally to terminate in the caudate-putamen. The second group, the mesolimbic projections, originates primarily from the ventral tegmental area in the midbrain and ascends to terminate in the nucleus accumbens, olfactory tubercle, septum, bed nucleus of the stria terminalis, amygdala and various cortical areas. Lateral hypothalamic self-stimulation is disrupted when 6-OHDA is unilaterally administered into either the ventral tegmental area or substantia nigra (Koob, Fray, & Iversen, 1978). In order to rule out the possibility of a performance deficit, two electrodes were implanted: one into the hemisphere ipsilateral to the lesion and another in the hemisphere contralateral to the lesion. Ipsilateral self-stimulation was disrupted for the full duration of post lesion testing, whereas contralateral self-stimulation

was initially disrupted but was followed by full recovery of responding. The response decrements observed from the contralateral electrodes were assumed to reflect general performance deficits following the lesion. The results suggested that dopaminergic neurons are important in the mediation of medial forebrain bundle brain stimulation reward since the lesion critically decreased 'ipsilateral' responding for a longer duration as compared to 'contralateral' responding.

Bilateral caudate self-stimulation was decreased after 6-OHDA lesion to the substantia nigra, however, self-stimulation from the contralateral hemisphere recovered faster than self-stimulation from the ipsilateral hemisphere (Phillips, Carter, & Fibiger, 1976), suggesting that dopaminergic cell bodies in the substantia nigra are implicated in caudate reward. Other data have not been supportive of a dopaminergic role in brain stimulation reward. Unilateral substantia nigra self-stimulation was equally disrupted by ipsilateral and contralateral lesions to the caudate nucleus (Clavier & Fibiger, 1977). A unilateral lesion to the substantia nigra resulted in self-stimulation decrements when electrodes were bilaterally implanted into the lateral hypothalamus (Carey, 1982). Bilateral recovery of self-stimulation occurred at the same time. It was suggested that the dopaminergic system interferes with self-stimulation by producing a motor deficit as opposed to a reward deficit. Another study suggesting that

dopamine does not play a role in brain stimulation reward has shown that when bilateral ablations are made to the dopamine terminal fields, rats are still capable of performing movements to obtain brain stimulation reward in the lateral hypothalamus (Huston & Borbely, 1973). Thus, lesions of the dopaminergic terminal fields do not produce the major effects on self-stimulation that would be predicted from the dopamine hypothesis. In summary, there are some lesion studies that tend to suggest some importance for dopamine in the mediation of medial forebrain bundle brain stimulation reward. These studies do not, however, tell us anything about whether dopamine is involved in the first-stage rather than at some later stage in the mechanism.

The pharmacological and lesion studies that have been reviewed do not indicate whether dopaminergic fibers are directly activated in medial forebrain bundle brain stimulation reward. Although dopamine appears to play some role in the mechanism of brain stimulation, it is quite possible that this role is not in the first-stage of the process. There are two methods that are capable of distinguishing between the various elements that are involved in this mechanism. These methods include anatomical mapping and behavioral electrophysioloy.

Several workers have systematically compared the rewarding effects of stimulation at different anatomical sites in the brain

(Bruner, 1967; Crow, 1972b). The early mapping studies indicated that there are either multiple first-stage neurons--in a wide range of regions--or that the first-stage neurons have long axons that traverse a number of nuclei.

The anatomical location of brain stimulation reward sites in the early mapping studies were found in and around the medial forebrain bundle. The discovery by Ungerstedt (1971) that catecholamine fibers follow an ascending course in the rat brain and are located within the medial forebrain bundle, influenced subsequent mapping studies for brain stimulation reward. More recent mapping studies were specifically designed to test the hypothesis of whether the boundaries of the first-stage system involved in brain stimulation reward correspond to the boundaries of the catecholaminergic neurons. If the catecholaminergic neurons were the first-stage neurons of medial forebrain bundle reward, then a close correspondence between the reward system and the catecholamine systems should be observed.

One technique that has been used in anatomical mapping studies is to implant each rat with a moveable electrode that can be lowered to test up to sixteen sites in the dorsal-ventral plane. When testing multiple sites in each rat, the dorsal-ventral distribution of the boundaries of the reward system can be estimated and the degree of homogeneity between sites can be ascertained.

Investigators who were interested in determining whether noradrenaline was critically involved in medial forebrain bundle brain stimulation reward, implanted movable electrodes into the region where the dorsal noradrenergic fibers are found (Corbett & Wise, 1979). The dorsal noradrenergic fibers course rostrally among the fibers of the medial forebrain bundle. When behavioral testing was completed, the anatomical sites that sustained self-stimulation were verified, by fluorescence histochemistry, for their contribution to the ascending noradrenergic system. This study showed no correlation between the locus of the boundaries for the rewarding sites and the boundaries of the noradrenergic fibers. Nor was there any correlation found between the density of the fibers and the goodness or threshold of the rewarding stimulation. The locus coeruleus, the site of origin for the dorsal tegmental noradrenergic system, was mapped for self-stimulation in 12 rats. Brain stimulation reward was observed in one of these rats even though no consistent relationship was evident between the density of noradrenergic cell bodies and self-stimulation sites. The remaining eleven rats did not self-stimulate despite the fact that multiple locus coeruleus sites were tested in each rat. In agreement with pharmacological and lesion studies, these data demonstrate that noradrenaline does not comprise a component of the first-stage neurons involved in medial forebrain bundle brain stimulation reward.

Anatomical mapping studies of brain stimulation reward sites in relation to the dopaminergic cell bodies in the substantia nigra zona compacta, zona reticulata and the ventral tegmental area (Corbett & Wise, 1980; Wise, 1981) followed the same procedure as that used in the noradrenergic mapping study. Moveable electrodes were implanted into the regions of the dopaminergic cell bodies (substantia nigra and ventral tegmental area) and of the efferent fibers of the dopaminergic systems that course rostrally from these cell bodies among the fibers of the medial forebrain bundle. All regions that supported self-stimulation were within the boundaries of the dopaminergic cell bodies in the substantia nigra zona compacta and the ventral tegmental area and efferent fibers as revealed by fluorescence histochemistry. Self-stimulation was not observed when electrode tips were dorsal or ventral to these cell bodies. The caudal portions of these cell bodies did not support self-stimulation. The medial-lateral boundaries of the dopaminergic cells in these areas were found to correspond with the lateral boundaries of the brain stimulation reward system. These results strongly suggest dopaminergic involvement in medial forebrain bundle brain stimulation reward.

Subsequent anatomical mapping studies of brain stimulation reward attempted to understand whether the involvement of dopamine was at the level of the first-stage or at the level of dopaminergic neurons lying efferent to the first-stage fibers.

The regions of the dopaminergic terminal fields were mapped for sensitivity to brain stimulation reward (Prado-Alcala, Streather &, Wise, 1984; Prado-Alcala & Wise, 1984). Moveable electrodes were implanted into eight regions of the caudate nucleus, four regions of the septal area, the amygdaloid complex, nucleus accumbens, olfactory tubercle, pyriform cortex, medial and sulcal prefrontal cortex as well as in the entorhinal cortex. Brain stimulation reward was found in all of these dopamine-containing regions, however stimulation was also rewarding at sites in the amygdaloid complex and the olfactory tubercle in areas that did not contain dopamine terminals. Furthermore, stimulation was not rewarding in some of the dopamine-containing terminal regions. In sharp contrast to the work involving dopamine cell body regions (Corbett & Wise, 1980), these studies revealed no relationship between dopamine-rich regions and sites that supported brain stimulation reward. It was concluded that rewarding brain stimulation in the dopaminergic regions tested is not due to the direct activation of the dopaminergic terminals; the dopaminergic neurons do not comprise the first-stage neurons involved in brain stimulation reward.

Brain stimulation reward has been mapped in some portions of the medial forebrain bundle, between the regions containing the dopaminergic cell bodies and the dopaminergic terminals. Several sections of the hypothalamus have been examined for involvement in brain stimulation reward (Corbett & Wise, 1980; Gratton &

Wise, 1983). Stimulation was rewarding when electrode tips were in a homogeneous region of the medial forebrain bundle at the level of the lateral hypothalamus with the lowest thresholds being concentrated in a discrete region in the middle of the medial forebrain bundle (Gratton & Wise, 1983). The finding of a small region containing low threshold values suggests that the first-stage system involved in brain stimulation reward is a single substrate with maximum density in the middle of the medial forebrain bundle. This does not fit with the view that the fibers involved in the first-stage of medial forebrain bundle brain stimulation reward are dopaminergic. The nigrostriatal dopaminergic fibers are not found in the same region as the brain stimulation reward sites and the mesolimbic dopaminergic fibers are too diffusely distributed throughout the medial forebrain bundle so as to find a concentrated region of low thresholds sites.

Based on the anatomical mapping data, it has been shown that the dopaminergic cell bodies bear a close relationship to the sites supporting brain stimulation reward, however, the dopaminergic fibers at the levels of the lateral hypothalamus and the dopaminergic terminal fields do not. It thus becomes evident that the dopaminergic neurons are not the first-stage neurons involved in medial forebrain bundle brain stimulation reward. Dopaminergic neurons are relevant to the brain stimulation reward system as is evident from the finding of a close relationship

between the boundaries of the sites supporting brain stimulation reward and the boundaries of the dopaminergic cell bodies. This finding as well as the findings from pharmacological studies makes it clear that dopamine does play an important reward-relevant role. The mapping methodology makes it clear that this role is not in the first-stage of the brain stimulation reward mechanism. Dopaminergic neurons may be reward-relevant in the second (Wise, 1981), third, or some later stage. Since the number of stages in this mechanism are at present unknown, it is difficult to suggest at which stage dopaminergic neurons are involved.

A set of techniques that are based on conventional electrophysiology and psychophysics has been used to examine some of the neurophysiological and anatomical properties of the first-stage neurons involved in medial forebrain bundle brain stimulation reward and has provided the brain stimulation reward specialist with valuable information. These neurophysiological properties include the refractory periods, the conduction velocities, and the direction in which the first-stage neurons conduct in order to transmit their reward message. The methodology used to estimate these neurophysiological properties involves the administration of trains of paired-pulses tested at different interpulse intervals (the interval between the two pulses in each pair). The rat's frequency threshold (that stimulation frequency that elicits an arbitrary amount of lever

pressing) is estimated under these paired-pulse conditions. The behavior observed under these conditions is then used to make inference to some of the neurophysiological and anatomical properties of the first-stage neurons.

The administration of a single depolarizing pulse to an axon results in an action potential. Following an action potential, there will be a period during which a second action potential cannot be generated. This period is referred to as the refractory period of the axon. The refractory periods for different axons can vary considerably.

Electrophysiologists have used the paired-pulse technique to estimate the length of the refractory period of single neurons. The paired-pulse technique can also be used to estimate the refractory periods for the population or populations of first-stage neurons involved in medial forebrain bundle brain stimulation reward. Rather than estimating these refractory periods based on observations from recording studies, one can estimate these refractory periods on the basis of behavioral inference.

The methodology for estimating refractory periods for medial forebrain bundle brain stimulation reward on the basis of behavioral inference first involves the administration of trains of single pulses (Conditioning pulses or C pulses) to find the

minimum stimulation frequency that will elicit some arbitrary amount of lever pressing, as defined by the experimenter. The stimulation frequency that elicits this arbitrary amount of lever pressing is referred to as the frequency threshold and is used as an indication of the sensitivity of the neural system to the rewarding impact of brain stimulation. The frequency threshold under this single C pulse condition is later compared to the frequency threshold observed under the paired-pulse condition, where each single C pulse is now followed by a second single pulse (Testing pulse or T pulse). The interval between the administration of the C pulse and the T pulse is referred to as the C-T interpulse interval. Under the paired-pulse condition, the frequency threshold is determined across a range of C-T intervals ranging from short to long. Each single C pulse will elicit an action potential that will be followed by a refractory period. The length of this refractory period may be inferred by determining the range of C-T interpulse intervals wherein each T pulse becomes effective in eliciting a second action potential. When the C-T interval is very short, such that each T pulse is administered while all the first-stage neurons are refractory from the preceding C pulse, the T pulses will not be effective (zero effectiveness) in eliciting action potentials. Responding for trains of paired-pulses at this short C-T interval will be similar to responding under the single C pulse condition and thus the frequency threshold observed under this paired-pulse condition will not differ from the frequency threshold observed

under the single C pulse condition.

If, however, the interpulse interval is sufficiently long such that each T pulse is administered after all of the first-stage neurons have recovered from refractoriness from the preceeding C pulse, the T pulses will be 100% effective in eliciting action potentials. Responding for these trains of paired-pulses at this long C-T interval will not be the same as responding for trains of single pulses. The frequency threshold observed under this paired-pulse condition should decrease by one-half from the single pulse condition; half as many paired-pulses should elicit the same frequency threshold as a given number of single pulses.

Between the very short interpulse interval tested and the long interpulse interval tested, the experimenter may test as many interpulse intervals as is desired. The effectiveness of a T pulse in eliciting action potentials is assessed at each of these C-T intervals. The effectiveness of the T pulse in eliciting action potentials will increase as the C-T interval lengthens. The percentage of T pulse effectiveness at each C-T interval tested, reflects the percentage of neurons that have recovered from refractoriness after the C pulse and will now fire in response to the T pulse. It is assumed that the percentage of T pulse effectiveness at each C-T interval tested is equal to the percentage of contribution of first-stage neurons which have

refractory periods shorter than the tested C-T interval. Since the refractory periods within a population of neurons vary, there will be a range of refractory period estimates. This range of refractory period estimates will take a sigmoidal shape. The refractory periods for the first-stage neurons of medial forebrain bundle brain stimulation reward range from 0.4-2.0 msec. (Yeomans, 1975). In comparison to known catecholaminergic cell body refractory period estimates, it appears that the first-stage medial forebrain bundle fibers may not comprise a catecholaminergic component since catecholamine cell bodies have refractory periods that are longer than 2.0 msec. (Guyenet & Aghajanian, 1978; German, Dalsass, & Kiser, 1980).

The paired-pulse technique can also be used to estimate the conduction velocities for the first-stage neurons of medial forebrain bundle brain stimulation reward. In order to estimate the conduction velocities, a connection between two electrode sites in the medial forebrain bundle must first be established. This connection may be established as follows. When trains of paired-pulses are administered to two electrodes (the C pulse to one electrode and the T pulse to the other electrode) that are located in the same fiber bundle, each pulse will elicit an action potential that will propagate in the direction towards the terminals (orthodromically) and in the direction towards the cell body (antidromically). If a very short interval is given between the administration of the C pulse and the T pulse, then the

orthodromic action potential from the C pulse will collide with the antidromic action potential from the T pulse (under the condition that the C pulse was placed afferent to the T pulse). The orthodromic action potential from the T pulse, however, will reach the synapse. This can be behaviorally inferred by looking at the frequency threshold. Under conditions in which only one orthodromic action potential reaches the synapse, the frequency threshold with paired-pulses is no different than when single pulses are administered to one electrode site.

If, however, the interval between the administration of the the C pulse and the T pulse is sufficiently long, then the orthodromic action potentials from both the C pulse and the T pulse will reach the synapse. Since the C pulse will have propagated past the second electrode site before the T pulse is administered, collision will not occur. Two orthodromic action potentials will reach the synapse and will be twice as effective as when one action potential reaches the synapse. Under these conditions, when two orthodromic action potentials reach the synapse, the frequency threshold with paired-pulses will be different than when single pulses are administered to one electrode. The rat's frequency threshold will decrease by one-half. Several C-T intervals are tested to find the range of intervals at which collision will occur.

Once collision between two sites in the bundle is established, the conduction velocities of the first-stage neurons can be estimated. The minimal interval at which no collision occurs (as inferred behaviorally from the observed frequency threshold) is referred to as the collision interval. This collision interval minus the refractory period is taken to reflect the conduction time of the first-stage neurons or the time it takes for one action potential to propagate past the second electrode. The conduction velocity can then be estimated by dividing the interelectrode distance by the conduction time. Bielajew and Shizgal (1982) have estimated that the conduction velocity for the first-stage neurons involved in brain stimulation reward ranges from 1.0 - 4.5 m/s. These conduction velocities are inconsistent with those of catecholaminergic neurons which are reported to range from 0.3-0.9 m/s (Dalsass, Germán, & Kiser, 1978; Guyenet & Aghajanian, 1978; Yim & Mogenson, 1980).

A two electrode technique has also been used to determine the normal direction of conductance for a major component of the first-stage neurons that are aligned along the two electrodes. Bielajew and Shizgal (1986) tested for the normal direction of conductance for the first-stage neurons between the lateral hypothalamus and the ventral tegmental area and demonstrated that

a major component of these first-stage medial forebrain bundle neurons course in a rostro-caudal direction.

Summary

Pharmacological and lesion studies have provided information regarding the involvement of dopamine in brain stimulation reward. The precise location of this dopaminergic involvement, however, cannot be determined with the use of these methodologies. Both the electrophysiological method and the anatomical mapping method have provided more relevant information regarding the first-stage neurons involved in medial forebrain bundle brain stimulation reward. Electrophysiological data have suggested that a portion of the first-stage neurons are fast, myelinated, descending fibers that travel through the lateral hypothalamic area to the ventral tegmental area, without any synapse in between these areas (Gallistel, Shizgal, & Yeomans, 1981). Based on these data it has been suggested that these first-stage neurons are not catecholaminergic. The anatomical mapping method has also provided relevant information regarding the first-stage neurons. A close correspondence has been observed between the boundaries of the dopaminergic cell bodies in the ventral tegmental area and positive sites for brain stimulation reward, with no positive sites observed caudal to the ventral tegmental area (Corbett & Wise, 1980). No close corresponding relationship, however, has been observed between the frontal cortex, nucleus accumbens, caudate nucleus or olfactory tubercle and positive sites for brain stimulation reward (Prado-Alcala & Wise, 1984).

The present investigation

Since collision has been found between the lateral hypothalamic area and the ventral tegmental area for a portion of the first-stage neurons, then perhaps these neurons originate from some region rostral or dorsal to the lateral hypothalamus. It has already been shown that this rostral or dorsal region is not compatible with the regions of the dopaminergic terminal fields (Prado-Alcala et al., 1984). As well, no suggestion of a rostral boundary of reward was observed at the level of the lateral hypothalamic area (Gratton & Wise, 1983). There are several regions in the anterior medial forebrain bundle, lying rostral to the lateral hypothalamic area, that have not been closely examined for their correspondence to brain stimulation reward. These regions include the stria medullaris, anterior hypothalamic area, the medial and lateral preoptic areas, the diagonal band of Broca and the medial and lateral septal areas.

The present research attempted to determine the anatomical boundaries and homogeneity of brain stimulation reward in the anterior medial forebrain bundle. By using a dorsal-ventral moveable electrode implanted at different medial-lateral coordinates across the lateral region, this thesis provides detailed information on the anatomy of the first-stage neurons and gives an indication of the relative distribution of these

neurons. Since several sites can be tested in each rat, behavioral mapping of the brain with a moveable electrode provides a greater resolution of the boundaries and of the regional specificity of the underlying reward system than do studies in which one site per rat is tested.

METHODS

Animals

Forty experimentally naive male Long-Evans rats were individually housed in stainless steel cages. Food and water were available ad libitum throughout the duration of the experiment.

Electrode Construction

The electrode consisted of a 254um (in diameter) stainless steel wire that was concentrically soldered to a male Amphenol pin. This pin was externally threaded with a 2-54 die and was screwed into a threaded nylon receptacle (10mm in length and 4mm in diamater). The electrode wire was coated several times with a wire insulating varnish and was baked at 400 degrees C for 20 minutes after each coating. The tip of the electrode wire was filed until it was flat and the entire electrode was microscopically checked for cracks in the insulation. Stopcock grease (Dow Corning) was applied to the base of the nylon receptacle.

Surgery

Each rat was anesthetized with sodium pentobarbitol (60mg/kg). Five stainless steel skull screws were screwed into the skull serving as an anchor for the electrode assembly. A stainless steel wire was wrapped around one of these screws to

serve as the current return. The electrode was lowered to the predetermined implantation coordinate. Dental acrylic cement was molded around the electrode assembly to hold it firmly in place. The stopcock grease that was applied to the base of the receptacle served to prevent cerebrospinal fluid from rising up the nylon receptacle to the uninsulated threads of the Amphenol pin and to prevent the dental cement from making contact with the threaded part of the electrode that was encased in the nylon receptacle. All rats were given at least one week to recover from surgery before testing procedures began.

Implantation Coordinates

Implantation coordinates ranged from 1.0 mm to 2.8 mm in the anterior-posterior plane and from 0.25 mm to 4.0 mm in the medial medial-lateral plane. The interaural line was 5 mm below the level of the upper incisor bar of the stereotaxic instrument.

Testing Procedure

Rats were tested for self-stimulation in standard operant boxes (28x28 cm) that were constructed of three stainless steel walls and one plexiglass wall. A stainless steel lever protruded from one of the steel walls. Stimulation was delivered to the rat each time the rat made a movement toward the lever. Rats were trained, by successive approximation, to approach and press the lever. Each lever press delivered a 500 msec. train of 60 Hz sine wave stimulation. A stimulation intensity was chosen that would elicit high rates of lever-pressing. Rats were trained at

this stimulation intensity to press the lever at a constant rate across successive ten-minute sessions. Rats were then tested for self-stimulation at a wide range of current intensities (rate-intensity curves). Stimulation current was first set at the intensity at which the rat was trained to lever-press. Rate of lever-pressing was recorded for one minute at this intensity. The current was then lowered by 2 uA and the rat was allowed one minute to adapt to the lower current intensity. Rate of lever-pressing was then recorded for one minute before the current was lowered again by 2 uA. Current intensities were successively lowered by 2 uA until the rat no longer self-stimulated.

Criteria for lowering moveable electrodes.

Rats were tested for self-stimulation at the first site for a total of 21 daily sessions. If self-stimulation was not observed after these sessions, the electrode was lowered to the next site. It was concluded that stimulation at the first site was not rewarding. Training procedures resumed at the next site for at least 5 days. If no lever-pressing for stimulation was observed within these 5 days, the electrode was lowered to the next site where training was resumed once again for at least 5 days. This procedure was carried out until the electrode had been lowered the maximal ventral extent.

If lever-pressing for stimulation was observed at a

particular site, rate-intensity curves were determined on a daily basis until threshold values across days were stable. Threshold was defined as the intensity at which 10% of the rat's maximal rate of lever-pressing was observed. The criterion for threshold stability was no change in threshold greater than 6 uA. When thresholds had stabilized, the electrode was lowered to the next site and the procedure was repeated. This procedure was carried out at each site tested.

Histology

At the end of testing, each rat was transcardially perfused with physiological saline followed by 10% formalin solution. Brains were removed and placed into a 95% solution of formalin. Brains were blocked and frozen on dry ice before being placed into the cryostat. Serial 40 um sections were cut in the coronal plane and thawed onto glass slides. All sections were traced from a projected enlargement. A portion of the sections was photomicrographed for verification of densely myelinated regions. All slides were then stained with thionin to allow for differentiation between cell body-containing regions and fiber tracts.

RESULTS

Positive sites for self-stimulation were found at each of the anterior-posterior levels tested in the anterior medial forebrain bundle. These levels included 1.0, 1.2, 1.4, 1.6, 1.8, 2.2, 2.4, 2.6 and 2.8 mm anterior to Bregma (Pellegrino and Pellegrino, & Cushman, 1979). Positive sites were more widely dispersed at the more rostral levels than the more caudal levels. At 2.8 mm anterior to Bregma, stimulation was rewarding at sites as near as 0.25 mm to the midline and as far as 4.0 mm lateral to the midline. In comparison, at 1.0 mm anterior to Bregma, stimulation was rewarding only at sites between 0.75 mm and 2.0 mm lateral to the midline. Stimulation sites are shown in Figures 1-4.

The relationship between response rate and stimulation intensity varied depending on the site at which stimulation was delivered. The maximum rate of lever pressing ranged from 5 to 15 presses per minute when electrode tips were in the lateral septal area (See Figure 5), and from 20 to 100 presses per minute when electrode tips were in the medial forebrain bundle (See Figure 6).

FIGURE 1. Histological reconstruction of stimulation sites tested at 2.4-2.8 mm anterior to Bregma (Pellegrino, Pellegrino, & Cushman, 1979). Numbers, on right side of the brain, indicate the threshold value (uA) obtained at each stimulation site. Dots, on the left side of the brain, indicate the maximum rate of lever-pressing observed at each of these stimulation sites. Dashes and open circles represent negative sites for self-stimulation.

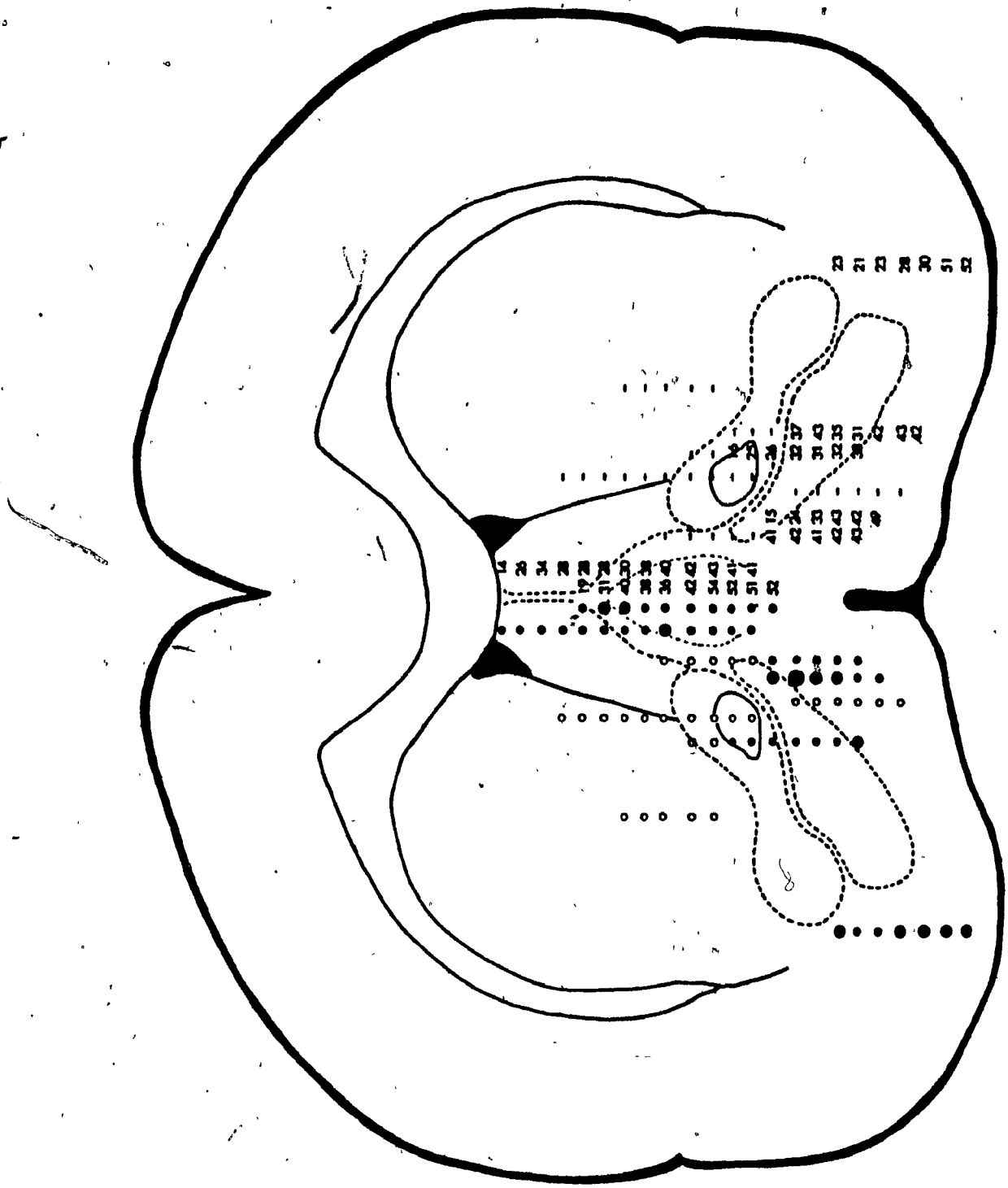


FIGURE 2. Histological reconstruction of stimulation sites tested at 1.8-2.0 mm anterior to Bregma (Pellegrino, Pellegrino, & Cushman, 1979). Numbers, on right side of the brain, indicate the threshold value (uA) obtained at each stimulation site. Dots, on the left side of the brain, indicate the maximum rate of lever-pressing observed at each of these stimulation sites. Dashes and open circles represent negative sites for self-stimulation.

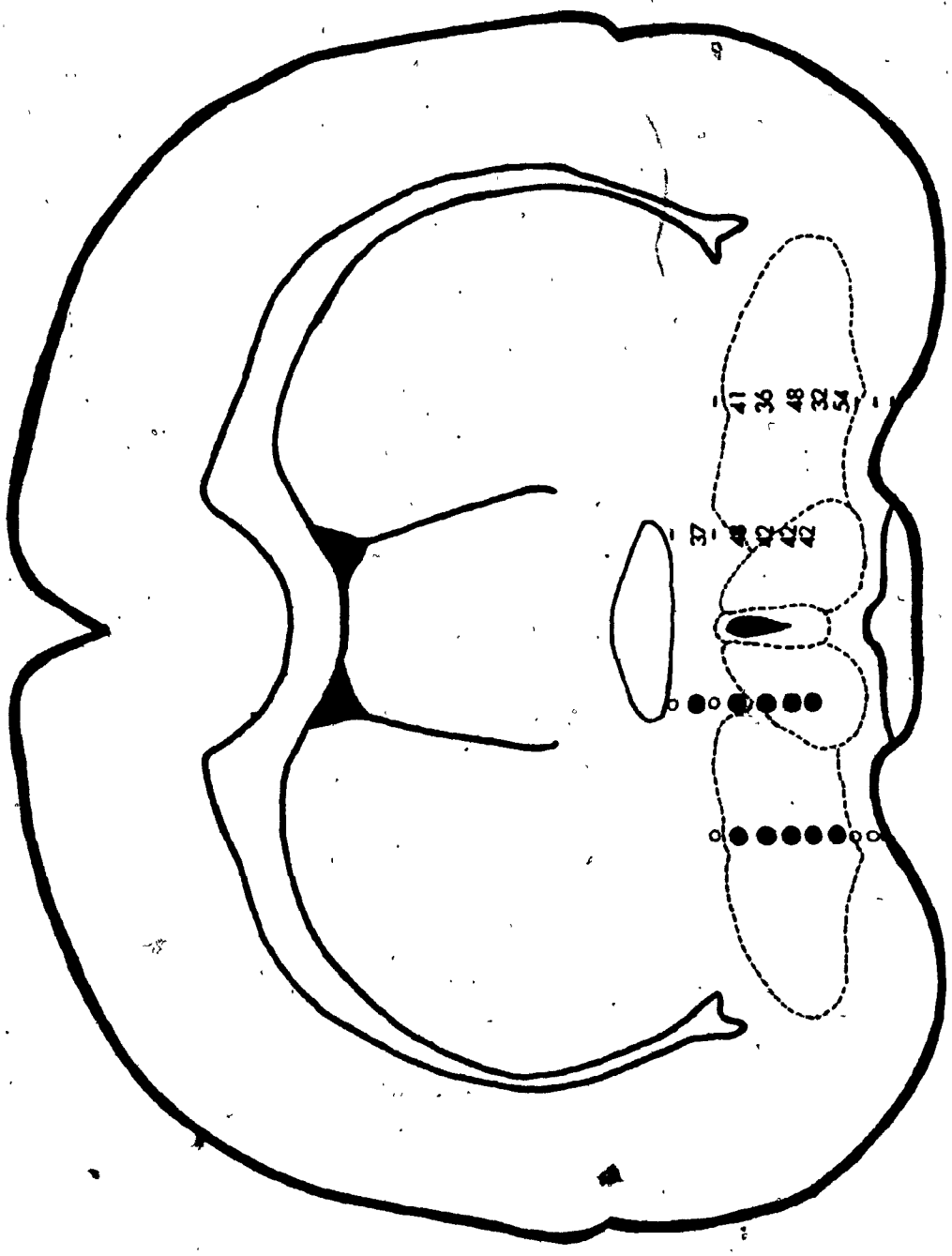


FIGURE 3. Histological reconstruction of stimulation sites tested at 1.4-1.6 mm anterior to Bregma (Pellegrino, Pellegrino, & Cushman, 1979). Numbers, on right side of the brain, indicate the threshold value (uA) obtained at each stimulation site. Dots, on the left side of the brain, indicate the maximum rate of lever-pressing observed at each of these stimulation sites. Dashes and open circles represent negative sites for self-stimulation.

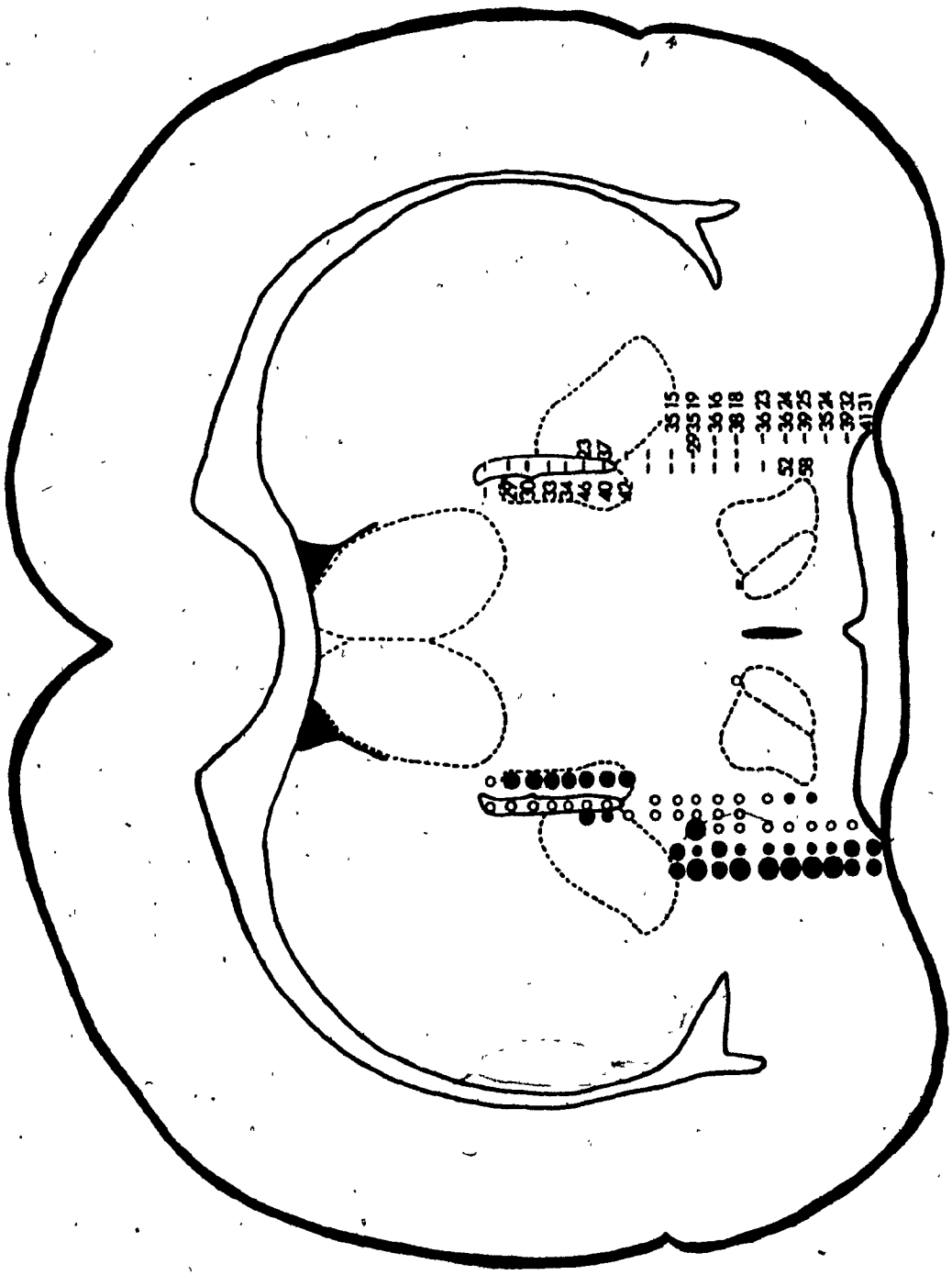

3515
2933 19
3616
3818
3623
3624
3625
3524
3932
4131
57
52
58

FIGURE 4. Histological reconstruction of stimulation sites tested at 1.0-1.2 mm anterior to Bregma (Pellegrino, Pellegrino, & Cushman, 1979). Numbers, on right side of the brain, indicate the threshold value (uA) obtained at each stimulation site. Dots, on the left side of the brain, indicate the maximum rate of lever-pressing observed at each of these stimulation sites. Dashes and open circles represent negative sites for self-stimulation.

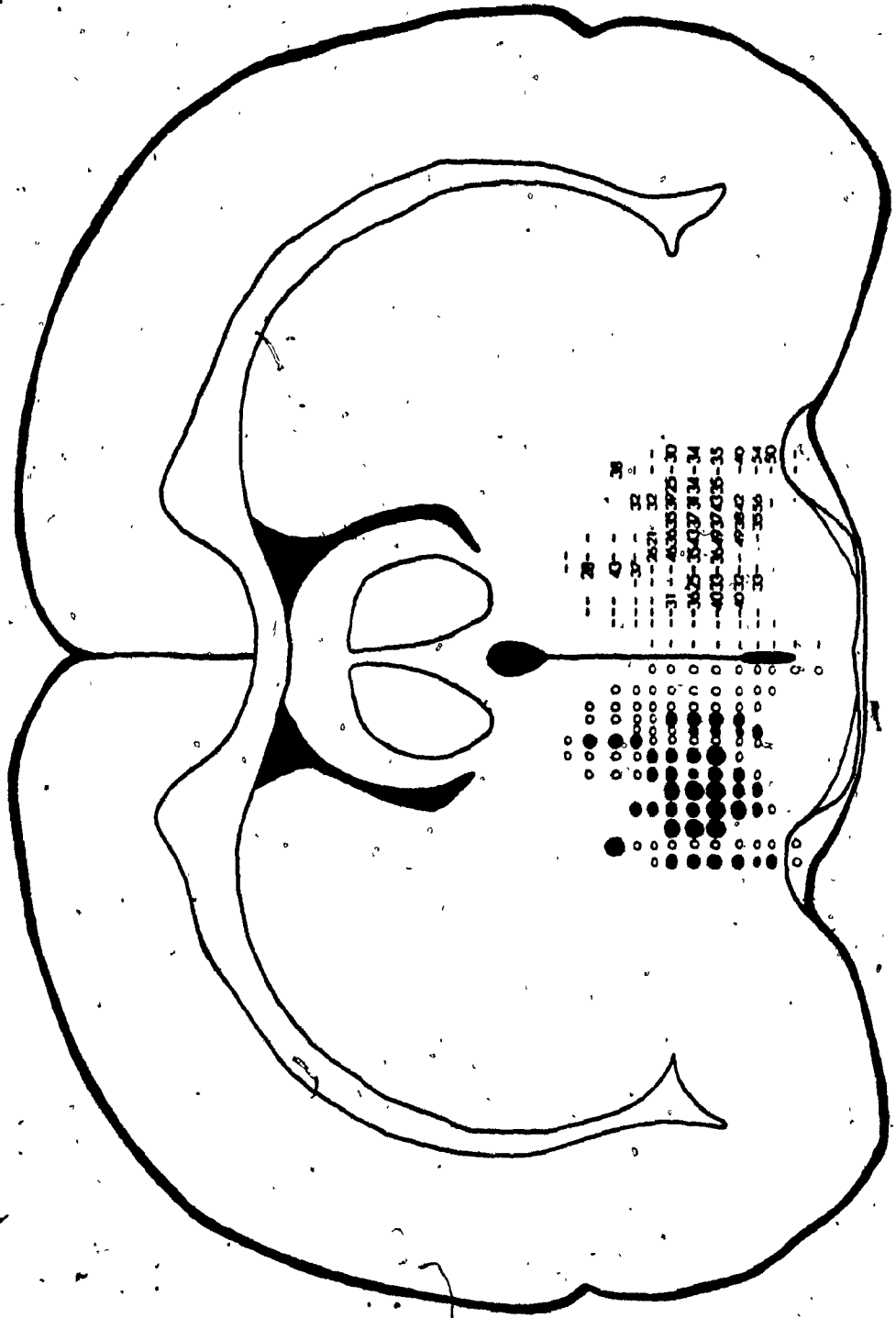
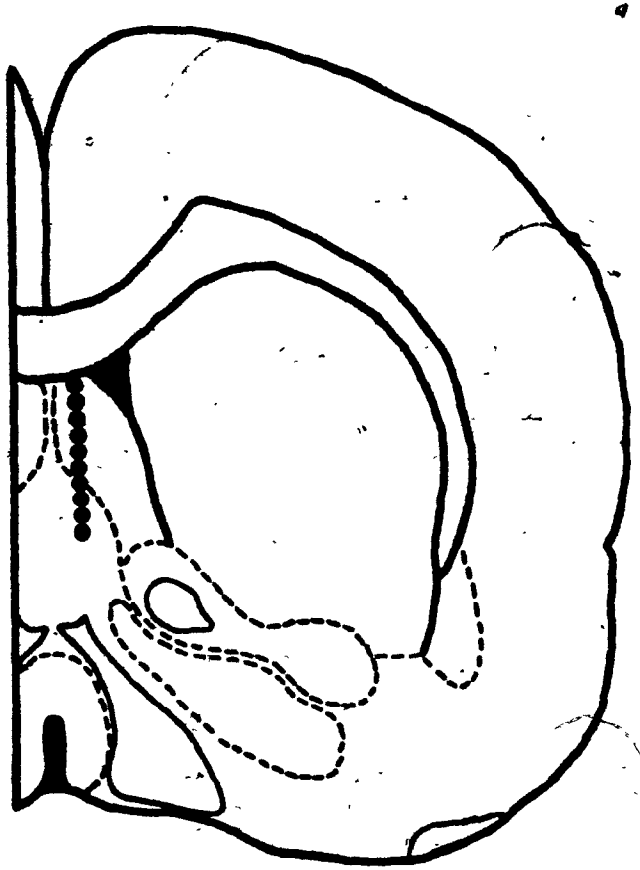


FIGURE 5. Mapping data for rat CP6. Left panel shows the histological reconstruction of stimulation sites at 2.4 mm anterior to Bregma. Positive sites are differentiated by different colors and negative sites are illustrated with open circles. The right panel shows the mean rate-intensity curve for each stimulation site. Curves correspond to stimulation sites on the left panel by colors and by numerical symbols.



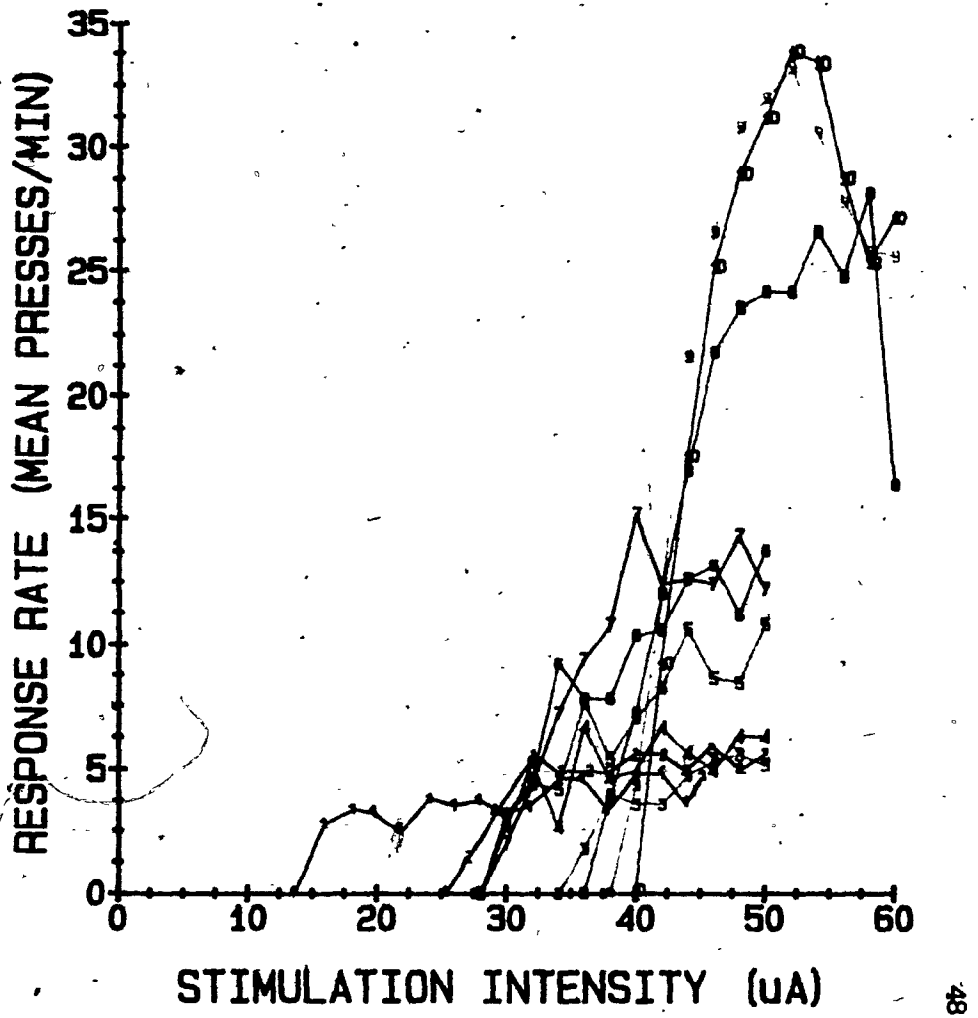
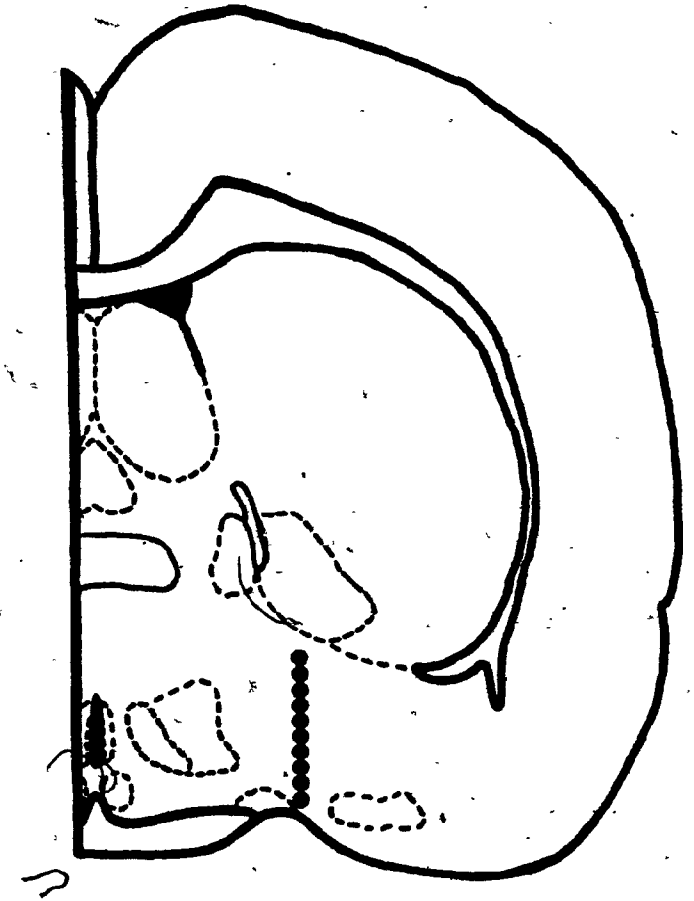
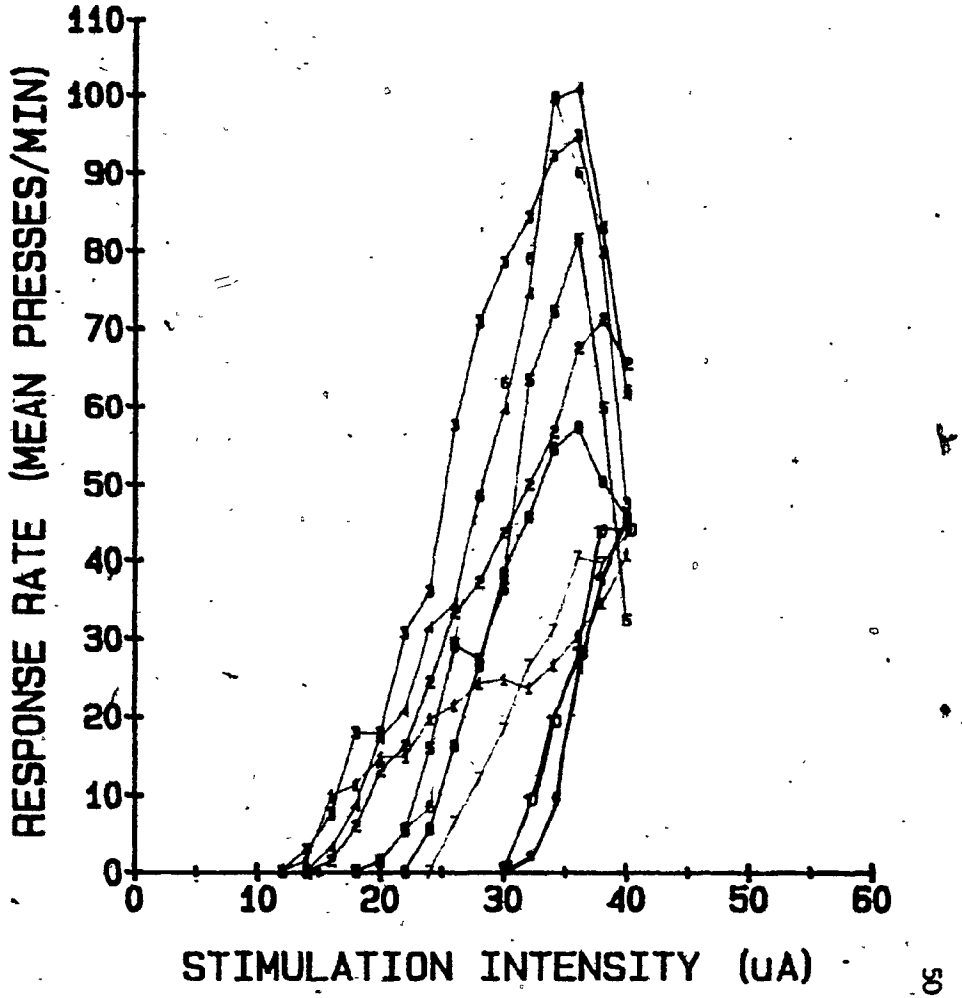

CP6
RESPONSE RATE (MEAN PRESSES/MIN)
0
5
10
15
20
25
30
35
0
10
20
30
40
50
60
STIMULATION INTENSITY (uA)

FIGURE 6. Mapping data for rat CP9. Left panel shows the histological reconstruction of stimulation sites at 1.4 mm anterior to Bregma. Positive sites are differentiated by different colors and negative sites are illustrated with open circles. The right panel shows the mean rate-intensity curve for each stimulation site. Curves correspond to stimulation sites on the left panel by colors and by numerical symbols.

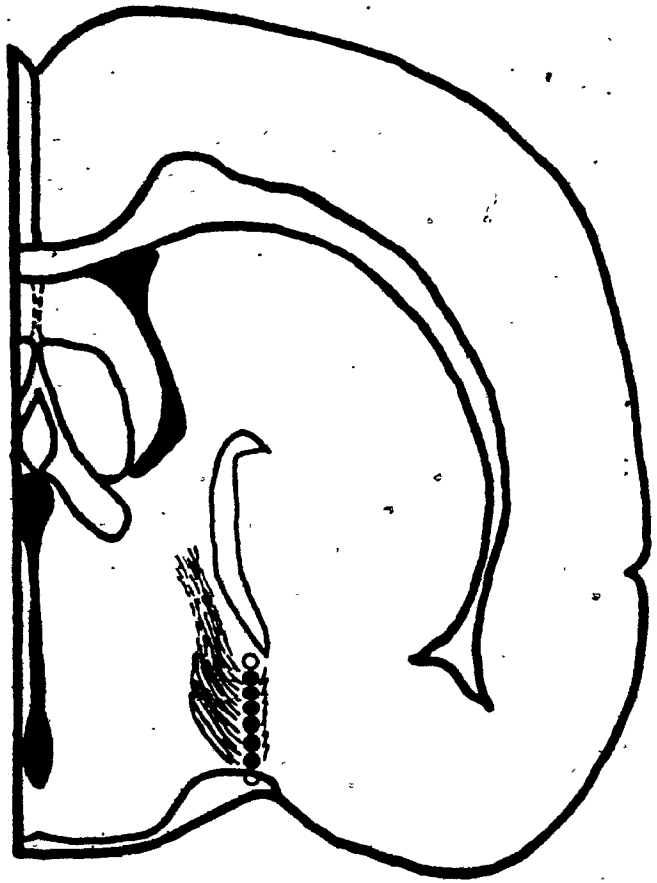



CP9
RESPONSE RATE (MEAN PRESSES/MIN)
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
STIMULATION INTENSITY (uA)

The stimulation threshold, defined as the stimulation intensity at which 10% of the maximum rate of responding was observed, was determined for each rate-intensity function. These thresholds ranged from 14-58 uA. There was no consistent relationship between the thresholds for responding and the maximum response rates associated with different sites. In the case of rat CP6, for example, high rates were associated with high thresholds and low rates were associated with low thresholds (See Figure 5). In the case of rat CP9, there was no consistent relationship between maximum rate of responding and threshold; the two lowest maximum rates of responding were associated with the highest and lowest thresholds (See Figure 6). In the case of rat AB25, low maximum rates were associated with high thresholds and high maximum rates were associated with low thresholds (See Figure 7).

A total of 95 sites in the region of the stria medullaris was tested for self-stimulation (See Figure 4). The densely myelinated tissue of the stria medullaris was easily discernable in wet sections which were traced and photographed for comparison. Thirty-three positive sites were found in the stria medullaris. The boundaries of reward sites in the stria medullaris were found to correspond with the dorsal and ventral boundaries of the myelinated tissue of the stria medullaris, with negative sites found just dorsal and ventral to this tissue (See Figures 7, 8, 9 and 10). The medial boundaries of regions

FIGURE 7. Mapping data for rat AB25. Left panel shows the histological reconstruction of stimulation sites at 1.0 mm anterior to Bregma. Positive sites are differentiated by different colors and negative sites are illustrated with open circles. The right panel shows the mean rate-intensity curve for each stimulation site. Curves correspond to stimulation sites on the left panel by colors and by numerical symbols.



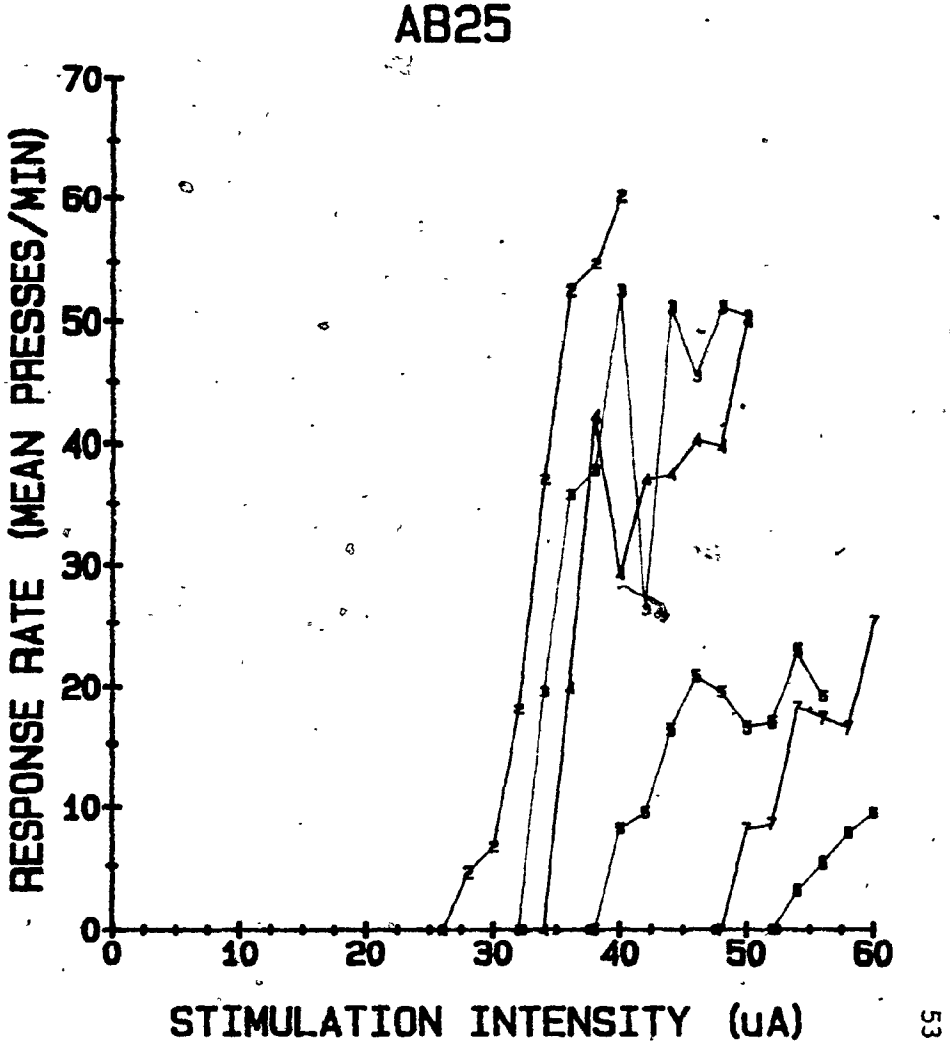

AB25
RESPONSE RATE (MEAN PRESSES/MIN)
0
10
20
30
40
50
60
70
STIMULATION INTENSITY (uA)

FIGURE 8. Rat AB25. Photomicrograph of the coronal section in which the electrode track was visible. The tip of the electrode was just ventral to the stria medullaris.

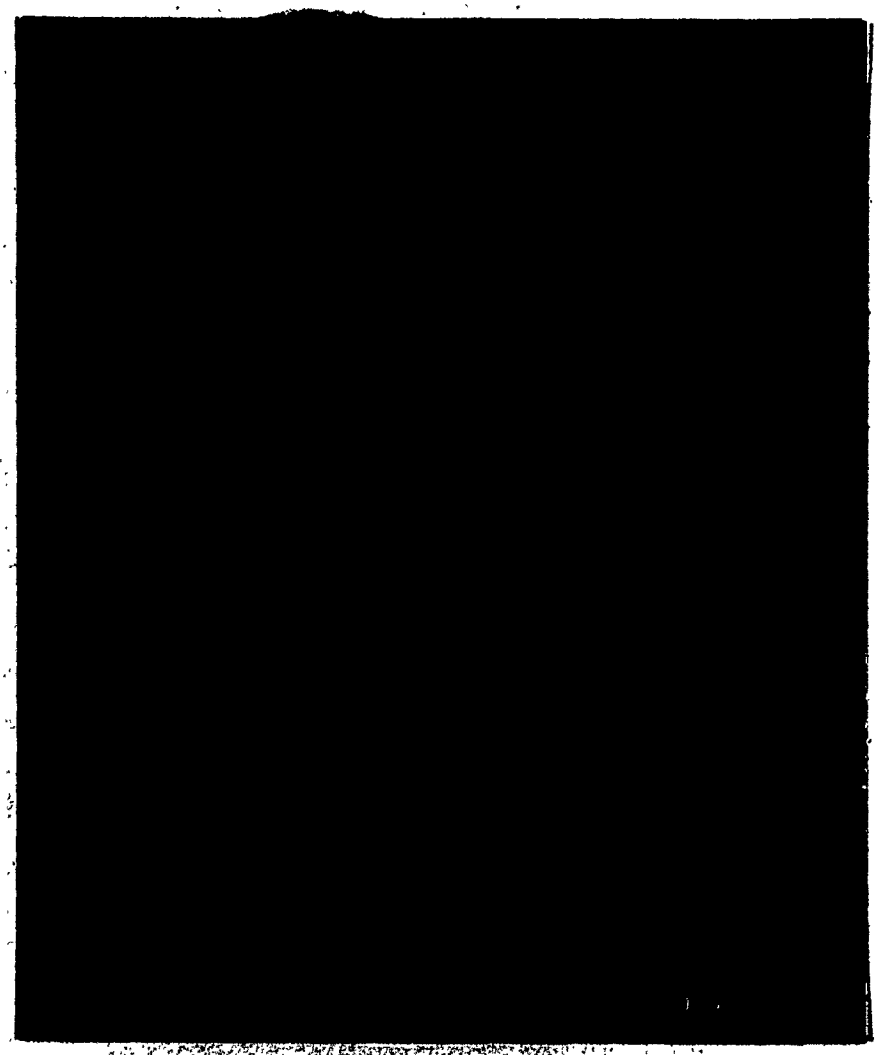
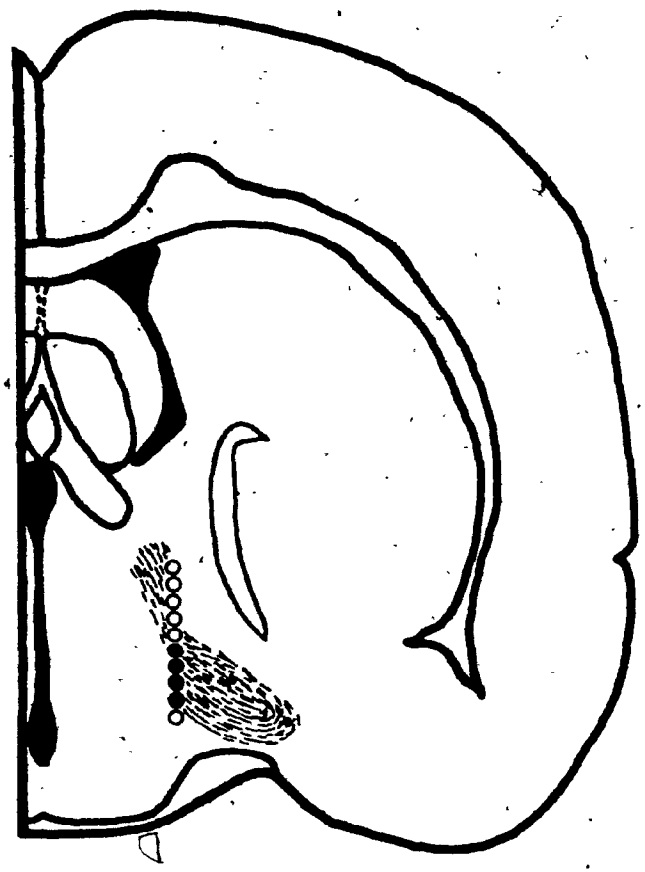


FIGURE 9. Mapping data for rat AB24. Left panel shows the histological reconstruction of stimulation sites at 1.0 mm anterior to Bregma. Positive sites are differentiated by different colors and negative sites are illustrated wih open circles. The right panel shows the mean rate-intensity curve for each stimulation site. Curves correspond to stimulation sites on the left panel by colors and by numerical symbols.



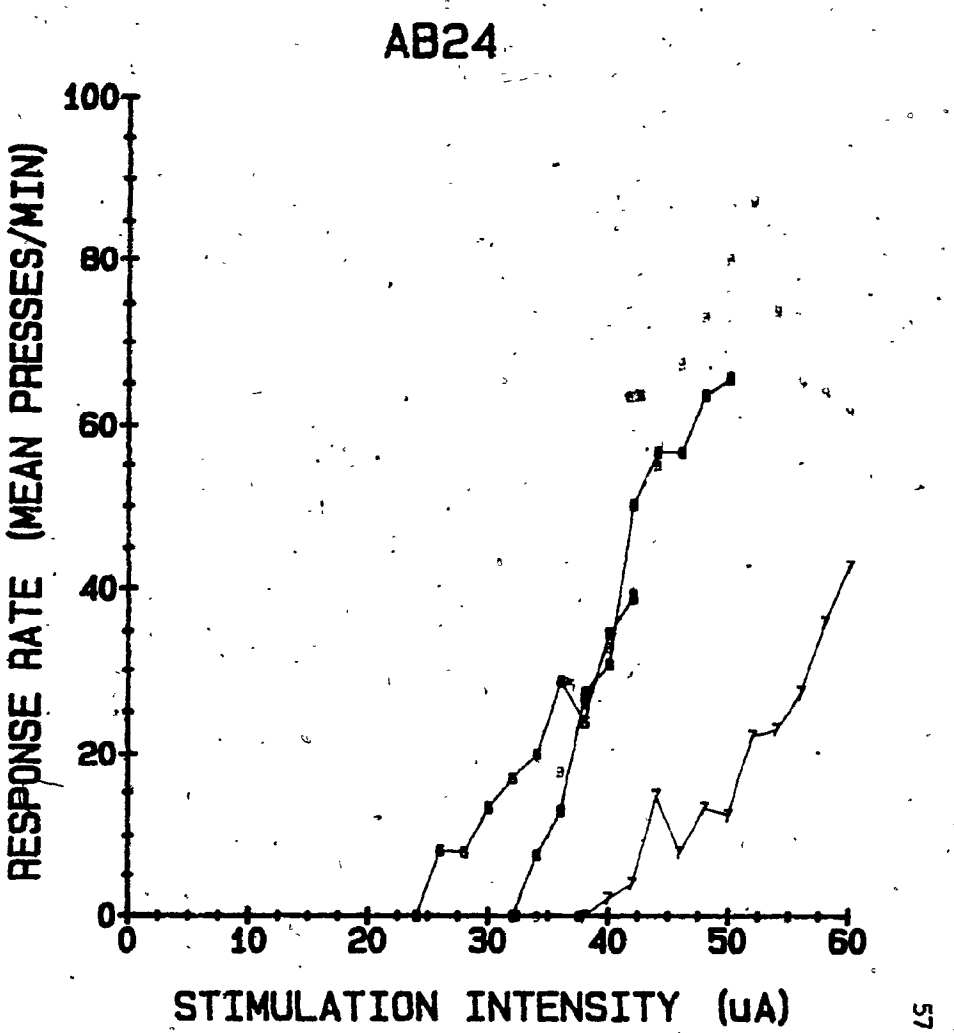
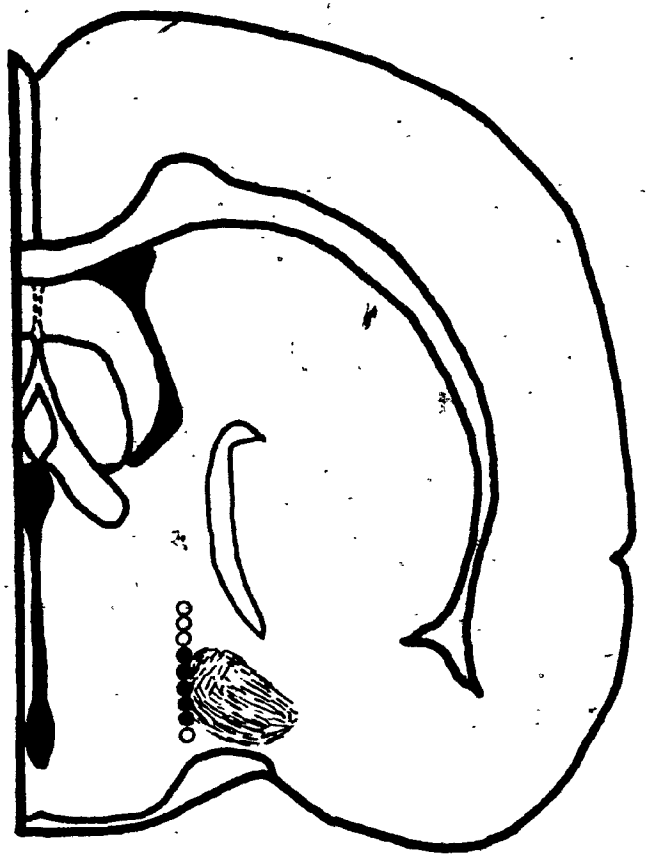
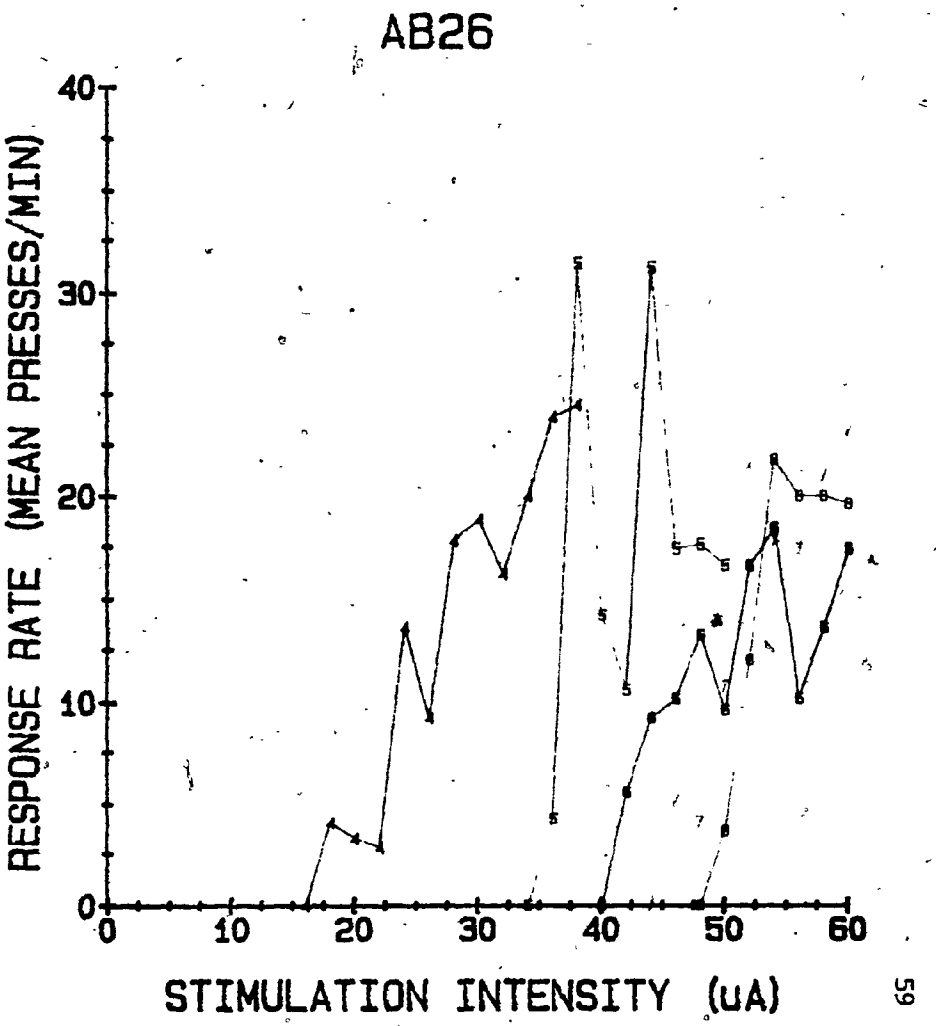

AB24
RESPONSE RATE (MEAN PRESSES/MIN)
100
80
60
40
20
0
0
10
20
30
40
50
60
STIMULATION INTENSITY (uA)

FIGURE 10. Mapping data for rat AB26. Left panel shows the histological reconstruction of stimulation sites at 1.0 mm anterior to Bregma. Positive sites are differentiated by different colors and negative sites are illustrated with open circles. The right panel shows the mean rate-intensity curve for each stimulation site. Curves correspond to stimulation sites on the left panel by colors and by numerical symbols.

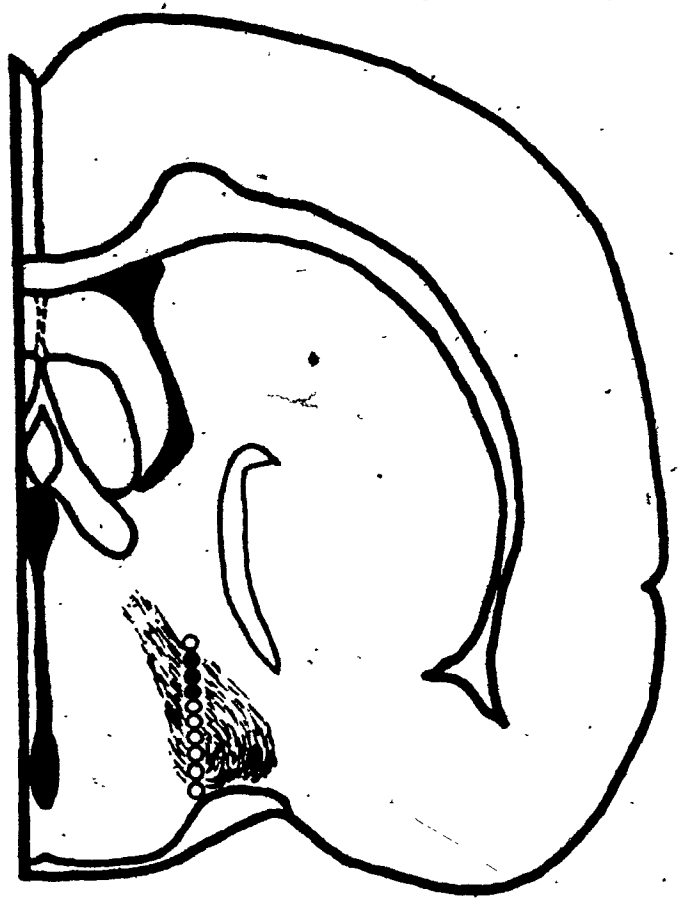



AB26
RESPONSE RATE (MEAN PRESSES/MIN)
0
10
20
30
40
0
10
20
30
40
50
60
STIMULATION INTENSITY (uA)

containing reward sites did not show good correspondence with the medial boundaries of the myelinated tissue of the stria medullaris. For example, consider the most medial electrode penetration through the stria medullaris. Positive sites were found when the electrode tip was in the dorsal portion of the stria medullaris, while negative sites were found as the electrode tip penetrated the more ventral portion of the stria (See Figure 11). One rat did not lever-press for stimulation in the stria medullaris (See Figures 12 and 13). The most lateral electrode penetration at the level of the stria medullaris was still within the myelinated region and was positive for self-stimulation.

Stimulation was rewarding when electrode tips were in the lateral preoptic area and the diagonal band of Broca (See Figures 1 and 2). The sites in the region of the lateral preoptic area at which stimulation began to have reinforcing properties corresponded with the dorsal portion of the lateral preoptic area. Stimulation was rewarding at all sites that were within the anatomical boundaries of the lateral preoptic area. Stimulation was not rewarding at sites that were dorsal or ventral to the lateral preoptic area (See Figure 14). Stimulation was rewarding when electrode tips were dorsal to the diagonal band of Broca and when electrode tips were in the diagonal band of Broca. There was one rat that did not lever-press for stimulation at several different sites within the

FIGURE 11. Mapping data for rat AB22. Left panel shows the histological reconstruction of stimulation sites at 1.0 mm anterior to Bregma. Positive sites are differentiated by different colors and negative sites are illustrated with open circles. The right panel shows the mean rate-intensity curve for each stimulation site. Curves correspond to stimulation sites on the left panel by colors and by numerical symbols.



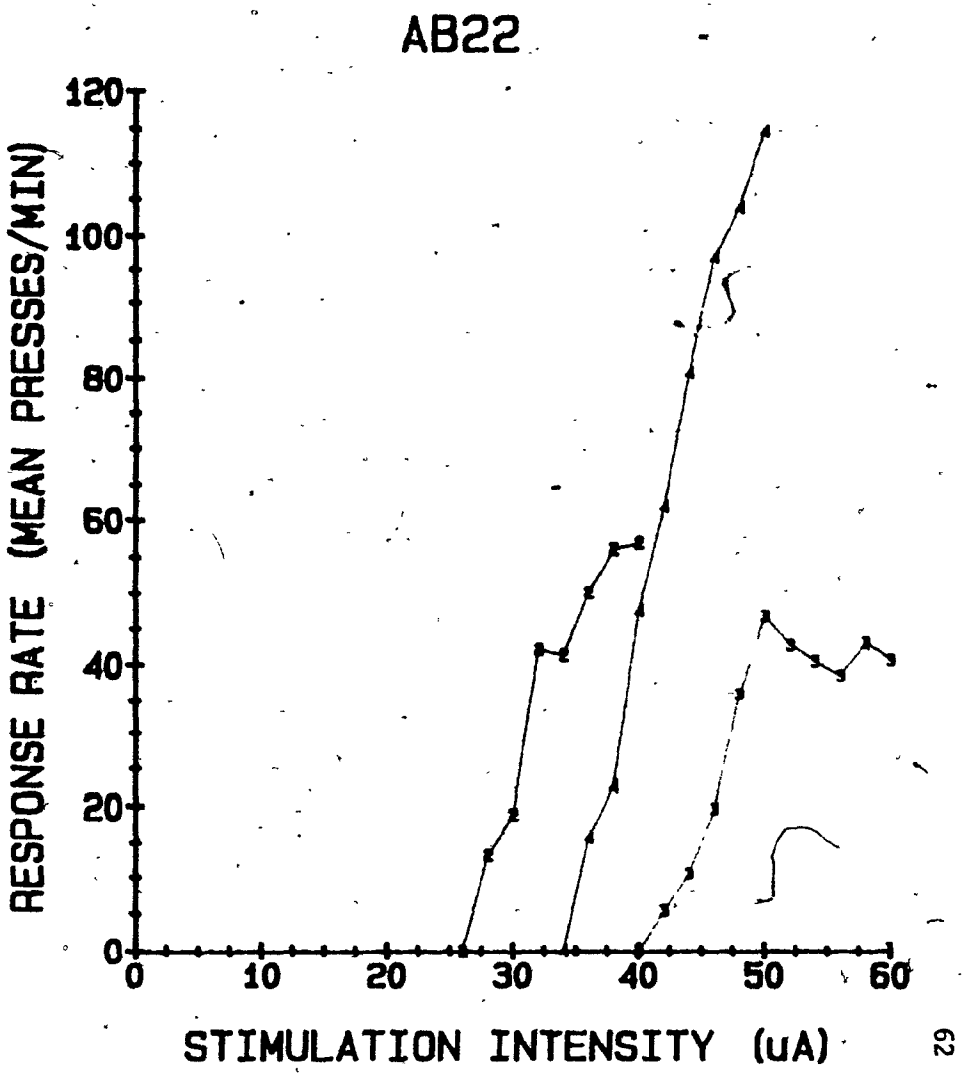
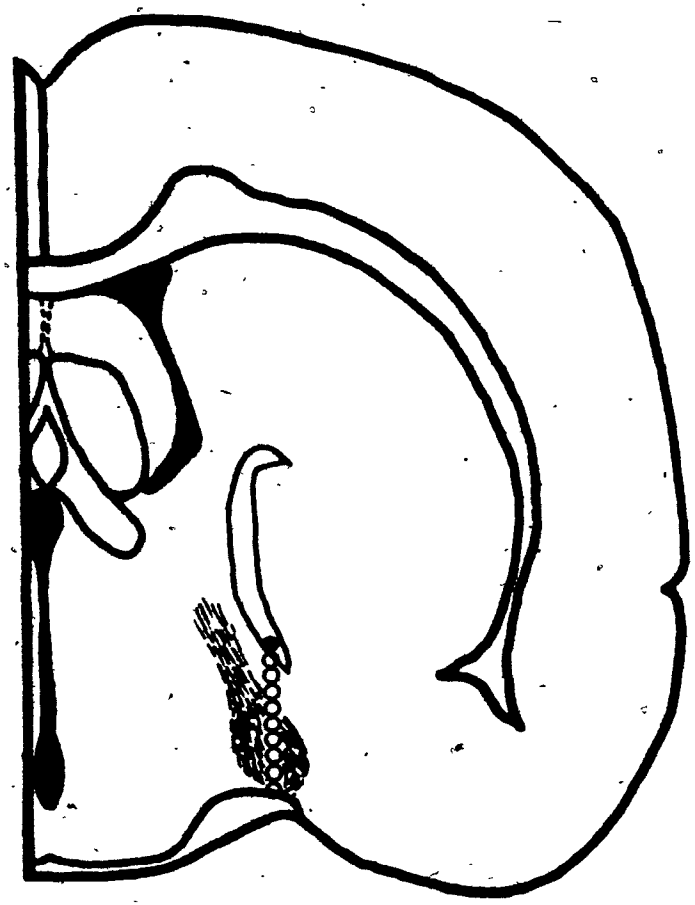

AB22
RESPONSE RATE (MEAN PRESSES/MIN)
120
100
80
60
40
20
0
0
10
20
30
40
50
60
STIMULATION INTENSITY (uA)

FIGURE 12. Mapping data for rat AB6. Left panel shows the histological reconstruction of stimulation sites at 1.0 mm anterior to Bregma. Positive sites are differentiated by different colors and negative sites are illustrated with open circles. The right panel shows the mean rate-intensity curve for each stimulation site. Curves correspond to stimulation sites on the left panel by colors and by numerical symbols.



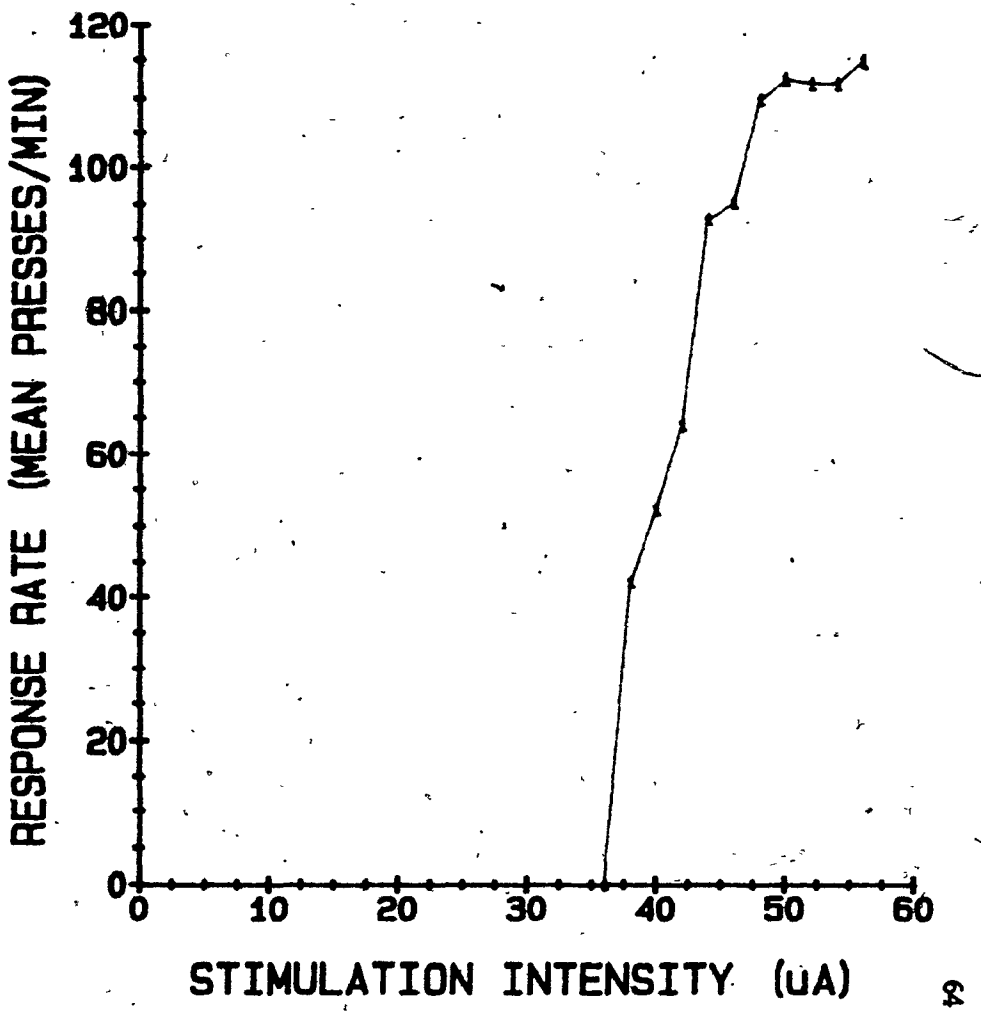
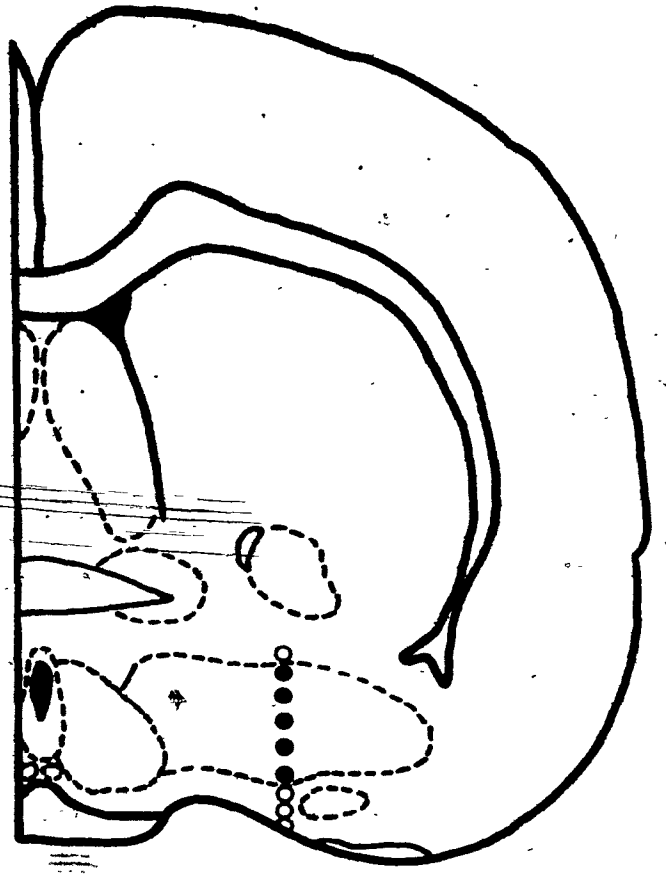
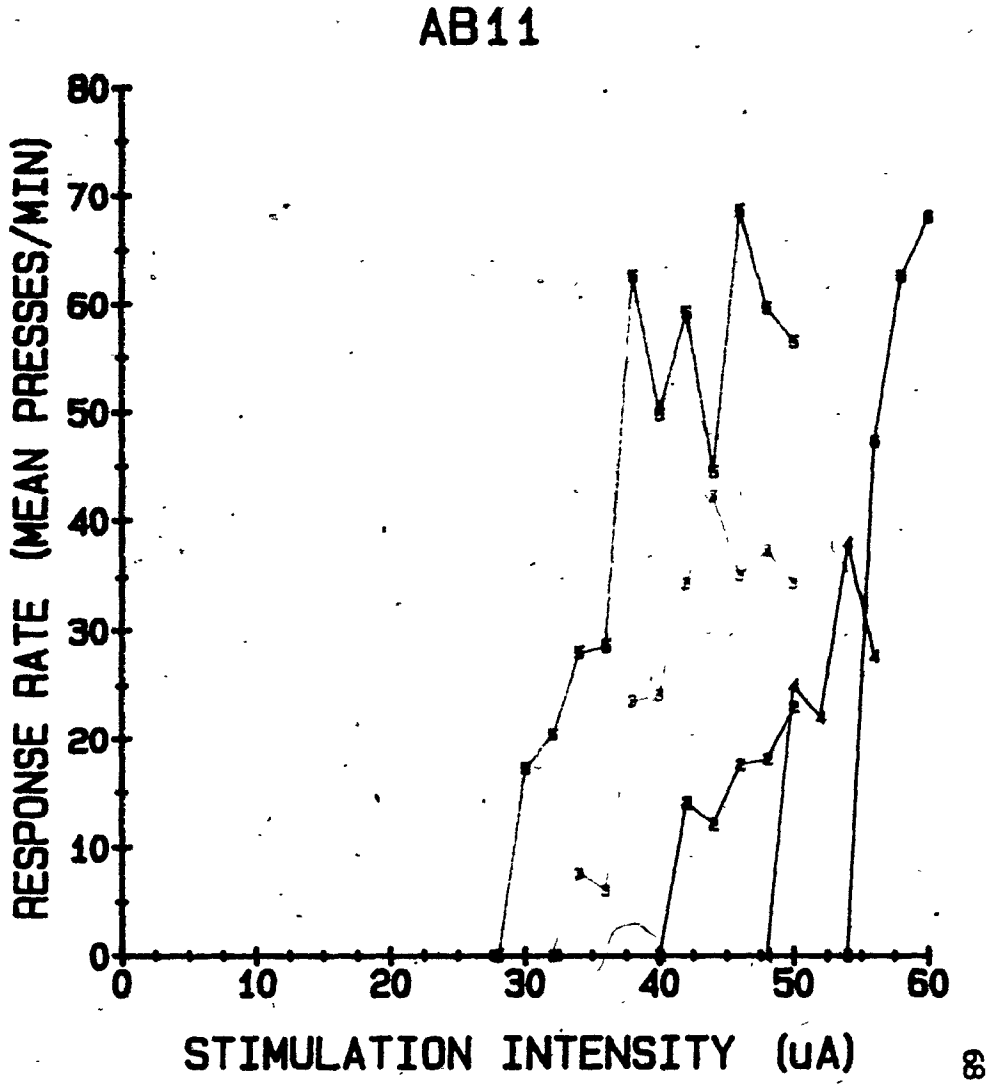

AB6
RESPONSE RATE (MEAN PRESSES/MIN)
120
100
80
60
40
20
0
0
10
20
30
40
50
60
STIMULATION INTENSITY (uA)

FIGURE 13. Rat AB6. Photomicrograph of the coronal section in which the electrode track was visible. The tip of the electrode was just ventral to the stria medullaris.

FIGURE 14. Mapping data for rat AB11. Left panel shows the histological reconstruction of stimulation sites at 1.8 mm anterior to Bregma. Positive sites are differentiated by different colors and negative sites are illustrated with open circles. The right panel shows the mean rate-intensity curve for each stimulation site. Curves correspond to stimulation sites on the left panel by colors and by numerical symbols.




AB11
RESPONSE RATE (MEAN PRESSES/MIN)
0
10
20
30
40
50
60
70
80
0
10
20
30
40
50
60
STIMULATION INTENSITY (uA)

diagonal band of Broca (See Figure 15).

Stimulation was rewarding when electrode tips were in the medial and lateral septal areas (See Figures 1, 5 and 16). Stimulation thresholds were lower when electrode tips were in the lateral septal area than when electrode tips were in the medial septal area. Stimulation at sites just lateral to the lateral septal area was not rewarding.

Stimulation at sites just medial to the myelinated tissue of the stria medullaris was rewarding (See Figures 4, 17, 18 and 19) Most of the threshold values were within the range of 31 to 40 uA. Stimulation was not rewarding at 7 sites just dorsal to the positive sites and at 33 sites immediately medial to the positive sites. Some of these negative sites were in the anterior hypothalamic area and others were possibly in the arcuate nucleus of the hypothalamus. Stimulation at all of the negative sites did not produce any observable signs of aversion, motoric difficulties or seizures.

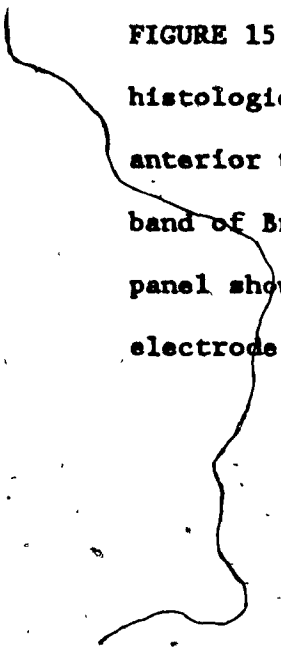
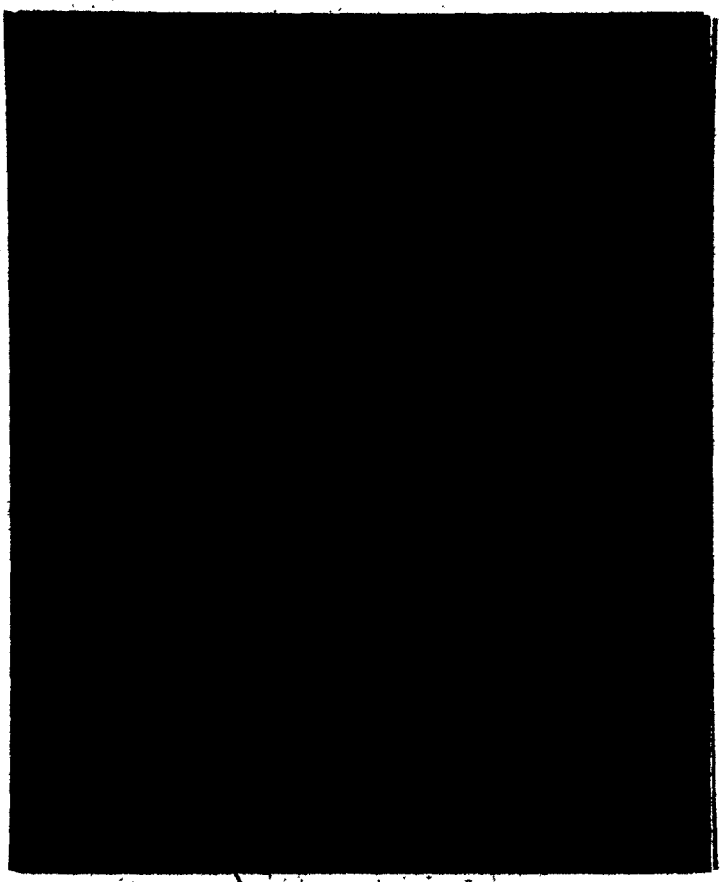


FIGURE 15. Mapping data for rat AB39. Left panel shows the histological reconstruction of stimulation sites at 2.4 mm anterior to Bregma. Negative stimulation sites in the diagonal band of Broca are illustrated with open black circles. The right panel shows a photomicrograph of the coronal section in which the electrode track was visible.



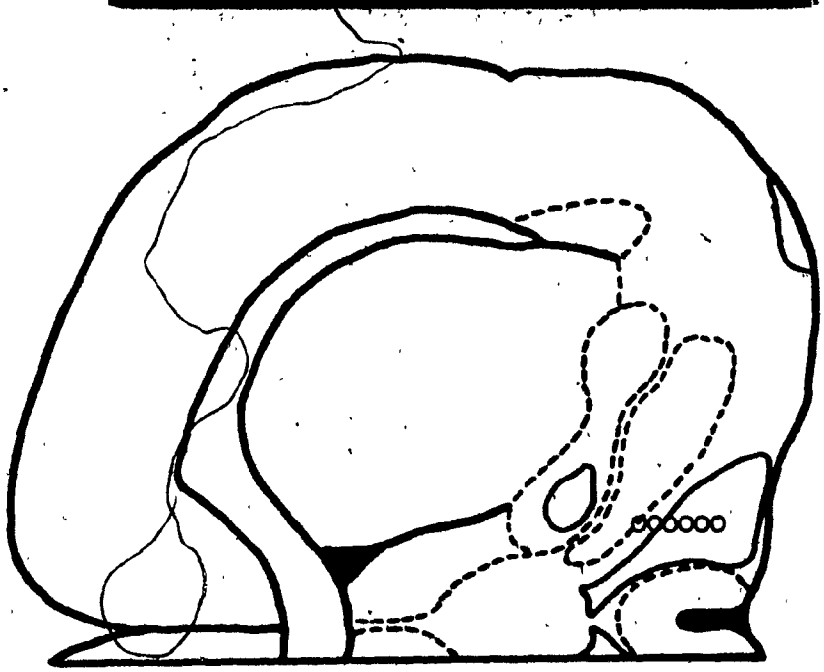
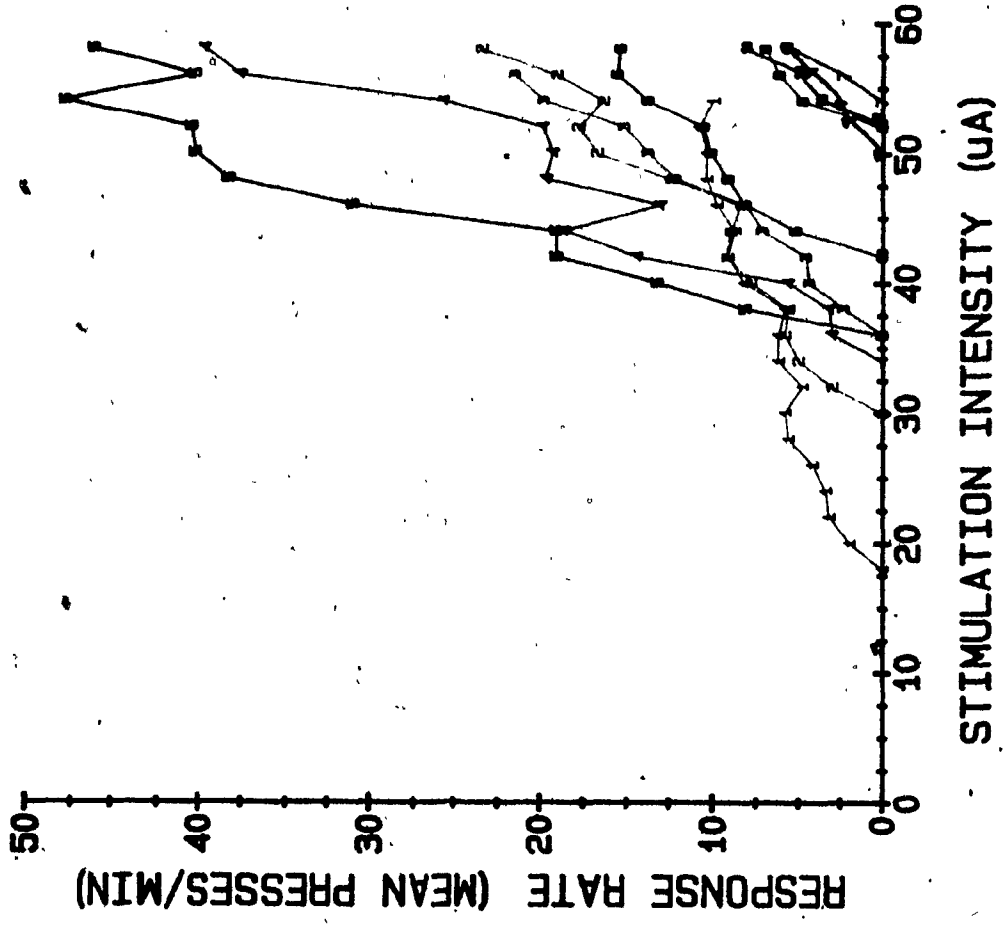


FIGURE 16. Mapping data for rat CP7. Left panel shows the histological reconstruction of stimulation sites at 2.4 mm anterior to Bregma. Positive sites are differentiated by different colors and negative sites are illustrated with open circles. The right panel shows the mean rate-intensity curve for each stimulation site. Curves correspond to stimulation sites on the left panel by colors and by numerical symbols.


CP7
RESPONSE RATE (MEAN PRESSES/MIN)
0
10
20
30
40
50
STIMULATION INTENSITY (uA)
0
10
20
30
40
50
60

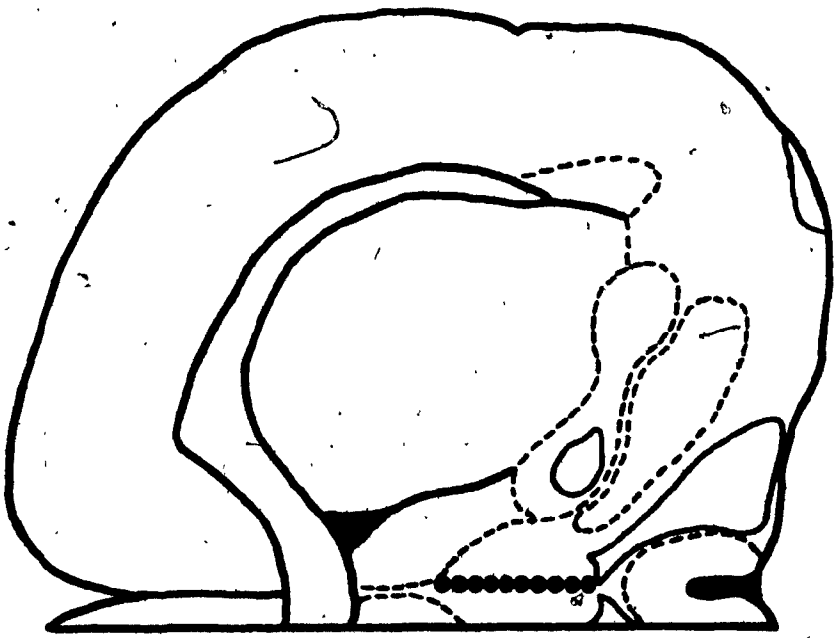
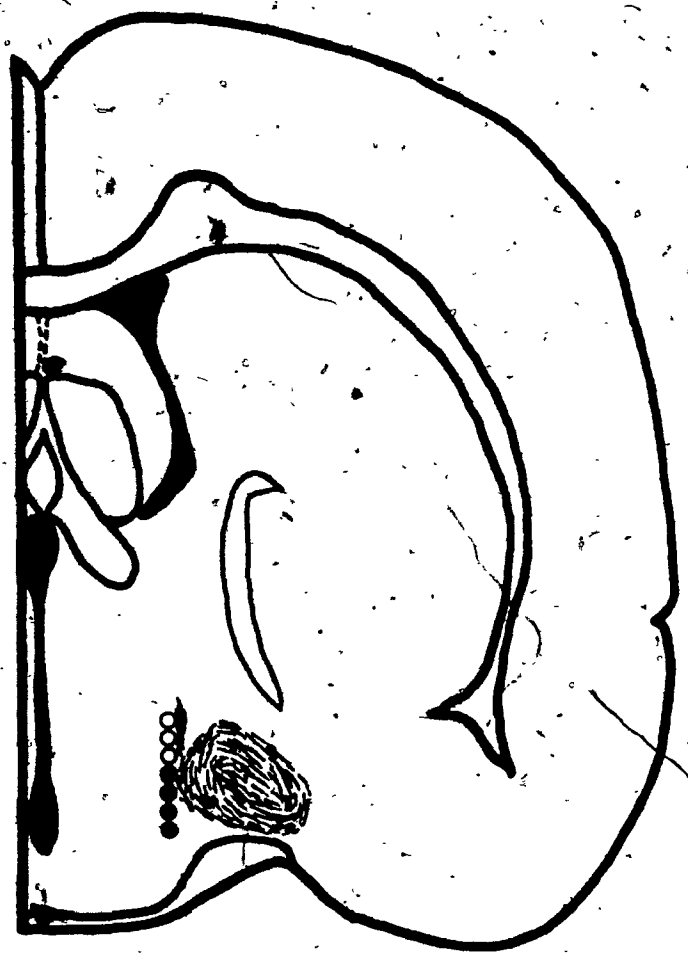


FIGURE 17. Mapping data for rat AB35. Left panel shows the histological reconstruction of stimulation sites at 1.0 mm anterior to Bregma. Positive sites are differentiated by different colors and negative sites are illustrated with open circles. The right panel shows the mean rate-intensity curve for each stimulation site. Curves correspond to stimulation sites on the left panel by colors and by numerical symbols.



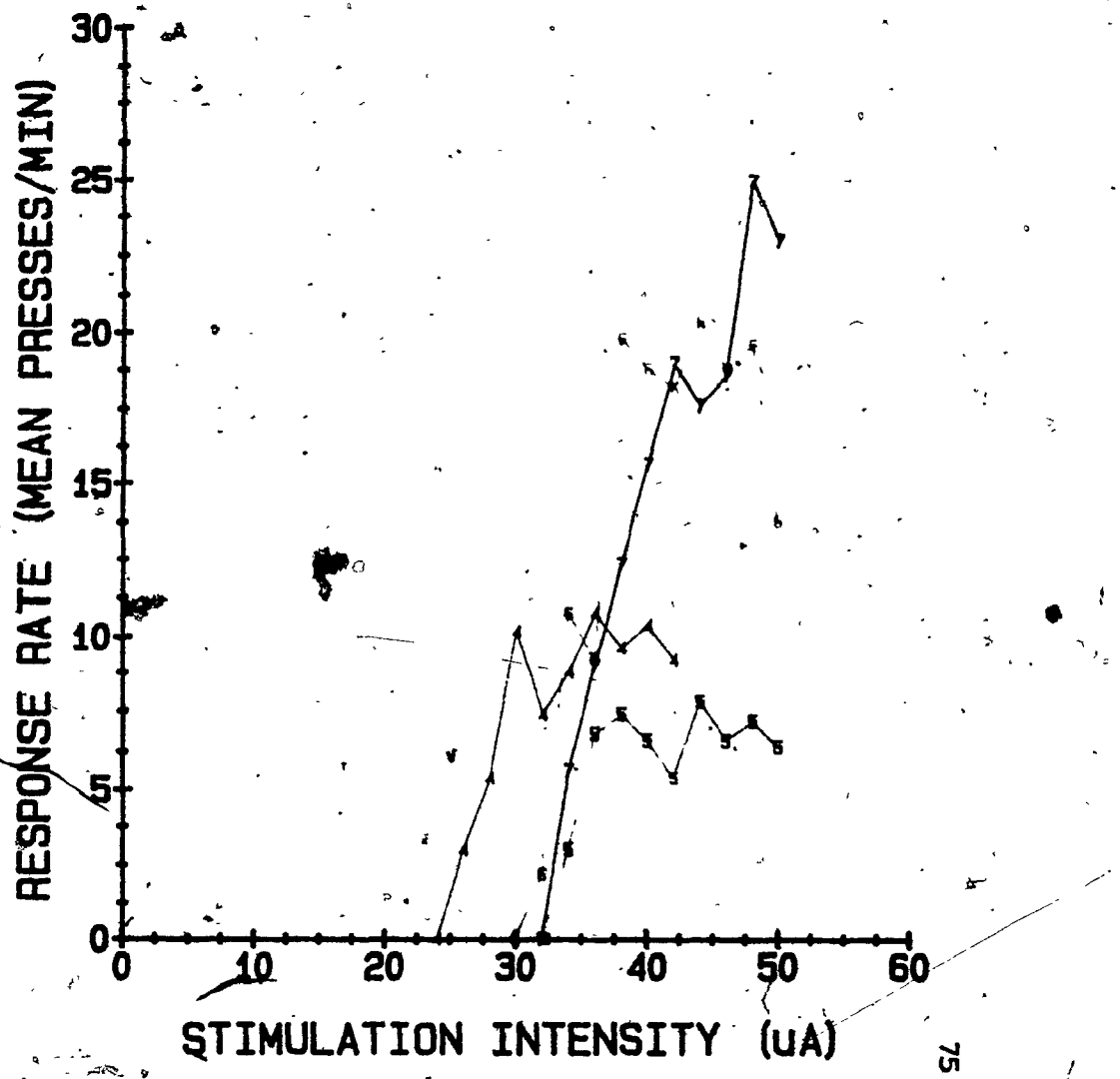

AB35
RESPONSE RATE (MEAN PRESSES/MIN)
0
5
10
15
20
25
30
0
10
20
30
40
50
60
STIMULATION INTENSITY (uA)

FIGURE 18. Rat AB35. Photomicrograph of the coronal section in which the electrode track was visible. The tip of the electrode was just medial to the stria medullaris.

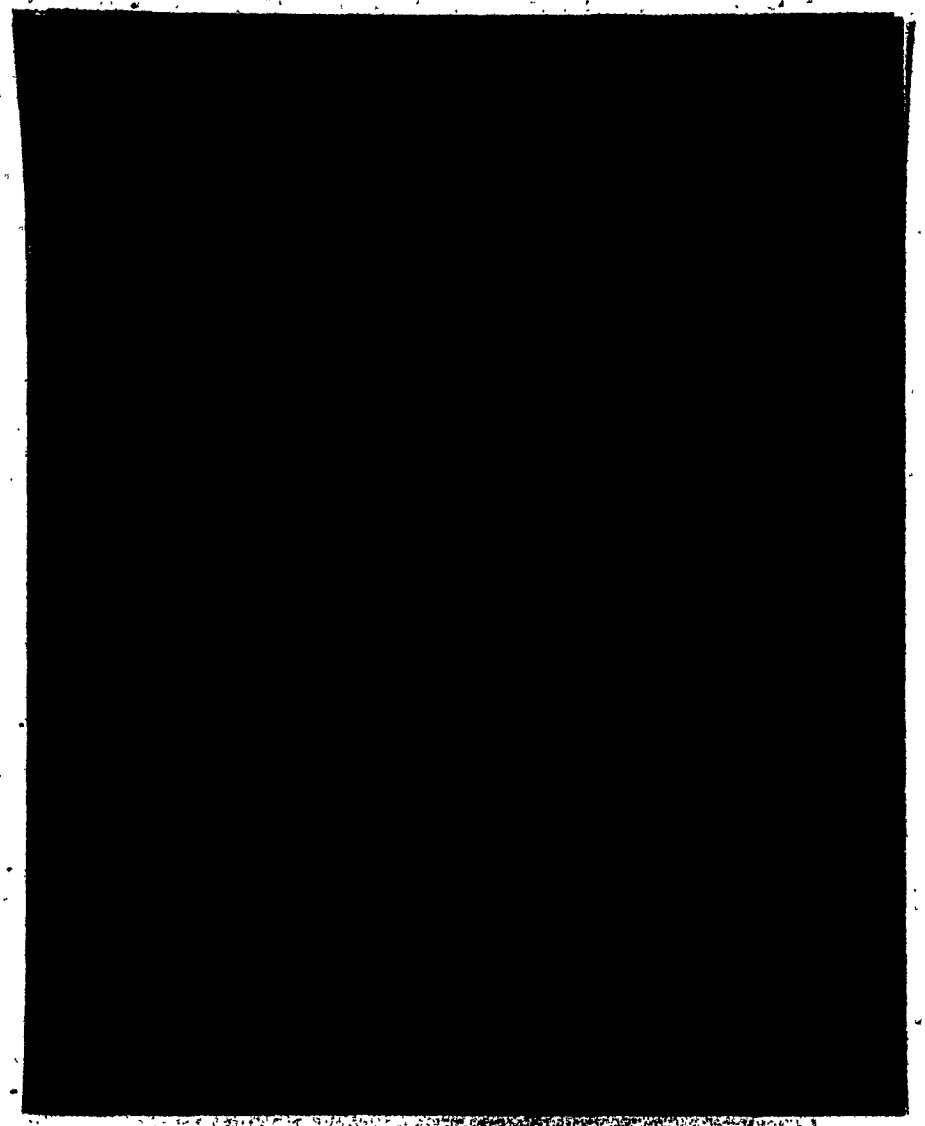
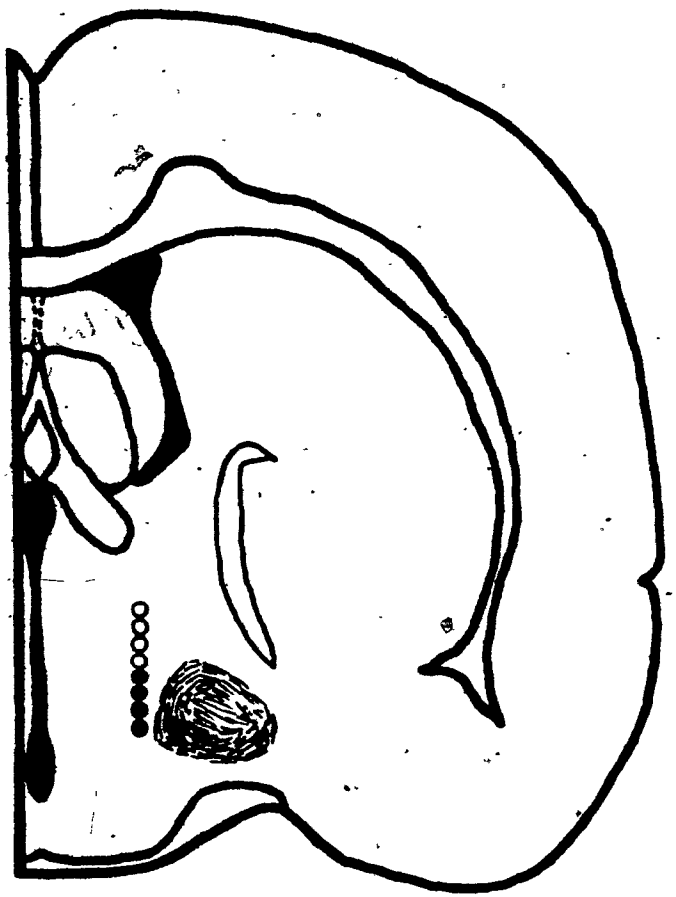
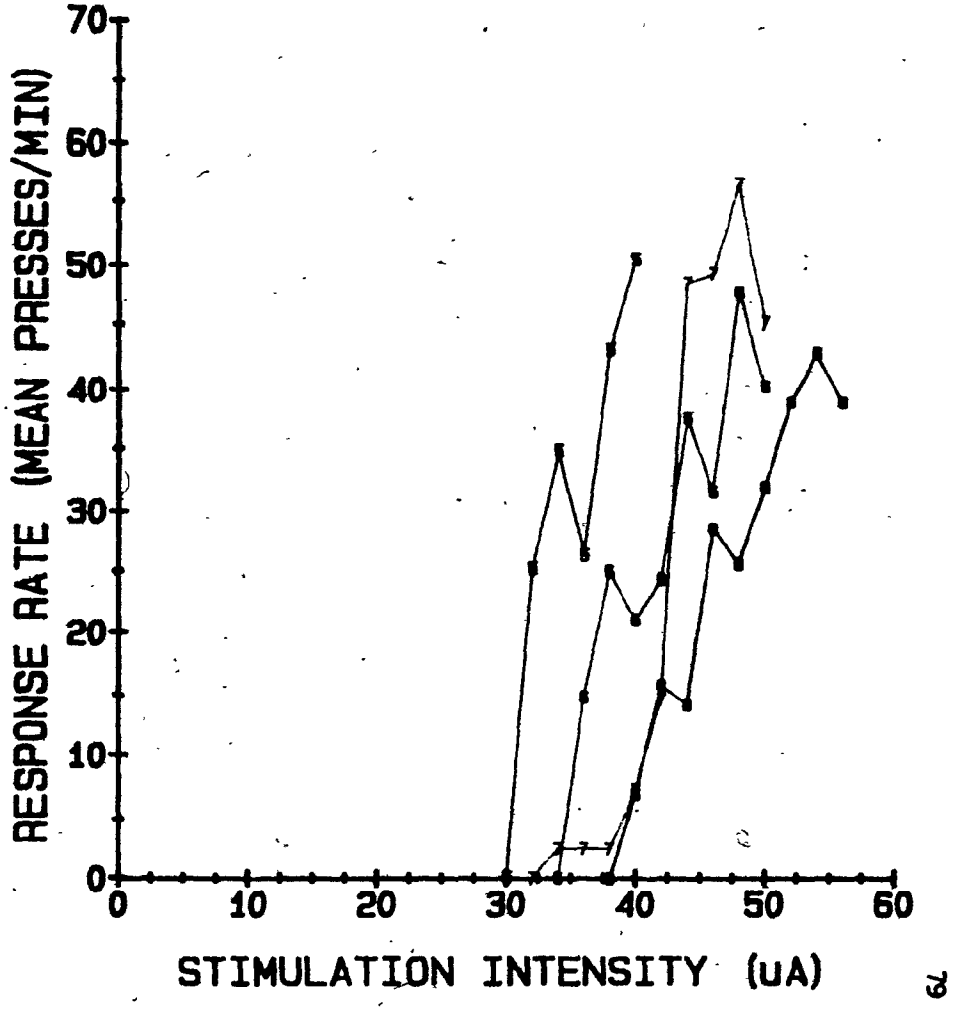


FIGURE 19. Mapping data for rat AB21. Left panel shows the histological reconstruction of stimulation sites at 1.0 mm anterior to Bregma. Positive sites are differentiated by different colors and negative sites are illustrated with open circles. The right panel shows the mean rate-intensity curve for each stimulation site. Curves correspond to stimulation sites on the left panel by colors and by numerical symbols.




AB21
RESPONSE RATE (MEAN PRESSES/MIN)
0
10
20
30
40
50
60
70
STIMULATION INTENSITY (uA)

DISCUSSION

The data from the present thesis suggest that the diencephalic reward fibers do not arise from a single, anatomically restricted group of cell bodies at the head of the medial forebrain bundle. At the most rostral level tested in the medial forebrain bundle, positive sites for brain stimulation reward were found as near as 0.25 mm to the midline, in the medial septal area and as far as 4.0 mm lateral to the midline, in the amygdala. Thus the various contributions to medial forebrain bundle reward circuitry may be widely dispersed in the anterior medial forebrain bundle. The wide medial-lateral dispersion of positive sites found in the anterior medial forebrain bundle suggests that there are first-stage fibers projecting to or from several independent rostral regions. In comparison, at the most caudal level tested in the medial forebrain bundle, positive sites for brain stimulation reward were found as near as 0.75 mm to the midline and as far as 2.0 mm lateral to the midline. Stimulation was not rewarding when electrode tips were medial to 0.75 mm from the midline. The medial-lateral dispersion of positive sites at an even more caudal level (lateral hypothalamic area) in the medial forebrain bundle ranges from 1.0 mm - 2.75 mm from the midline (Gratton & Wise, 1983). Thus the various contributions to medial forebrain bundle reward circuitry appear to be less widely dispersed at the level of the lateral hypothalamic area. The present data may

explain a recent study by Stellar and Neeley (1982) who showed that a lesion at a caudal level of the medial forebrain bundle fully disrupted reward from a rostral level of the medial forebrain bundle, while a lesion at the rostral level of the medial forebrain bundle just partially disrupted reward from the caudal level of the medial forebrain bundle. It is possible that the rostral lesion damaged only a part of the widely dispersed anatomical contributions to the medial forebrain bundle reward system(s). Given the wide medial-lateral dispersion of positive sites found in the rostral medial forebrain bundle, it seems likely that there are at least two and perhaps more anatomically distinct contributions to medial forebrain bundle reward circuitry.

A second major finding was that positive sites were found in a continuous progression between 1.0 mm and 2.8 mm anterior to Bregma. The finding of a continuous progression of positive sites from the level of the anterior hypothalamic area to the more rostral levels of the medial forebrain bundle suggests, though it does not prove, anatomical connection between the reward fibers at these different levels. Stimulation at some of the positive sites in the anterior medial forebrain bundle may be activating reward fibers that project down past the lateral hypothalamic area, contributing to self-stimulation in this area.

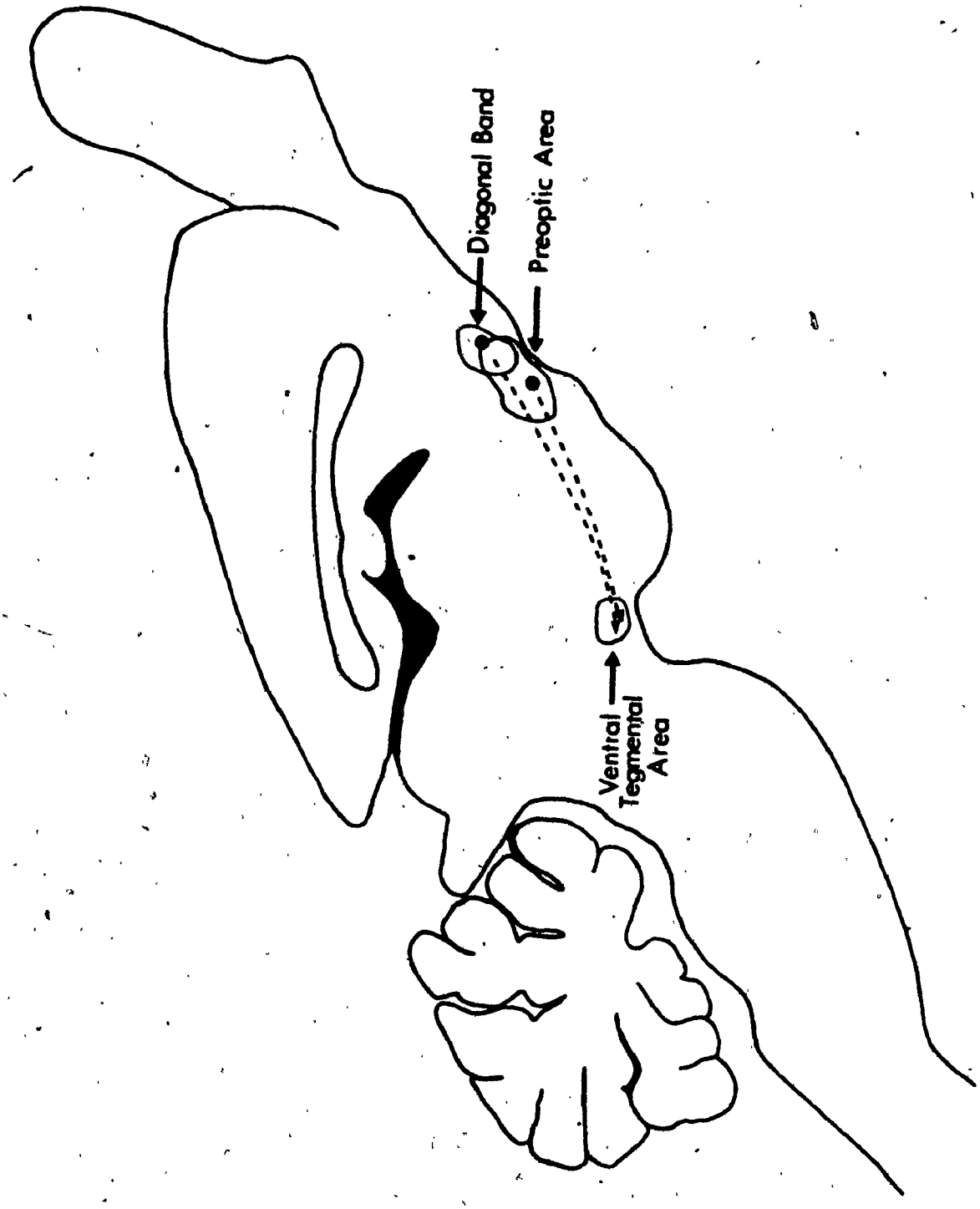
Similarly, a continuous progression of reward sites has been found between the level of the lateral hypothalamic area and the

level of the ventral tegmental area (Corbett & Wise, 1980; Gratton & Wise, 1983). It has been shown by "collision" tests that at least a portion of the lateral hypothalamic reward system depends on the same axons that are involved in ventral tegmental reward (Shizgal et al., 1980). The possibility that stimulation at some of the reward sites in the anterior medial forebrain bundle activates the same axons as are involved in lateral hypothalamic and ventral tegmental reward is consistent with the views of several investigators (Gallistel et al., 1981; Yeomans, 1982; Gallistel, Gomita, Yadin, & Campbell, 1985; Rompré & Shizgal, 1986). Figure 20, based on Yeomans (1982) illustrates the working hypothesis of these workers.

The finding of continuity of self-stimulation is not inconsistent with the view that more than one set of medial forebrain bundle fibers contributes to brain stimulation reward. Continuity in the anterior-posterior plane may reflect more than one set of caudally or rostrally projecting first-stage systems.

Of the number of regions in the anterior medial forebrain bundle where stimulation was rewarding, the regions containing myelinated fibers that pass near the lateral hypothalamic area and the ventral tegmental area were of particular interest, because of the implications of refractory period (Yeomans, 1975) and conduction velocity (Bielajew & Shizgal, 1982) studies. The myelinated fibers that are of particular interest include

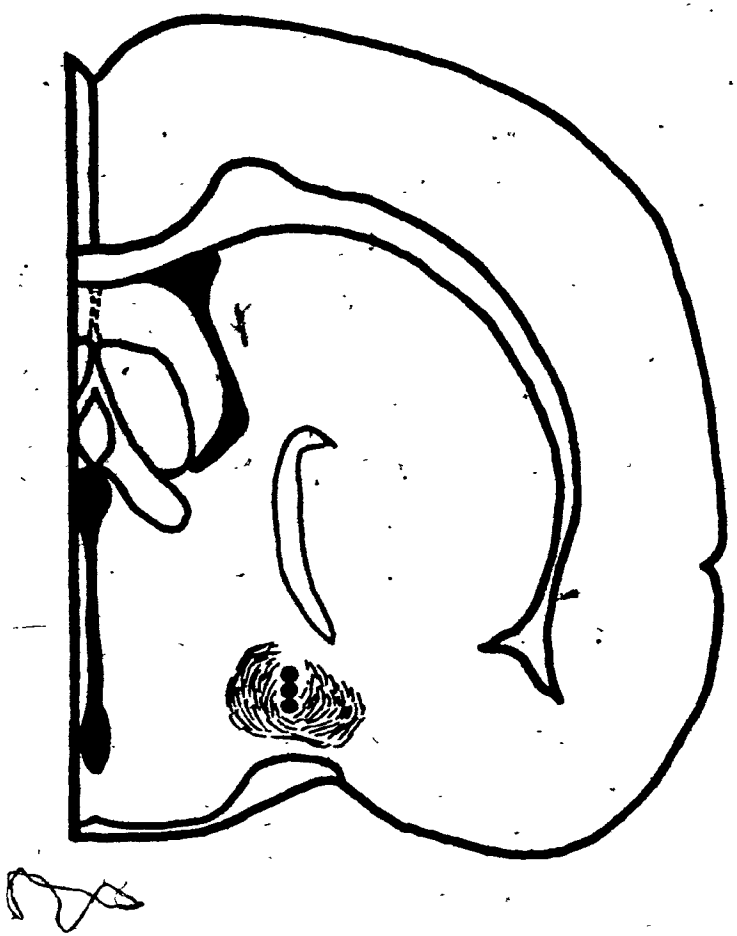
FIGURE 20. Diagram of the model of cells and axons mediating medial forebrain bundle reward (Yeomans, 1982).


Diagonal Band
Preoptic Area
Ventral Tegmental Area

those of the stria medullaris, the diagonal band of Broca and the fornix.

The myelinated fibers of the stria medullaris are interesting since nearly all sites tested in this fiber bundle were positive for self-stimulation. Stimulation at many of these sites produced very high rates of lever pressing. Self-stimulation was not found when electrode tips were immediately dorsal to the myelinated region, but was found as these tips were lowered into this region (See Figures 7,8,9 and 10). The ventral boundary of the reward system was reached as the electrode tips reached the ventral boundary of the stria medullaris. There were three further rats whose electrode sites were clearly in the stria medullaris, however there were not enough sites tested in these rats to determine the dorsal or ventral boundaries of the system (See Figure 21 and 22). There was one rat that did not lever-press for stimulation at 6 sites in the stria medullaris. This rat was tested for brain stimulation reward at 10 sites in total. Lever-pressing was found at the most dorsal site, however no further lever-pressing was found (See Figures 12 and 13). It is not clear why this rat failed to work for stimulation at 6 sites in the stria medullaris, particularly since the rat had shown the ability to learn the task at the most dorsal site. The fact that all other rats worked for stimulation at all sites in the stria medullaris together with the fact that rats did not work for stimulation at sites immediately dorsal or ventral to the stria medullaris makes

FIGURE 21. Mapping data for rat AB20. Left panel shows the histological reconstruction of stimulation sites at 1.0 mm anterior to Bregma. Positive sites are differentiated by different colors and negative sites are illustrated with open circles. The right panel shows the mean rate-intensity curve for each stimulation site. Curves correspond to stimulation sites on the left panel by colors and by numerical symbols.



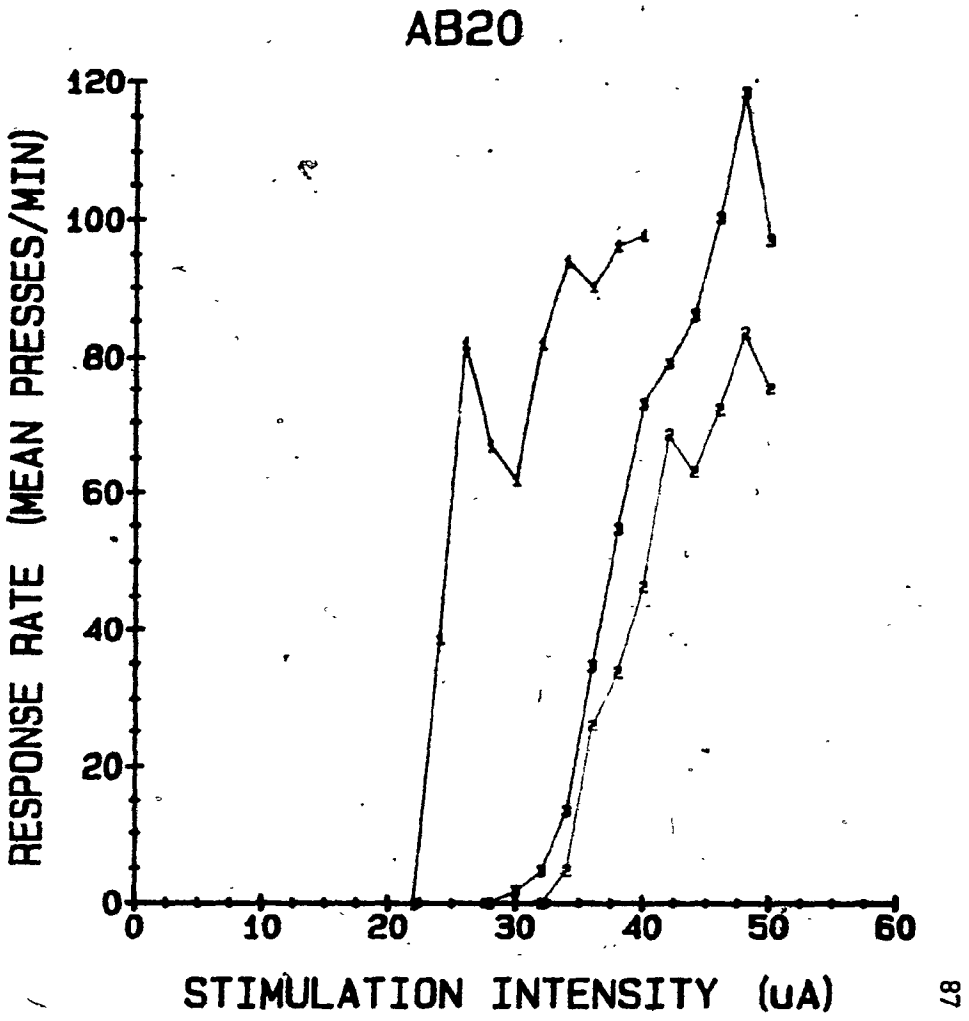

AB20
RESPONSE RATE (MEAN PRESSES/MIN)
120
100
80
60
40
20
0
0
10
20
30
40
50
60
STIMULATION INTENSITY (uA)

FIGURE 22. Rat AB20. Photomicrograph of the coronal section in which the electrode track was visible. The tip of the electrode was in the stria medullaris.

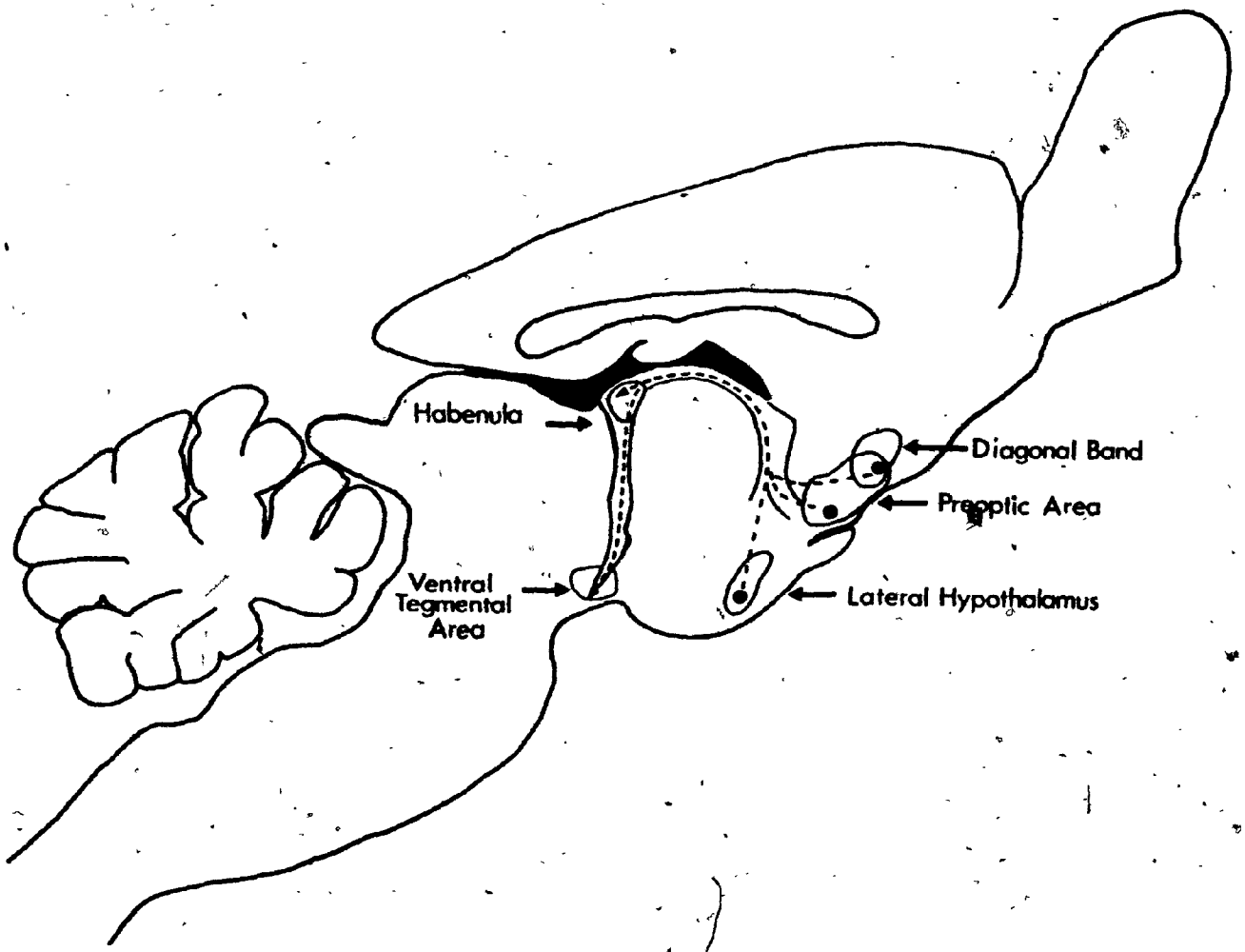
it appear that there are first-stage reward fibers in the stria medullaris.

It is interesting to speculate as to what role stria medullaris fibers might play in lateral hypothalamic or ventral tegmental self-stimulation. Might the stria medullaris fibers contribute to brain stimulation reward at the levels of the lateral hypothalamic area and the ventral tegmental area, or do the stria medullaris fibers make up a reward mechanism that is independent of these areas?. While the stria medullaris fibers do not follow the same trajectory as the medial forebrain bundle of fibers, some of the fibers of the stria medullaris do project to the ventral tegmental area. Stria medullaris fibers that course in a rostro-caudal direction have cell bodies in such regions as the vertical limb of the nucleus of the diagonal band of Broca, the horizontal limb of the nucleus of the diagonal band of Broca, the interstitial nucleus of the stria terminalis, the lateral preoptic area nucleus and the medial septal area nucleus (Niewenhuys et al., 1982; Marchand, Riley, & Moore, 1980; Meibach & Seigel, 1977; Gottesfeld & Jacobowitz, 1979). From these regions, stria medullaris fibers travel dorsally and caudally to the region of the habenular nuclei where some fibers appear to terminate (Niewenhuys et al., 1982) but others turn ventrally to terminate in the ventral tegmental area (Marchand et al., 1980) or the interpeduncular nucleus (Gottesfeld et al., 1979). Some stria medullaris fibers have cell bodies in the lateral hypothalamic area (Yamadori, 1969; Berk & Finkelstein,

1982). These fibers course rostrally to enter the stria medullaris, then turn dorsally and caudally toward the habenula. The major contributions to and terminations of the stria medullaris are shown in Figure 23. Stimulation at sites in many of the cell body regions and regions of termination of stria medullaris fibers has been shown to be rewarding. These regions include the diagonal band of Broca, lateral preoptic area (present study; Olds, 1956), medial septal area (present study; Valenstein & Campbell, 1966), lateral habenula (Sutherland & Nakajima, 1981; Gomita & Gallistel, 1982) and the ventral tegmental area (Corbett & Wise, 1980). Thus fibers of the stria medullaris are very likely to mediate rewarding effects of stimulation at a number of sites, including some of the classic reward sites in the medial forebrain bundle.

Stimulation was also rewarding at many of the sites tested within the boundaries of the myelinated fibers of the diagonal band of Broca. The range of threshold values associated with sites in these myelinated fibers was 31 to 49 uA. One rat did not lever-press for stimulation at sites in the diagonal band of Broca (See Figure 15). The finding of positive sites in the myelinated fibers of the diagonal band of Broca is consistent with the suggestion of Yeomans (1982) that a portion of the first stage-fibers involved in medial forebrain bundle reward has cell bodies in the nuclei of the diagonal band of Broca. It has also been demonstrated that rewarding medial forebrain bundle stimulation elevates glucose utilization in the cells of the

FIGURE 23. Diagram of the major origins and terminations of the stria medullaris fibers.


Habenula
Diagonal Band
Preoptic Area
Ventral Tegmental Area
Lateral Hypothalamus

diagonal band of Broca (Gallistel et al., 1985).

Stimulation in the fornix was not rewarding. Rats did not lever-press for stimulation when electrode tips were in the densely myelinated fibers of the fornix; however lever-pressing was observed as the electrode tip penetrated below the ventral boundary of these fibers (See Figures 17 and 18). The present data are inconsistent with the data of Brown and Winocur (1973) who argued that stimulation in the ventral fornix was rewarding. In Brown and Winocur's study, rats were implanted with one fixed electrode in the fornix and another just lateral to the fornix in the medial forebrain bundle. Stimulation at sites in the fornix and at sites in the medial forebrain bundle were each rewarding. Due to the proximity of these two fiber bundles, it is possible that electrode tips aimed at the fornix were in the medial forebrain bundle. This possibility might explain the discrepancy between the results in the present study and the results in the study by Brown and Winocur (1973). A subsequent finding in their study, however, was that lever-pressing for stimulation at sites in the fornix and in the medial forebrain bundle was differentially affected following septal lesions. Since fibers in the fornix originate in the septum, it would appear that Brown and Winocur's finding of fornix reward was due, at least in part, to the activation of fornix fibers. There is no obvious explanation for the discrepancy between the findings of Brown and Winocur and those of the present study.

Stimulation at each of the sites in the medial and the lateral septal areas was rewarding. Thresholds at sites in the lateral septal area were lower than thresholds at sites in the medial septal area, in agreement with Prado-Alcala and Wise (1984). Rats did not lever-press for stimulation at sites that were just lateral to the septal area. Fibers that have their cell bodies in the lateral septal area and the medial septal area both enter the medial forebrain bundle to terminate in such regions as the lateral hypothalamic area and the ventral tegmental area. The fact that stimulation at sites in the septal areas was rewarding, together with the fact that septal fibers enter the medial forebrain bundle of fibers, suggests that reward fibers from the septal area contribute to the medial forebrain bundle reward system.

Two rats lever-pressed reliably for stimulation at a total of 8 sites in gray matter just medial to the stria medullaris. (See Figures 17, 18 and 19). These sites were clearly not in the densely myelinated region of the stria medullaris. One explanation is that these positive sites were in cell bodies that send fibers into the stria medullaris. Another possibility is that stimulation at these sites was activating descending medial forebrain bundle fibers that course from the forebrain to the midbrain.

Summary

Stimulation was rewarding at sites in each of the levels tested in the anterior medial forebrain bundle. The reward sites in the anterior medial forebrain bundle were more dispersed medial-laterally than the reward sites in the lateral hypothalamus. The fact that stimulation was rewarding at a wider range of medial-lateral sites in the more rostral levels of the medial forebrain bundle suggests that more than one rostral nucleus supplies or receives reward fibers of the medial forebrain bundle. Three candidates for such contributions include the stria medullaris, cells or fibers in a medial region involving the septal areas and diagonal band of Broca and cells or fibers in a far lateral region involving the amygdala. Fibers from these three or more regions may converge into one dense reward system or may each be involved in separate reward systems.

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