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Electrically Elicited Feeding: Dissociation From 'natural' Feeding And Catecholamine Involvement

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ELECTRICALLY ELICITED FEEDING: DISSOCIATION FROM 'NATURAL' FEEDING AND CATECHOLAMINE INVOLVEMENT

by

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ABSTRACT

There is a continuing controversy over the essential nature of electrically elicited eating and its relationship to "normal" eating. In the first study the majority of electrode sites (62%) maintained elicited eating only despite a procedure which favoured the occurrence of elicited drinking through the removal of food as a competing stimulus. Such findings argue against a nonspecific neural system for feeding and drinking in rats but are consistent with the notion of separate - although probably overlapping - neural systems.

The relationship of elicited eating to "normal" eating was examined by lesioning the tissue surrounding the stimulating electrodes and observing the effects on elicited eating and the daily intake of food. Animals with bilaterally effective placements received small symmetrical lesions whereas animals with only one effective placement received asymmetrical lesions. Although electrically elicited eating was abolished in all cases there was no disruption of daily food and water intake or body weight. These two forms of eating can be dissociated with respect to the tissue necessary to maintain these behaviors. It was also observed that the preference for three diets differed

during electrical stimulation as compared to 48 hours of food deprivation. Under deprivation, the diets showed a clear hierarchy (going from least to most preferred) of pellets, wet mash, and high fat diet. With brain stimulation there was no difference between wet mash and the high fat diet, although both were preferred over the pellets.

The nature of elicited eating was further considered through an analysis of the involvement of the catecholamine system in this phenomenon. Since lesion work had implicated the nigrostriatal bundle in feeding, stimulating electrodes were implanted in this system in an attempt to obtain elicited ingestive behavior. Electrical stimulation failed to induce ingestion but did elicit forced turning. Catecholamine involvement was also assessed by damaging various components of this system while noting the effects on elicited feeding. Intraventricular injection of 6-hydroxydopamine (6-OHDA) and a monoamine oxidose inhibitor severely disrupted daily food and water intake temporarily. Although food and water intakes completely recovered, electrically elicited feeding continued to be completely abolished. The contributions of the various components of the catecholamine system were assessed by lesioning the dorsal noradrenergic pathway (electrolytic lesions in the locus coeruleus and 6-OHDA into the pathway), the combined dorsal and ventral noradrenergic system, nigrostriatal dopamine pathway, and the ventral periventricular system (all by intracerebral 6-OHDA). Neither unilateral nor two-stage bilateral lesions specifically disrupted elicited eating. It would seem, therefore, that the presence of any one component of the catecholamine system is not necessary for elicited eating although damage to the entire system results in severe disruption. The lesioned animals were subjected to a variety of challenges

designed to highlight more subtle deficits in ingestive behavior. Deficits with intraventricular 6-OHDA were observed but not with the other lesions: this was attributed to the two-stage lesioning procedure.

Pharmacological manipulations further reinforced the involvement of the catecholamine system. Haloperidol was the only blocker to reduce elicited feeding; it did not, however, reduce feeding induced by deprivation. These results also suggest that a functionally intact catecholamine system is necessary for elicited eating but not for deprivation-induced eating.

It would seem that elicited feeding differs from deprivation-induced feeding in a number of ways. Further research should consider the relationship between electrically elicited eating and other "types" of eating.

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ANOVA	analysis of variance
C	centigrade
CA	catecholamine
cm	centimetre
DA	dopamine, dopaminergic
E	voltage
ESB	electrical stimulation of the brain
F	Fahrenheit
g	gram
HFD	high fat diet
hr, hrs	hour, hours
HZ	Hertz
I	current
kg	kilogram
L	lateral
LH	lateral hypothalamus
M	mean
mA	milliampere

MAOI	monoamine oxidase inhibitor
min., mins.	minute, minutes
ml	millilitre
mm	millimetre
N	number
NA	noradrenalin, noradrenergic
NSB	nigrostriatal bundle
P	posterior
p	probability
R	resistance
sec., secs.	second, seconds
6-OHDA	6-hydroxydopamine
2-DG	2-deoxy-D-glucose
V	ventral
VMH	ventromedial hypothalamus
μ	micron
μA	microampere
μg	microgram
μl	microlitre
>	greater than
<	less than

INTRODUCTION

Survival is a complex process. There are many conditions which must be met if the individual is to continue to exist. It is necessary, for example, that the internal environment of the body be held relatively constant, or in other words, that homeostasis be maintained (Cannon, 1932). In order to provide this internal constancy there are a variety of physiological processes which can operate to keep the body's internal environment within the narrow bounds necessary for the critical biochemical events which sustain life. These processes, however, are limited since the body cannot function for long as a self-contained system. It is at this point that the animal's overt behavior becomes important. Through behavior the animal can alter the external environment by seeking out those conditions which will help re-establish the internal environment as when a rat builds a nest in response to a drop in ambient temperature (Kinder, 1927) or when it consumes food following a period of deprivation (e.g., Adolph, 1947). Such regulatory behaviors, of course, are not independent of the internal body regulation but rather closely interact with the physiological processes (LeMagnen, 1971).

A large part of the scientific analysis of feeding behavior--especially that part which has concerned itself with mechanisms--has taken this type of homeostatic view. Animals, as self-regulating adaptive systems, require food both as a source of energy for work and heat production, and as a source of the chemical components necessary for tissue growth and maintenance. Accordingly, complex mechanisms--primarily under the control of the nervous system--have evolved for the initiation of feeding behavior, as well as for regulating the internal processing of nutrients and the expenditure of energy. Generally the neural and endocrine control systems

ensure that food intake approximates energy expenditure in the mature animal as indicated by the relative stability of body weight. This approach of using a systems analysis has been relatively successful in uncovering some of the factors which control feeding (see, for example, Mogenson & Calaresu, 1977). The limitations, however, of analyzing feeding solely in terms of a homeostatic model which stresses internal deficit signals has been noted (LeMagnen, 1967). It has been suggested that brain mechanisms have developed, especially in the higher species with more complex nervous systems, which enable the animal to make adaptive, behavioral responses which anticipate homeostatic deficits.

Conditions Which Induce Feeding

In order to get a better grasp of the area of feeding it would probably be helpful to review some of the conditions under which animals have been induced to eat. It is not intended that this presentation should be exhaustive but rather illustrative of the complexities and diversity involved. Before getting into that, however, a more general point should be made: most mammals feed periodically. If an animal such as the rat is given free access to food it will show cyclic feeding behavior by consuming its food in meals (see Munn, 1950). Under this condition of "spontaneous" feeding, the size of a given meal does not appear to be related to the time since the last meal. However, the amount eaten at a given meal does seem to determine how long the animal will wait until its next bout of feeding; the larger the meal, the longer the pause before eating (LeMagnen, 1971). This observation is quite significant since it suggests that the factors which start a meal are not the ones which stop it. One would predict that an animal would need more food if a long time had elapsed since the last meal, and less food if a short time had elapsed. But the duration of a meal, once started,

appears to be relatively independent of the time since the previous meal; the amount eaten appears to be relatively independent of need. This suggests that other factors, such as taste or the amount of food already in the stomach--and not primarily bodily deficits--determine how much is eaten whereas bodily need determines the onset of feeding.

An obvious way to induce an animal to start feeding is to deprive it of food for several hours. Such a deprivation forces the body to draw on its reserve stores of energy and brings into play the internal regulatory events whereby fats stored in adipose tissue (and even muscle protein if the deprivation persists long enough) are broken down to supply energy. The precise way in which this depletion of reserves induces feeding is not entirely understood but it is clear that this depletion plays an important part in the control of feeding since it appears that the body's supply of stored energy is regulated. Adolph (1947), for example, demonstrated that even if undigestible roughage was added to rats' diet they maintained energy intake by increasing the volume of food consumed. Each of the principal sources of energy has been suggested as the factor being monitored in this control of feeding, i.e. glucose (Mayer, 1955; Russek, 1975), lipids (Kennedy, 1953), and amino acids (Mellinkoff, Frankland, Boyle & Greipel, 1956).

Part of the support for the glucostatic theory comes from the observation that eating can be produced by systemic injection of an unmetabolizable glucose, 2-deoxy-D-glucose (2-DG) (Smith & Epstein, 1969). By entering into competition with natural glucose, 2-DG produces a metabolic paradox in the sense that there is a decrease in glucose utilization coupled with high blood sugar. Furthermore, injections of 2-DG into the ventricles of the brain have resulted in eating (Miller &

Epstein, 1970). Eating can also be induced by injections of the hormone insulin (Booth & Brookover, 1968; Steffens, 1969) which produce low blood sugar levels.

Besides these physiological manipulations, feeding has been found to be produced by a variety of environmental factors. In many gregarious species the presence of other members of the species has been found to increase the amount of food eaten over the alone situation (e.g., rats-Harlow, 1932), and in the chicken, a satiated bird will start to eat if put with another chicken which is eating (Tolman, 1968). The situation can get even more complex: it has been reported that young cocks of the Burmese Jungle Fowl, in a conflict between the tendencies to attack and to flee during fights, will engage in food-pecking at rates beyond those seen in hungry cocks in nonconflict situations (Kruijt, 1964). Such "displacement" feeding has also been suggested as a major source of overeating in humans (Hamburger, 1960). The physical properties of the food itself have been shown to influence feeding since if laboratory animals are fed a highly palatable diet they increase their food intake and gain body weight (Hamilton, 1964). LeMagnen (1956) gave rats four different flavours of the same food in succession at a given meal and found that they will eat more than they normally do if given only one flavour. These animals will eat up to 270% of their normal intake under such conditions. Not only do the food-related cues modulate the amount eaten but they also appear to control the onset of eating, at least in some humans (Schachter, 1971).

There is another broad category of events which elicit feeding in animals: manipulation of the brain (and perhaps other organs) through lesions, and thermal, chemical, or electrical stimulation. Bilateral damage to the region of the ventromedial hypothalamus (VMH) produces

a characteristic syndrome which involves an increase in eating and subsequent obesity (Hetherington & Ranson, 1942; Brobeck, 1946). Typically, immediately following recovery from the anaesthetic the animal is hyperactive for a few hours and attacks its food voraciously (Stevenson, 1969). A detailed analysis of this syndrome, however, has revealed that there are some marked differences between the eating of these lesioned animals and that of intact animals. Initially, the intake is quite high but eventually it levels off to slightly above normal (Stevenson, 1969). Although VMH animals overeat they are very finicky and will starve for long periods if the food is even slightly unpalatable (Kennedy, 1950; Teitelbaum, 1955); furthermore, they will not work hard to obtain food (Miller, Bailey & Stevenson, 1950). Affective responses to contrast seem to be involved since if they become used to eating unpalatable foods or working hard for it before the lesion the animals continue to overeat and overwork, and gain weight (Singh, 1973, 1974). Finally, VMH rats are more sensitive to the anorectic effects of amphetamine than are normal rats (Stowe & Miller, 1957; Reynolds, 1959). Clearly this lesion has not simply removed an inhibition to eat. More recently, Ahlskog and Hoebel (1973) have damaged the ventral noradrenergic bundle (Ungerstedt, 1971a) using the neurotoxic 6-hydroxydopamine (6-OHDA) and have also produced hyperphagia. Since this pathway runs close to the VMH it was suggested that loss of these fibres may have been responsible for the VMH syndrome. A more complete analysis of the deficits following the 6-OHDA lesion, however, revealed that the two syndromes are not the same; for example, these hyperphagic animals are not finicky and are much less sensitive than VMH animals to the anorectic action of amphetamine (Ahlskog, 1974; Ahlskog & Hoebel, 1973).

Although the hypothalamus has received a considerable emphasis in studies on feeding it has long been known that many extrahypothalamic structures contribute to the initiation of feeding behavior. Animals with temporal lobe lesions not only ingest more food (e.g., Grossman & Grossman, 1963) but often display other abnormalities in their feeding behavior. Monkeys have been reported to eat bacon, sausages (Klüver & Bucy, 1937, 1939) and even feces (Wieskrantz, 1953). They are not deterred by quinine adulteration of their diet (Pribram & Bagshaw, 1953) and they do not respond normally to food deprivation (Schwartzbaum, 1961). Hyperphagia of varying degree has also been reported with damage to the mammillary region (Graff & Stellar, 1962), thalamus (Schreiner, Rioch, Pechtel & Masserman, 1953), septum (Lorens & Kondo, 1968), frontal lobes (Kirschbaum, 1945) and other extrahypothalamic structures (see review by Grossman, 1972). Eating has also been obtained by reversible lesions, as in the report of Huston & Bureŝ (1970) in which single waves of spreading cortical depression induced in one, or both, hemispheres elicited a variety of behaviors including eating.

Direct stimulation of neural tissue has proven to be quite effective in producing feeding. Thermal stimulation (i.e., cooling) of the rostral and preoptic hypothalamus has been found to cause eating in the goat (Andersson & Larsson, 1961) and has been attributed to the effects of reduced internal temperature on food intake. Larsson (1954) also obtained a feeding response from injection of hypertonic solutions lateral to the fornix in the goat. Both of these techniques, however, are relatively indiscriminant in stimulating neural tissue. Grossman (1960) used intracerebral injections of putative neural transmitters and was able to obtain elicited feeding with a relatively short latency (5-10 min.).

Norepinephrine and epinephrine produced eating whereas injections of acetylcholine or carbacol into the same perifornical region of the hypothalamus produced drinking. Subsequent studies of this phenomenon (e.g., Wagner & DeGroot, 1953; Booth, 1967; Coury, 1967; Whishaw & Veale, 1974; Leibowitz, 1976) have shown that feeding can be elicited by injections of alpha adrenergic compounds into various other parts of the hypothalamus as well as the globus pallidus, thalamus, septum, and hippocampus. The use of dosages approaching physiological levels (Leibowitz, 1974, as reported in Grossman, 1975) have increased confidence that the effect is specific to a noradrenergic system. Catecholamines have also been linked to suppression of feeding (see Leibowitz, 1976 for a review) and sex hormone action on feeding (Simpson & DiCara, 1973). Perfusion of the cerebral ventricles with calcium (Myers, Bender, Krstić & Brophy, 1972) and magnesium (Seoane & Baile, 1973) induced feeding. A transfer of cerebrospinal fluid from a fasted sheep into the ventricles of satiated recipients also elicited eating (Martin, Seoane & Baile, 1973). Various other drugs (e.g., chloralose - Booth & Nicholls, 1974; diazepam - Wise & Dawson, 1974; marijuana - Abel, 1971) administered systemically also stimulate the animal to feed.

Another relatively simple way of exciting brain tissue is to pass low levels of current through the tissue. Components of the feeding response were obtained by Brügger (cited in Stevenson, 1969) in the cat by stimulating the substantia grisea centralis. A more complete sequence was obtained by Delgado and Anand (1953) and Miller (1960) from the hypothalamus of rats. The feeding response--in varying degrees of completeness--has been reported from the lateral hypothalamus (e.g., Hoebel, 1969), ventral tegmentum (Wyrwicka & Doty, 1966), dorsal motor nucleus of the

vagus (Larsson, 1954), septum (Delgado, Ushiyama & Garotte, 1958), cerebellum (Ball, Micco & Bernston, 1974), dorsal pontine tegmentum (Micco, 1974) as well as other forebrain structures (Robinson & Mishkin, 1962). These feeding responses have also been obtained in a variety of species in addition to the standard laboratory animals of rat, cat, and monkey (e.g., herring gulls-Delius, 1971; opossum-Roberts, Steinberg & Means, 1967). Not only does electrical stimulation directly elicit feeding but it has also been found to produce "rebound" eating (i.e., eating which occurs after the stimulation has been terminated) from a variety of sites including the ventromedial nucleus (Morgane, 1961b), hippocampus (Milgram, 1969), thalamus (Smith, McFarland & Teitelbaum, 1961), septum (Wishart, Bland, Vanderwolf, & Altman, 1973), and substantia nigra (Phillips & Fibiger, 1973).

It should be apparent from this deluge of research reports that the initiation--let alone the termination--of feeding is an extremely complex event. Feeding has been shown to be elicited by cyclic events (apparently partly related to energy consumption), deprivation of food, 2-DG and hormones, social factors, conflict situations, incentive properties of the food, brain lesions, as well as thermal, chemical and electrical stimulation. In the context of this complexity we will now take a closer look at the phenomenon of electrically elicited feeding in order to try to better understand its nature. There will be an examination of differing views about how electrically elicited feeding relates to the feeding observed in "normal" animals and ultimately how it may relate to the proposed neural mechanisms of feeding.

Electrically Elicited Feeding

As has already been pointed out, electrical stimulation of the brain

has produced feeding responses in varying degrees of completeness which range from the individual eating components (such as licking and mastication-Larsson, 1954) through to "motivated" feeding (Morgane, 1961a). Most researchers concerned with feeding are not very interested in the elicitation of fragments of the feeding sequence, but as Mogenson (1976) has pointed out, this has left us with an imbalance in our knowledge of the output side of feeding. It should be obvious that until we understand how the various components of a complex behavioral sequence are put together we cannot claim to understand the mechanisms underlying the behavior. Nevertheless, the main emphasis has been on the more complete form of elicited feeding in which a satiated animal will move to the food and begin the ingestive sequence with the onset of the ESB. When the brain stimulation terminates so does the eating. It should be noted, however, that this sequence will not occur unless the appropriate goal object (i.e. food) is present.

Elicited Feeding and Hunger

The completeness of the sequence soon led investigators to compare this phenomenon with eating as it occurs in the natural situation. Within the drive reduction model of the day, the brain stimulation was hypothesized to induce a state very similar to the hunger normally produced by deprivation (e.g., Coons, Levak & Miller, 1965). Miller (1957) demonstrated that ESB of the lateral hypothalamus resembled food deprivation in that when stimulated, animals performed a response they previously had learned as a way of getting food. Morgane (1961a) also found that rats would use a previously acquired response to get food--in this case, crossing an electrified grid and bar pressing--when stimulated in the lateral hypothalamus. It was pointed out, however, that

such results could also be attributed to a nonspecific facilitation of conditioned responses rather than to a specific arousal of the "hunger mechanism" (Grastyán, Lissák & Kekesi, 1956). This alternative interpretation can be ruled out since Coons et al. (1965) were able to teach satiated rats to press one of two bars which delivered Noyes pellets while being continuously stimulated in the lateral hypothalamus. Successful reversal learning also eliminated the possibility that the initial learning merely reflected the facilitation of an already dominant response. These animals, moreover, were able to use this acquired response to obtain food when they were deprived of food for 48 hrs. In these cases, not only does the ESB elicit the consummatory behaviors of chewing and swallowing but also the appetitive ones of actively seeking out the food. Elicited feeding, therefore, can be considered "motivated" in that it appears to be the result of the integration of separate responses into a functional sequence and it has direction (Hinde, 1970, p. 194).

There has been a detailed examination of the relationship between the variables which influence eating in the normal animal and electrically elicited eating in order to determine whether ESB is activating the neural mechanism responsible for normal eating. Since changes in the ambient temperature produce changes in feeding (i.e., lowered temperature produces eating whereas increased temperature inhibits eating-Brobeck, 1948), Baettig and Weber-Tschopp (1973) manipulated ambient temperature during elicited feeding and found that elicited feeding was decreased after exposure to 39°C but increased after exposure to 9°C. After termination of the exposure to both the elevated and lowered ambient temperature, the elicited feeding returned to control levels within a short period. Devor, Wise, Milgram, and Hoebel (1970) also showed that elicited feeding

from the hypothalamus is under the control of the same factors which modulate normal feeding. Food deprivation produced a consistent increase in elicited feeding but did not affect the elicited drinking which was also obtained. Food intake (induced by ESB) raised the threshold for elicited feeding whereas water intake, or just the ESB without any goal objects, did not; in other words, the inhibition of elicited behavior was specific to the appropriate consummatory response. Furthermore, intragastric loadings of food--but not water--red ed elicited eating just as they do for spontaneous eating (Stellar, 1967). Berthoud and Baettig (1974), however, found that both nonnutritive and nutritive intragastric loads immediately raised thresholds for elicited feeding. The durations of these elevated feeding thresholds were similar to the times for which spontaneous feeding was inhibited when the gastric load was delivered at the onset of a spontaneous meal. It is evident that just as with spontaneous feeding postingestinal factors are sufficient to inhibit elicited consummatory behavior without the sensory or motor feedback normally accompanying ingestion. It also seems that the elicited behavior is under the control of factors specific to the response.

It is clear from other studies, however, that the hypothalamic stimulation can supersede the level of normal homeostatic cues. Tenen and Miller (1964) noted that a slightly suprathreshold current intensity induces feeding only for a short time because of the increased satiety cues from eating, but that these cues can be overcome by increasing the current. In fact, Steinbaum and Miller (1965) observed that rats who were forced to overeat by prolonged stimulation of the hypothalamus became obese by maintaining an intake and rate of weight gain far greater than non-stimulated animals or animals similarly stimulated without food

present. Furthermore, when rats were stimulated to eat varying fractions of their normal daily intake in a short time each day they compensated by abruptly reducing their intake the rest of the day so that their total daily intake remained normal.

Tenen and Miller (1964) were also concerned with whether the sensory qualities of the food would influence elicited eating as it does spontaneous eating (Miller, 1956). As the concentration of quinine in the food increased, the amount of elicited eating decreased; however increasing the current intensity did increase the rats' tolerance for the quinine in their milk. They go on to suggest that the larger amount of quinine required to stop eating with stronger currents seems to parallel the larger amount required to stop eating with longer periods of food deprivation. Furthermore, when the electrical stimulation was combined with food deprivation, the rats tolerated more quinine in their food than when tested under either condition experienced separately; but there was no such summation in quinine-tolerance thresholds in water when the stimulation was combined with food or water deprivation.

Normal feeding can be suppressed in a number of other ways: for example, by introducing a stimulus into the eating situation which has acquired aversive characteristics through an association with foot shock (Estes & Skinner, 1941). Perera and Glusman (1968) demonstrated that the rate of elicited feeding can also be suppressed by presenting a discriminative stimulus (a light) which had been followed by foot shock. The suppression of elicited feeding, furthermore, was sensitive to environmental manipulation in that it increased as a function of shock intensity. Perhaps a more ecologically meaningful form of the suppression of eating occurs with bait-shyness or poison avoidance which involves

the rat avoiding the taste of food that has made it ill (Barnett, 1963; Rozin & Kalat, 1971). Wise and Albin (1973) have shown that it is possible to selectively suppress the elicited eating of a particular diet (cat food) without also disrupting the elicited eating of pellets using the poison avoidance paradigm of lithium chloride injections. This avoidance--established with elicited eating--was also found with spontaneous eating. Since both of these conditions appear to involve a form of classical conditioning it might be worth mentioning here that attempts to classically condition the consummatory response of elicited feeding have been just as unsuccessful (Puston & Brozek, 1972) as attempts with deprivation-induced feeding (Cravens & Renner, 1970). It is possible, however, to establish elicited feeding as an operant or instrumental response (Wyrwicka, 1976).

A number of potent anorectic drugs have also been found to be effective in suppressing elicited feeding. Amphetamine, for example, clearly raises the threshold to elicit eating in satiated animals (Miller, 1960) as do four other chemically related anorectic agents (Stark & Totty, 1967). The effects of these drugs and their duration of effect are generally dose-dependent. Amphetamine, however, has some peculiar effects inasmuch as it can increase lever pressing for food while decreasing the actual ingestion of food (Cole & Gray, 1974). Hoebel, Hernandez and Thompson (1975), however, have found that the anorectic drug phenylpropanolamine--which has little of the psychomotor stimulation effects of amphetamine--can also inhibit elicited feeding. Once again, this inhibition is selective in that electrically elicited drinking was not disrupted.

A final set of experiments which have been used to argue that

elicited feeding is a result of the activation of the drive mechanisms in the hypothalamus which normally give rise to eating involve hoarding. Laboratory rats will not hoard food which is continuously available but if they are placed on intermittent deprivation schedules for some days they will begin to hoard (Morgan, Stellar & Johnson, 1943). Herberg and Blundell (1967) observed that hypothalamic stimulation which elicited feeding led to immediate and sustained hoarding in satiated animals at a level almost as high as during 16 hrs of food deprivation. Hoarding was not obtained, however, with stimulation which did not produce elicited feeding. This effect was also observed in animals which have never hoarded before (Blundell & Herberg, 1973). These authors argue that the ESB and food restriction influence hoarding by acting on the same hypothalamic mechanism concerned in the regulation of body weight.

In summary, then, electrically elicited feeding appears to be quite similar to normal feeding inasmuch as the animal will learn and perform an operant response to obtain food when stimulated. Moreover, the appropriate goal objects must be present for the behavior to be displayed--it does not occur in vacuo. In addition a number of conditions which are known to influence normal eating have been found to have similar effects on elicited feeding. Clearly, elicited feeding is neither an immutable nor capricious consequence of brain stimulation since it can be modified by both internal and external variables. Consequently, a number of investigators (e.g. Miller, 1960; Blundell & Herberg, 1973) have suggested that the ESB which produced elicited feeding is activating the neural mechanisms responsible for feeding.

An Alternate Approach to Elicited Feeding

Not everyone, however, agrees with this view. Valenstein and his

co-workers are ardently opposed to the idea that stimulus-bound behavior is elicited by activation of specific neural circuits responsible for "hunger", "thirst", etc. (Valenstein, Cox & Kakolewski, 1968a; reviews-Valenstein, Cox & Kakolewski, 1970 and Valenstein, 1973). Distinguishable from this issue of specific neural circuits, they also disagree with the idea that relatively discrete hypothalamic regions are involved in the regulation of behavior related to specific biological needs. Cox and Valenstein (1969) claim that, with the exception of a few structures, the sites eliciting eating, drinking, and gnawing overlapped with sites which elicit only nonspecific exploratory behavior. Furthermore, a more detailed analysis indicated that it was not possible to distinguish the sites that elicited eating from those eliciting drinking or gnawing in the rat. Roberts (1969) points out that one must not, however, set unrealistically high standards for topographical differentiation given the appreciable amount of gross anatomical overlap in the classic motor system. He also notes that massing data from different brains substantially overestimates the amount of overlap in individual brains because it adds a between animal variance to the scatter in the individual case. According to Roberts (1969), this lack of specificity in the rat is in sharp contrast to other studies in the opossum and cats. Wise (1974) argues that the apparent lack of specificity in the rat may be a result of the size of the rat hypothalamus relative to the spread of current from typically-used electrodes. This idea gains support from the finding that there is greater specificity of response in the rat when very small stimulating electrodes are used (Olds, Allan & Briese, 1971). It seems, therefore, that there is strong evidence to support the notion that there are discrete hypothalamic regions from which different classes of behavior can

be elicited.

Valenstein has mustered, however, a variety of evidence against the idea that brain stimulation activates specific neural circuits responsible for normal motivated behavior. Valenstein et al. (1968a, 1969) have shown that the behavior elicited by hypothalamic stimulation could be changed without modifying the stimulation parameters. If a rat initially eats in response to the ESB, removal of the food is generally followed in time by elicited drinking or wood-gnawing. They felt it is important to remove the initial goal object (Valenstein et al., 1970) to produce this switching although Milgram, Devor and Server (1971) did find spontaneous elicitation of a second behavior in most animals over time without altering the situation. Valenstein (1971) points out that ample opportunity must be provided to observe this switching and that test procedures which provide a great deal of exposure to the initially preferred goal can make it very difficult to produce a second response. Valenstein is particularly interested in the time course of the development of this second, or third, response pattern. He points out that if one were stimulating discrete neural circuits one would expect that the removal of the initially preferred goal object should allow the other response patterns to appear almost immediately. It has consistently been found, however, that the second behavior generally appears slowly (e.g., Cox & Valenstein, 1969; Milgram et al., 1971; Mogenson, 1971). This suggests that some form of learning is required which Valenstein argues is incompatible with activation of specific neural systems.

Evidence to support their position also comes from several situations in which animals showing stimulus-bound eating or drinking did not behave as if hungry or thirsty. For example, animals showing elicited feeding

did not readily switch to another food when the first was removed but rather started to show elicited drinking. Simply changing the form of the food, as when pellets were ground, produced similar effects (Valenstein et al., 1968b). A large percentage of rats reared from infancy on a liquid diet showed elicited eating of food pellets when mature, but, if deprived of them, they did not eat the familiar liquid diet in response to stimulation (Valenstein & Phillips, 1970). Observations from elicited drinking also seem relevant: Animals did not switch from a different, but familiar, container under stimulation-induced drinking. Their taste preferences also differed from those of water deprived animals in that naturally thirsty animals prefer water to a glucose solution. Furthermore, animals exhibiting stimulus-bound drinking often continued to lap at an empty water tube (Valenstein, Kakolewski & Cox, 1968). Valenstein (1970) also reports that in several instances whether the animal ate or drank in response to the stimulation seemed to depend on the location of the food or water. In summary, then, it would appear that the behavior of animals under ESB differs from the behavior of animals under deprivation conditions--this, of course, is in contrast to the body of data reviewed earlier which showed a great deal of similarity.

Valenstein (1970) suggests a paradox exists inasmuch as animals consistently show self-stimulation of the brain from electrode sites which elicit feeding (Hoebel, 1969), drinking (Mogenson & Stevenson, 1966), and copulation (Caggiula & Hoebel, 1966). Why should an animal stimulate itself to become "hungry", "thirsty", or "sexually aroused" without an opportunity to consummate these drives? Valenstein instead suggests that the ESB excites the neural substrate underlying species-

specific response patterns which is inherently reinforcing (Glickman & Schiff, 1967). In line with this emphasis on species-specific behaviors, Valenstein points out that object-carrying can be elicited only when the ESB bears some relationship to the animal's behavior, location in the environment, or both (Phillips, Cox, Kakolewski & Valenstein, 1969). He suggests that object-carrying by the rat should be viewed as a pre-potent, adaptive response which can serve the purposes of specific motivational states related to hunger and maternal behavior. Pre-potency is not only related to the species but also to the individual inasmuch as Valenstein and Cox (1969) have found that often--but not always--when two hypothalamic electrodes in an animal elicit stimulus-bound behavior, the behavior will be the same in quality even though the anatomical location may be widely disparate. Wise (1971) reports a similar observation. This suggests that individual animals have some sort of "response hierarchy".

Valenstein et al. (1970) conclude that hypothalamic stimulation does not create hunger, thirst or gnawing drives but seems to create conditions which excite the neural substrate underlying well-established response patterns ("fixed action patterns"). Discharging this excited substrate is reinforcing and it can provide the motivation to engage in instrumental behavior which is rewarded by the opportunity to make the response. Hypothalamic stimulation does not activate a specific behavior pattern but rather a group of responses that in a given species are related to a common state. The states induced by ESB are not sufficiently specified to exclude the possibility of response substitution. This interpretation of elicited behavior emphasizes the motor system and reinforcement produced by the execution of a consummatory response as

well as the learning involved in response selection.

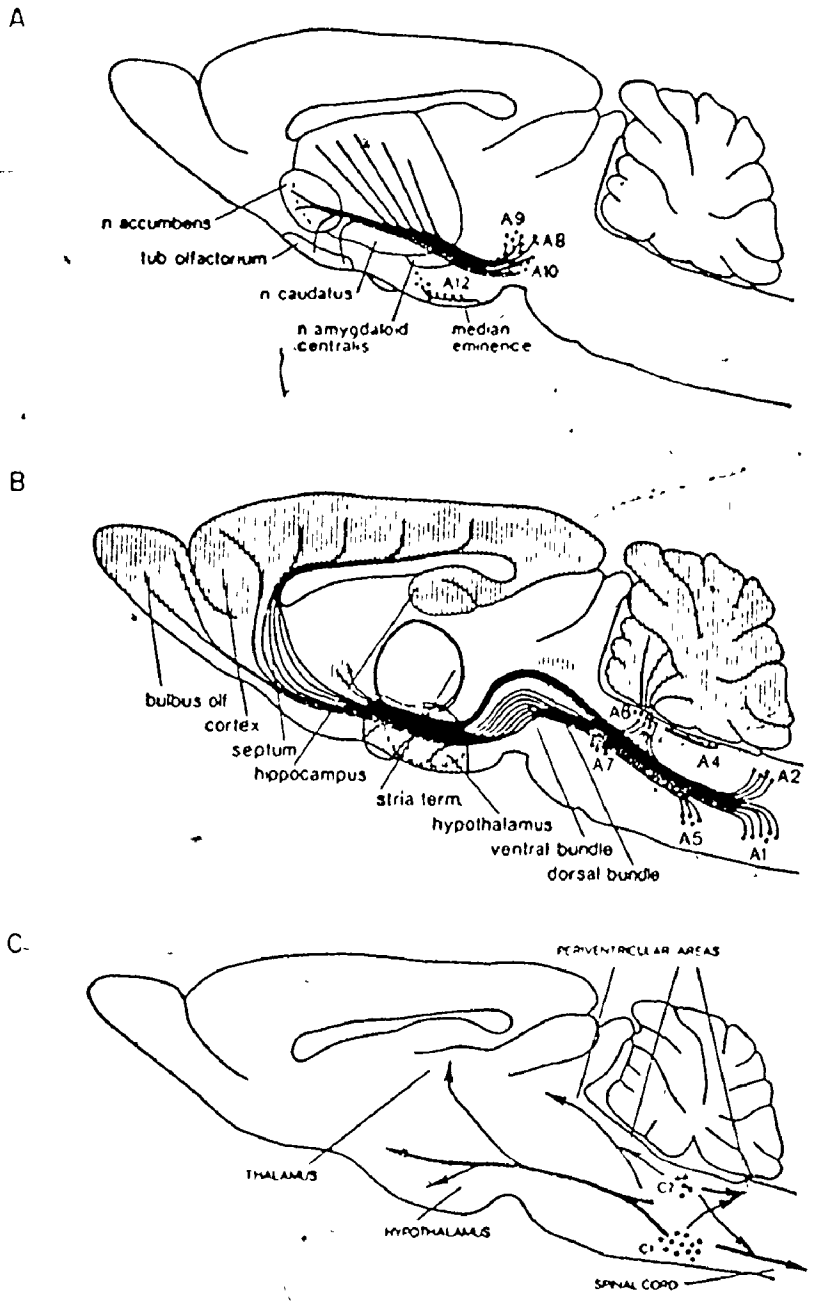
Catecholamines and the Physiological Substrates of Motivation

Catecholamine Anatomy

Recent technological developments have produced a new chemical anatomy of the brain based on the mapping of transmitter-specific pathways which have resulted in a reassessment of the role of the hypothalamus and other neural structures in motivated behaviors (Mogenson, 1974; Morgane, 1975). During the 1960's, neurochemical and histochemical studies revealed catecholamine (CA) pathways projecting from the midbrain and lower brain stem through the region of the lateral hypothalamus to forebrain structures. Combining the sophisticated histochemical techniques with lesions and pharmacological manipulations has permitted the detailed description of the course of the CA systems through the brain (Andén et al., 1966; Hökfelt et al., 1974; Jacobowitz & Palkovits, 1974; Lindvall & Bjorklund, 1974; Palkovits & Jacobowitz, 1974; Ungerstedt, 1971a). The pathways, shown in Figure I-1, are primarily ascending projections from the midbrain and brain stem to a variety of diencephalic and telencephalic structures including the hypothalamus, septum, hippocampus, and cerebral cortex.

Initial reports emphasized that the ascending noradrenergic (NA) fibres were distributed in dorsal and ventral pathways, the former originating mainly from the dorsolateral region of the locus coeruleus (Olson & Fuxe, 1971; Ungerstedt, 1971a) and the latter from subcoeruleus cell bodies (Olson & Fuxe, 1972) and nuclei in the medulla oblongata (A1-A5,A7) (Fuxe et al., 1970; Ungerstedt, 1971a). The ascending dorsal NA bundle projects throughout the neocortical areas and most of the older cortical areas (Lindvall et al., 1974a). Another component of the dorsal

Figure I-1 Sagittal section of the brain showing (A) the ascending dopaminergic pathways, (B) the ascending noradrenergic pathways (from Ungerstedt, 1971a), and (C) the ascending adrenergic pathways (from Hökfelt et al.,1974).



NA bundle appears to give rise to extensive projections to thalamic, metathalamic, and pretectal areas (Lindvall et al., 1974b). There appears to be some confusion as to whether the subcoeruleus and medullary projections of the ventral NA bundle are separate systems as they seem to innervate different regions of the diencephalon. Maeda and Shimizu (1972) have proposed a distinct intermediate pathway originating in the subcoeruleus area and projecting mainly to the periventricular and medial preoptic regions of the hypothalamus. The medullary component of the ventral NA bundle is thought to innervate the basolateral areas of the hypothalamus and preoptic nuclei as well as the stria terminalis (Olson & Fuxe, 1972; Tohyama et al., 1974).

In addition to these major pathways, ascending NA pathways have also been identified using the more sensitive glyoxylic acid method. This technique has revealed a NA component of the dorsal longitudinal fasciculus that has been called the dorsal periventricular bundle. This system originates in an elongated region located in the dorsal raphe, mesencephalic gray and periventricular gray of the caudal thalamus. Fibres in this system form a thalamic and hypothalamic periventricular system projecting to thalamic, epithalamic, and pretectal areas. A ventral periventricular bundle has also been identified in the supra mammillary region and coursing rostrally into the dorsal medial nucleus where it joins the dorsal periventricular bundle to form the ascending hypothalamic periventricular NA fibre systems (Lindvall et al., 1974b).

The cell bodies of the dopaminergic (DA) pathways have been localized in the zona compacta of the substantia nigra (A9), as well as in the area dorsolateral to the interpeduncular nucleus (A10) and caudally dorsolateral to the nucleus cuneiformis (A8) (Palkovits & Jacobowitz, 1974). Axons

from A9 cell bodies form the nigrostriatal bundle (NSB) which projects rostrally with the medial forebrain bundle through the dorsolateral region of the hypothalamus, where they fan out dorsolaterally before entering the caudate-putamen. A second major DA pathway, the mesolimbic pathway, originates in the A10 region and ascends medial to the nigrostriatal pathway in the dorsal part of the medial forebrain bundle eventually innervating the nucleus accumbens and the olfactory tubercle (Ungerstedt, 1971a). In addition to these well-established DA projections, the existence of DA terminals in the limbic and cerebral cortices has recently been demonstrated (Lindvall et al., 1974a). Dopaminergic innervation is localized in the frontal cortex, the anterior cingulate cortex, the ventral aspect of the entorhinal cortex, and the transition zone along the rhinal fissure. This dense and localized innervation is in contrast to the diffuse projections of the dorsal NA system.

To complicate the picture even more there also appear to be epinephrine-containing neurons which have similar distributions to NA neurons (Hokfelt et al., 1974). As Mogenson and Phillips (1976) warn, it is important to consider that some of the functions ascribed to NA pathways may well be subserved by epinephrine systems.

Catecholamine Pathways and Ingestive Behavior

As has already been mentioned, Grossman (1962) found that intracerebral injections of norepinephrine (noradrenalin) into the hypothalamus initiated feeding in satiated rats and so implicated noradrenergic neurons in the control of food intake. Later it was shown that lesions to the lateral hypothalamus (LH) reduce the levels of NA in the forebrain (Heller & Moore, 1965) whereas the aphagia from LH lesions could be reversed

by infusing NA into the ventricles (Berger, Wise & Stein, 1971). When the catecholamine pathways were finally mapped it was apparent that both noradrenergic and dopaminergic pathways projected through the area of the hypothalamus in which lesions produce aphagia and adipsia (Anand & Brobeck, 1951).

Ungerstedt (1971b) found that destruction of the nigrostriatal DA pathway using the neurotoxin 6-OHDA produced severe aphagia and adipsia. The introduction of this relatively selective lesioning technique not only provided researchers with a useful tool in unravelling the mechanisms of the brain but also implicated DA neurons in ingestive behavior for the first time. Oltmans and Harvey (1972) provided supporting evidence by comparing the effects of bilateral electrolytic lesions of the NSB and the medial forebrain bundle as they pass through the lateral hypothalamus; catecholamine assay confirmed the pathway's destruction. In both studies nigrostriatal damage produced more severe effects. Detailed comparisons of catecholamine damage with the effects of LH damage associated with the classical LH syndrome have been carried out (Fibiger, Zis & McGeer, 1973; Marshall & Teitelbaum, 1973). Marshall and Teitelbaum (1973) observed aphagia and adipsia following bilateral injection of 6-OHDA into the cell bodies of the NSB (A9-substantia nigra). The lesion produced an impairment in feeding to injections of 2-DG and in the drinking to cellular dehydration or hypovolemia. These animals recovered the control of food and water intake in the same sequence usually observed in rats with LH lesions (e.g., Epstein, 1971). Similar findings were reported by Fibiger et al. (1973): 6-OHDA damage to the substantia nigra produced decreased water intake, prandial drinking, finickiness, and

failure to drink after injection of hypertonic saline--all deficits produced by electrolytic lesions of the LH. Interestingly, several of the regulatory deficits were greater in rats with LH electrolytic lesions even though these lesions produced less damage to the DA system than did the 6-OHDA in the substaintia nigra. It was concluded that the effects of the LH lesions cannot be attributed entirely to NSB damage. Further support for this conclusion comes from Zeigler and Karten (1974) who found that extrahypothalamic lesions of central trigeminal structures can also produce aphagia, adipsia, and finickiness.

There have also been effects on ingestive behavior following intraventricular injections of 6-OHDA (Zigmond & Stricker, 1972: Breese et al., 1973; Fibiger et al., 1973). Two distinct syndromes have been observed which appear to be correlated with the amount of depletion in striatal dopamine. With a moderate reduction in DA levels but large depletions of NA animals appear indistinguishable from controls unless subjected to acute homeostatic challenge produced by glucoprivation, hypovolemia, or exposure to cold (Zigmond & Stricker, 1974). Although the animals can make normal physiological adjustments they fail to make the appropriate ingestive responses. When the striatal DA depletion was severe (by pretreating the animals with a monamine oxidase inhibitor before the 6-OHDA), there were both acute and chronic impairments. These animals required tube feeding to prevent death by starvation and dehydration. If the striatal depletion was 98%, or more, the animals never recovered but with 90-98% depletion there was a gradual recovery of feeding and drinking in a pattern similar to the LH syndrome (see reviews by Epstein, 1971 and Teitelbaum, 1971). The recovery of ingestion in these animals is attributed by Stricker and Zigmond (1976) to a functional recovery of

damaged DA fibres as well as to increased synthesis and release of DA from undamaged neurons.

Although aphagia and adipsia are clearly associated with damage to the DA nigrostriatal bundle, a major consideration is whether feeding and drinking are subserved exclusively by this system. In recent reviews of their work, Zigmond and Stricker (1974, 1976) have concluded that damage to the DA neurons is responsible for the disruption of motivated ingestive behavior and Ungerstedt (1974) has reached a similar conclusion. On the other hand, Marshall, Richardson and Teitelbaum (1974) were reluctant to attribute aphagia and adipsia exclusively to damage to the DA nigrostriatal bundle even though they had injected 6-OHDA directly into the substantia nigra. Since telencephalic noradrenergic levels were depleted as much as dopamine in the striatum (both by 89%), a possible contribution of noradrenergic pathways could not be excluded.

As Mogenson and Phillips (1976) point out, it is important to realize that most of the permanent regulatory deficits to acute homeostatic imbalance are also observed when NA levels are preferentially suppressed. This raises the possibility that noradrenergic pathways are involved in ingestive behavior initiated by deficit signals. However, if NA fibres contribute to ingestive behaviors it seems unlikely that the different pathways subserve the same functions. As has already been discussed, destruction of the ventral noradrenergic pathway produces rats which become hyperphagic and obese (Ahlskog & Hoebel, 1973). Although the syndromes are not identical it is unlikely that damage to this pathway produces the regulatory deficits noted above.

The Present Study

The present study tries to bring together the major lines of research considered so far by comparing electrically elicited and naturally occurring feeding. Natural feeding, of course, is under multifactor control so that it is possible to induce it through a variety of techniques. In this study, elicited feeding is compared to both spontaneous intake (which is a complex blend of many factors) as well as deprivation-induced feeding. The controversy surrounding the specificity of elicited behaviors is considered in the first experiment in order to establish the appropriateness of the preparation used since the primary concern of this thesis is electrically elicited feeding. The involvement of the CA system in feeding behavior was examined using the generalized destruction to this system provided by intraventricular injection of 6-OHDA. The contribution made by some of the component pathways was assessed using both electrolytic and intracerebral chemical lesions as well as pharmacological agents. In the process of determining the involvement of CA in elicited feeding, a comparison of diet preferences exhibited with ESB, as opposed to food deprivation, was also made. It is hoped that by such a comparison between elicited feeding and naturally occurring feeding a better understanding of the nature of both phenomena will develop to the extent that essential similarities and dissimilarities can be revealed.

GENERAL METHODS

Subjects

One hundred and seventy-two male Wistar rats (Biobreeding, Ottawa) weighing between 240 and 520 g at the time of operation, were used. The animals were housed individually in wire mesh cages with food and water available ad libitum unless otherwise specified. The animal room was maintained on a light-dark schedule controlled to give 12 hrs of light (0800 - 2000) and 12 hrs of darkenss. The room temperature was set for 68°F (20°C).

Apparatus

Animals were tested for electrically elicited ingestive behavior in a clear Plexiglas chamber (35 x 20 x 35 cm) in front of the partially reflective window of a sound attenuating room. The test chamber rested on a wire mesh floor above a tray filled with sawdust. A metal cup (9 mm in diameter and 6 mm deep) was secured to the floor in a corner of the chamber directly in front of the observation window. The food dish from the home cage could be placed in the metal cup and tap water could be provided from a graduated cylinder via a glass "spill-proof" Richter spout protruding through the front wall.

A Wavetex Voltage Controlled Generator (Model 111), connected to a voltage adaptor, was programmed to alternatively deliver 30 sec. of electrical brain stimulation (120 Hz sine wave) and 30 sec. of no stimulation using a Hunter timer (Model 124 S). Attachment of the electrode leads (Plastic Products Co., receiver cord #303-32) to a mercury commutator (Scientific Prototype, MC4) allowed the rats free movement within the chamber. The voltage drop across a 50 ohm resistor in series with

the electrode was displayed continuously on a Telequipment Dual Beam Oscilloscope (Model D52). From this, the current flowing during stimulation was calculated using Ohm's Law (I = E/R); the numerical values given below indicate peak current. The apparatus was duplicated with the electrical stimulation of the brain (FSB) 180° out of phase so that two animals could be tested simultaneously.

General Procedure

Surgery

The rats were prepared for surgery by anaesthetizing them with sodium pentobarbital (Nembutal, 50 mg/kg) given intraperitoneally and supplemented with ether when necessary. The head was shaved and the animal placed in a David Kopf sterotaxic instrument (#1204). An incision 15-20 mm long was made along the midline of the skin covering the skull. The skull was scraped and cleaned with 0.9% saline to expose the skull sutures. The skull was then made level with respect to lambda and bregma. Bregma was used as a zero point for the stereotaxic coordinates with all reference to the ventral coordinate taken from the surface of the skull above the point of entry unless otherwise indicated. Burr holes (1.0 - 1.5 mm) were drilled through the skull to the level of the dura; dura was then carefully cut using the point of a 23 gauge needle. Prior to surgery, fine, bipolar electrodes (Plastic Products Co., MS 303-.018-.312-.005, 127 μ) were straightened, dipped in Insulex, cut to length and then tested for breaks in the insulation. Chronic, indwelling cannulae were constructed from 23 gauge needles cut to length (15 mm, ±0.1 mm) with an inner stylus made from insect pins (00). All animals received a bilateral implantation of electrodes; in addition, some animals received indwelling cannulae or indwelling lesioning electrodes

constructed from nichrome wire insulated excepted at the cross-section of the tip. These assemblies were secured with acrylic cement to jeweller's screws inserted into the skull around the burr holes. After the cement had hardened, the wound was closed with stitches and cleaned. The rats were then removed from the stereotaxic frame and placed under a heat lamp until they had recovered from the anaesthetic. Ear punches were used to identify all animals.

Screening for Elicited Ingestive Behavior

In order to determine a suitable current level for electrically elicited ingestive behavior some of the animals were pretested in the presence of both food and water (see individual experiments). The high fat diet (20% casein; 33.7% white cane sugar; 40.0% animal lard; 3.8% mineral mix; and 2.5% vitamin mix by weight; the mineral and vitamin mix obtained from Mogul Corp.) available in the home cage was used because of the minimal amount of spillage and consequent accuracy of measurement. Tap water was provided from a "spill-proof" Richter spout similar to the one used in the home cage. The current level was systematically increased until either stable ingestive behavior was elicited, or until the maximum output (100 μA) of the stimulator was attained.

A strict criterion for ingestive behavior was established: clear jaw movements after contact with the food was necessary for eating, whereas for drinking there had to be rising air bubbles in the water tube after contact with the spout. Moreover, such behavior could not continue more than five seconds after the termination of the ESB in order to be considered elicited. This criterion was used to exclude any rebound eating. No animal, however, was excluded from the study for rebound eating.

Electrode placements which failed to show stable elicited ingestive

behavior were tested at least one more time before being excluded from further stimulation.

Histology

Each rat was anaesthetized with ether. Before the heart stopped beating, the thoracic cavity was opened and the right auricle of the heart was perforated. The animal was then perfused by injection through the left ventricle, first with isotonic saline (about 40 ml) and then with 10% formalin (about 40 - 60 ml). The brains were removed from the skull immediately after decapitation and placed in 10% formalin for a minimum of three days before sectioning. Frozen sections were cut 60 to 70 µm thick, mounted on slides prepared with albumen and later, when dry, stained for cell bodies with a cresyl violet stain.

For the most part the histology is reported on the drawings of brain sections from König and Klippel (1963). This atlas was used to determine the placement of all the stimulating electrodes and cannulae; the atlas by Fifková and Marsala (1967) was used for locating the locus coeruleus lesions. All the histology is reported on the left half brain and so it was necessary to transpose the electrode locations from the right half brain (the reverse is true for the locus coeruleus lesions).

Appendix 1 contains the location of the stimulating electrodes which supported elicited feeding and they are all in the lateral hypothalamic - medial forebrain bundle region. Electrode placements which did not support feeding are not shown but they often overlapped with the effective placements.

Statistical Procedures

Appendix 2 contains the summary tables for the analyses of variance as well as the comparison amongst means. The method of least squares (Winer, 1971) was used to conduct the ANOVA's which had unequal group

sizes and repeated measures.

The figures presented in the body of the paper are based on the average effect over animals unless otherwise indicated.

EXPERIMENT 1

As was pointed out in the Introduction there is a controversy over the nature of electrically elicited ingestive behavior. One side of the controversy (eg. Miller, 1960; Blundell & Herberg, 1973) holds that electrically elicited feeding is the result of the activation of specific neural circuits responsible for "hunger" whereas elicited drinking results from activation of a different system. Valenstein (eg. Valenstein et al., 1970), however, has argued that the stimulation is not activating specific mechanisms but rather is inducing a more general and plastic state under which response substitution is quite likely.

As was also pointed out in the Introduction the recently elucidated catecholaminergic pathways appear to be involved in ingestive behavior. Not only have the catecholamines been implicated by Grossman's (1960) chemical stimulation work but they have also been implicated in both the LH syndrome (Ungerstedt, 1971b; Oltmans & Harvey, 1972) and the VMH syndrome (Ahlskog & Hoebel, 1973).

In this first experiment, then, the specificity of the ingestive behaviors elicited from the area through which CA fibres are concentrated was examined. Furthermore, if the elicited behavior is dependent on the same system of neurons responsible for spontaneous feeding and

drinking then damage to the neural tissue surrounding the stimulating electrode should disrupt both elicited and spontaneous ingestive behavior. Since unilateral lesions generally do not result in as severe deficits (Gold, 1966) as bilateral lesions, it is necessary to bilaterally disrupt the same functional tissue. This can be accomplished by lesioning through bilateral stimulating electrodes, both of which support elicited behavior, or by using an asymmetrical lesion technique. With the latter technique, a small lesion was produced at the tip of the electrode which maintained elicited behavior whereas a much larger lesion - designed to damage the same functional tissue - was made through the ineffective electrode. In this way, the same neural tissue could be destroyed bilaterally.

Method

Subjects

Twenty-five male Wistar rats, divided into two series (Series I, N=15; Series II, N=10) received bilateral electrode implantations aimed at the catecholaminergic pathways (2.7 mm posterior, 1.6 mm lateral and 8.8 mm ventral) using the procedures outlined in the General Methods section. All animals were maintained on a high fat diet (HFD) and tap water.

Procedure

Brain stimulation. All animals were subjected to the screening procedure for electrically elicited ingestive behavior using the food dish (containing HFD) from the home cage and tap water. Electrode placements which showed stable elicited ingestive behavior (as outlined in the General Methods section) were tested further. A test session consisted of a 3 min. adaptation period, followed by three 10 min. stimulation periods separated by 5 min. rest periods of no stimulation. Because of the alternating nature of the ESB, each stimulation period contained ten 30 sec. stimulation intervals. The presence or absence of an elicited ingestive behavior was recorded for each 30 sec. interval of the stimulation periods, as was the total amount of food and water consumed during the entire test session (43 min.).

Two series of animals were used: For Series I, both food and water were available during the first two stimulation periods of the session with only water available during the final stimulation period; measures were taken for three consecutive days. The procedure used for Series II was similar to Series I except that the period during which only water was available was counterbalanced: i.e., for Series II, only water was

available during either the first stimulation period or the third stimulation period depending on an ABBA order of presentation (A - water only during the first period; B - water only during the third period) with both food and water available for the other two stimulation periods. Accordingly, measures were taken for four consecutive days. The stimulation period with only water available was used as an indication of the "purity" of the elicited feeding obtained by biasing for elicited drinking through the removal of the competitive food stimulus. Control levels of food and water intake for the duration of the test session were obtained by testing the animals with these procedures but without the ESB.

Electrolytic lesions. Those animals in Series I who displayed elicited ingestive behavior (as defined in the Results below) from both stimulating electrodes received a bilateral electrolytic lesion (1 mA for 3 sec.) through their bipolar stimulating electrodes (N=5). Animals in Series I with only one electrode supporting elicited ingestive behavior received a small electrolytic lesion (1 mA for 3 sec.) through the effective electrode and a larger lesion (1 mA for 10 sec.) through the ineffective electrode (N=5). Lesions were performed on unanaesthetized, restrained animals. Animals were tested for elicited behavior using the procedure described above the day following the lesion and one week later. Daily food and water intakes were recorded between testings and were compared to levels obtained by control animals.

Results

Elicited Behavior

Of the 44 electrode placements tested for electrically elicited ingestive behavior, 21 placements (47.7%) supported elicited feeding. See Tables 1-1, 1-2, and 1-3.) The current levels used ranged from 10 μA to 25 μA. Elicited feeding was defined as at least one bout of

Table 1-1

The Occurrence of Ingestive Behavior for Animals in Series I (Bilateral Group) During Control and Electrically Elicited Sessions

Subject		Feeding		Drinking		Drinking During Water Only Condition
		% [a]	M Intake [b] (g)	%	M Intake (ml)	%
3 L	control	4.0	1.17	2.0	0.25	
	elicited	90.0	9.97	0	0.58	1.6
3 R	control	4.0	1.17	2.0	0.25	
	elicited	50.0	4.11	0	0.25	0
6 L	control	6.0	0.65	2.0	0.50	
	elicited	60.0	7.57	0	1.00	0
6 R	control	6.0	0.65	2.0	0.50	
	elicited	68.3	7.02	0	0	0
8 L	control	2.0	0.90	8.0	0.88	
	elicited	81.6	9.32	0	0.33	10.0
8 R	control	2.0	0.90	8.0	0.88	
	elicited	81.6	8.95	3.3	1.50	20.0
11 L	control	2.0	0.66	4.0	0.75	
	elicited	58.3	8.28	0	0.08	0
11 R	control	2.0	0.66	4.0	0.75	
	elicited	91.6	15.13	0	0	0
15 L	control	0	0	2.0	0.25	
	elicited	53.3	3.38	0	0.16	1.6
15 R	control	0	0	2.0	0.25	
	elicited	65.0	4.91	0	0.01	1.6

[a] Percent of stimulation intervals containing a bout of ingestive behavior

[b] Mean intake over test session

Table 1-2

The Occurrence of Ingestive Behavior for Animals in Series I (Unilateral Group) During Control and Electrically Elicited Sessions

Subject		Feeding		Drinking		Drinking During Water Only Condition
		%[a]	M Intake[b] (g)	%	M Intake (ml)	%
4 L	control	4.0	0.28	2.0	0.25	
	elicited	63.3	4.06	0	0	0
5 R	control	0	0.73	4.0	1.25	
	elicited	52.5	3.65	3	1.25	13.0
7 R	control	4.0	0.90	0	0	
	elicited	50.0	4.29	0	0.08	0
12 R	control	12.0	1.19	6.0	1.25	
	elicited	100.00	10.61	0	0	0
13 L	control	4.0	0.85	6.0	1.25	
	elicited	50.0	4.93	0	0	0

[a] Percent of stimulation units containing a bout of ingestive behavior

[b] Mean intake over test session

Table 1-3

The Occurrence of Ingestive Behavior for Animals in Series II During Control and Electrically Elicited Sessions

Subject		Feeding		Drinking		Drinking During Water Only Condition
		%[a]	M Intake[b] (g)	%	M Intake (ml)	%
19 R	control	0	0.20	0	0	0
	elicited	72.25	7.48	0	0.12	0
20 R	control	6.0	1.15	0	0.88	0
	elicited	85.0	13.68	18.7	1.50	37.5
21 L	control	4.0	0.41	2.0	0.50	0
	elicited	63.7	4.90	0	0.75	0
22 R	control	4.0	0.25	0	0	0
	elicited	53.7	9.09	0	1.12	0
23 R	control	2.0	0.10	2.0	0.12	0
	elicited	97.5	19.83	0	0.31	5.0
25 R	control	10.0	2.20	0	2.12	10.0
	elicited	81.2	7.81	0	0.12	0

[a] Percent of stimulation units containing a bout of ingestive behavior

[b] Mean intake over test session

eating during 50%, or more, of the stimulation intervals, as well as at least twice the food intake obtained during the control procedure. A comparison of the control and stimulation sessions ("elicited") indicates the magnitude of increase in both the frequency of eating and the intake which occurred with electrical stimulation. The strongest effect was obtained with animal 23R who consumed 94.4% of his daily intake (21 g) during the 15 min. of electrical stimulation. Similar, although less dramatic effects were obtained from the other electrode placements. In all cases, the eating was restricted to the period of ESB; i.e., no animal displaying elicited feeding ever ate when the stimulation was turned off.

No electrode placement attained a comparable criterion for elicited drinking (i.e., at least one bout of drinking during 50%, or more, of the stimulation intervals, as well as at least twice the water intake obtained during the control procedure). Even the test periods in which only water was present, failed to evoke elicited drinking although some placements did demonstrate increased frequency of drinking as compared to stimulation periods with both food and water available. It is clear, however, that even this arrangement, which was designed to maximize the occurrence of elicited drinking, failed to produce any drinking whatsoever in the majority of placements.

Electrolytic Lesions

None of the animals after receiving electrolytic lesions through their stimulating electrodes displayed elicited eating or elicited drinking as defined above. Furthermore, both the frequency of ingestive behavior and intake were comparable to the levels observed under the control procedures. The lesions, however, did not disrupt the daily intake of food or water as indicated by one-way analyses of variance (mean daily food

intake: Control - 14.88 g; Symmetrical Lesion - 15.23 g, Asymmetrical Lesion - 15.12 g; mean daily water intake: Control - 19.8 ml, Symmetrical Lesion - 18.2 ml, Asymmetrical Lesion - 19.4 ml).

Figure 1-1 illustrates the extent of the lesions produced in the Asymmetrical Lesion group. It should be noted that in all cases the "large" lesion includes the area destroyed by the "small" lesion produced through the tip of the stimulating electrode which maintained elicited feeding. For the Symmetrical Lesion group, the area destroyed in each animal can be determined by finding the electrode placements of the pair of electrodes in Figure 1-2. The "small" lesion did not extend much past the electrode tip.

Discussion

Electrical stimulation of the area of the hypothalamus through which CA fibres pass produced elicited feeding but not elicited drinking. The criteria for elicited ingestive behavior were strict: at least one bout of ingestive behavior during 50%, or more, of the stimulation intervals, as well as at least twice the intake recorded during the control procedure. The elicited feeding was well directed at the food dish occurring irrespective of the animals' initial position in the box. The actual eating was similar to the pattern observed in the home cage: that is, the animal would place its forepaws on the rim of the jar, bite into the HFD, and commence chewing with little, if any, spillage. In many cases (especially in those animals which ate on 80%, or more, of the ESB intervals), once the elicited feeding had commenced it continued until the ESB was terminated. The failure to obtain elicited drinking occurred despite a procedure which was designed to promote its development. During one of the three periods the animal was tested with only the water

Figure 1-1. The extent of the lesions produced in the Asymmetrical Lesion group. Both the "large" and "small" lesions have been transposed to the same side of the brain to better illustrate the amount of overlapping damage. The "large" lesion is represented by the stipled area where the "small" lesion is represented by the filled circle. The brain sections are from König and Klippel (1963) and correspond to their Figures 35b, 36b and 37b.

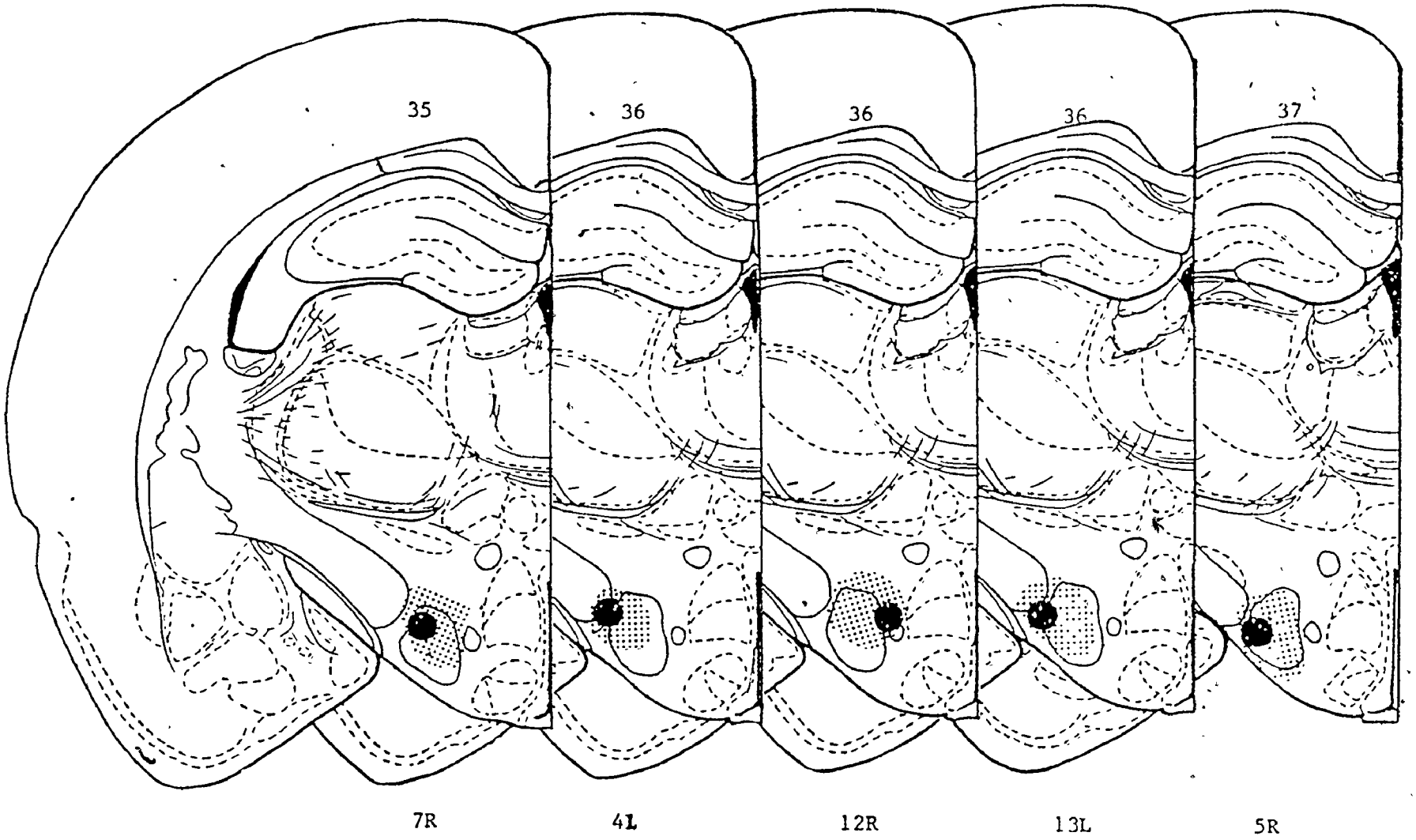
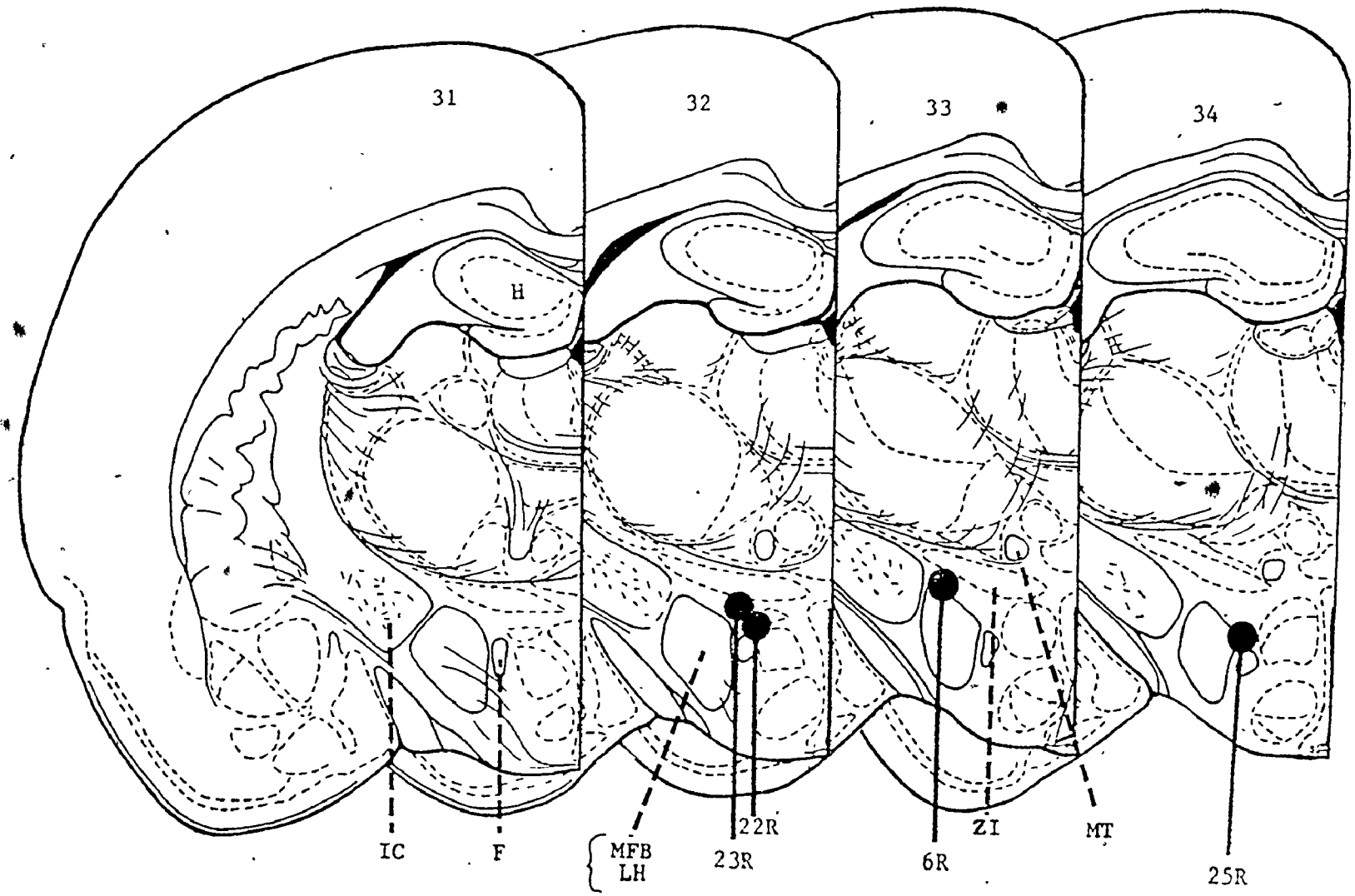
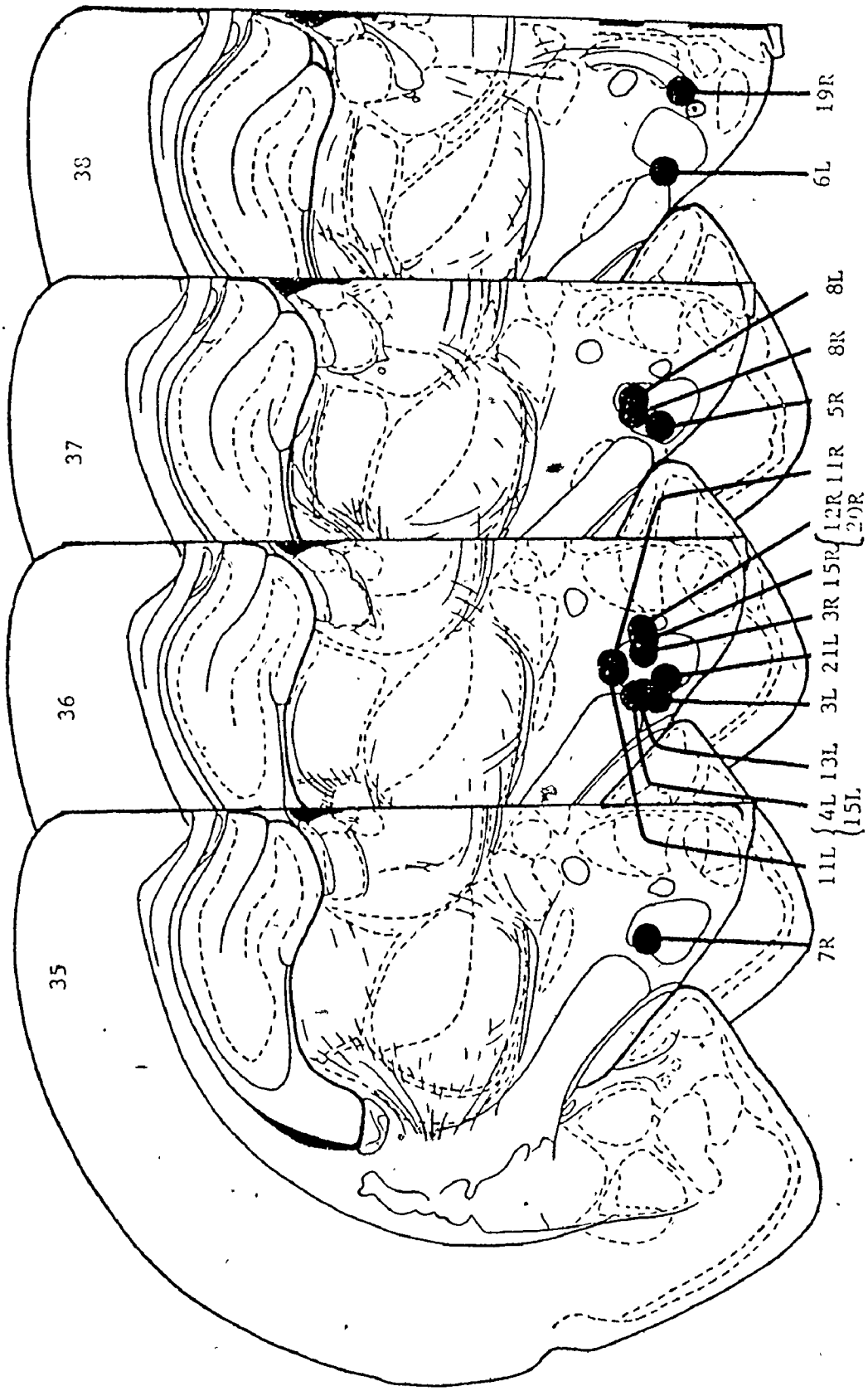

35
36
36
36
37
7R
4L
12R
13L
5R

Figure 1-2. Electrode sites which supported electrically elicited ingestive behavior in Experiment 1. The serial sections are from Konig and Klippel (1963), their Figures 31b-38b. The position of these sections with respect to the interaural line are as follows: anterior 5.50, 4.89, 4.62, 4.38, 4.11, 3.99 and 3.75 mm respectively: (F - fornix; H - hippocampus; IC - internal capsule; LH - lateral hypothalamus; MFB - medial forebrain bundla; MT - Mammillothalamic tract; ZI - zona incerta).


31
32
33
34
H
IC
F
MFB
LH
23R
22R
6R
ZI
MT
25R


38
37
36
35
19R
6L
8L
8R
5R
11R
12R
20R
15R
21L
3R
3L
13L
4L
15L
11L
7R

available, thus removing any competing stimuli from the HFD. Valenstein et al. (1970), as well as Mogenson (1971), argue that it is important to remove the initial goal object in order to observe the emergence of a new response. Milgram et al. (1971), however, have reported that spontaneous emergence of a second response can occur with continued testing. Nevertheless, even under these conditions elicited drinking did not occur. It is, of course, possible that a behavior other than drinking would have emerged if the appropriate goal object were available but still it is clear that most of the feeding placements were uncontaminated by drinking. This observation is in line with other reports which also found relatively pure elicited behaviors (eg. Olds, Allan & Briese, 1971; Huang & Mogenson, 1972; Roberts, 1969).

It should be pointed out, however, that although drinking during the ESB did not meet the standards set for elicited behavior some drinking did occur in a few animals. Nevertheless, such drinking never occurred in an animal which did not also show elicited feeding. The pattern of consumption of the animal showing the greatest amount of drinking (20 R) is informative. When both food and water were present, elicited feeding began shortly after the onset of the ESB and continued for its duration. Further into the session, however, the latency of the feeding response increased with the animal patting and pushing the food dish before eating; eating now did not continue for the duration of the ESB. Close to the end of the session, after a considerable amount of food had been consumed, the animal would eat briefly or make a pass over the food and then drink. When only water was available the animal did not display drinking until after several ESB intervals and then drank only for short bouts - never did it drink for the entire

30 sec duration of the ESB. It should be noted that relatively little water was actually consumed by any animal during the ESB, and in fact the greatest amount consumed (1.50 ml) fell within the range consumed under control conditions (2.0 ml). Such mixed effects suggest that two behaviors are being elicited simultaneously. As the feeding response is weakened by the feedback cues of food ingestion (Tenen & Miller, 1964) the drinking response is able to emerge (Teitelbaum, 1974). Similarly, when the competing stimuli have been removed there is an increase in the amount of drinking during the ESB. However, even with this additional experience the drinking response was not strengthened to the point where it could meet the criteria established for elicited ingestive behavior. These observations are in line with the idea that there are separate but overlapping neural systems in the hypothalamus (Wise, 1968). These data, however, cannot be used to support the more extreme position in the specificity controversy which holds that activation of these systems produce "hunger" or "thirst". In fact, the results following lesions through the tips of the stimulating electrodes tend to weaken this position.

Bilateral lesions at sites which supported elicited feeding presumably destroyed the same functional tissue - although not necessarily the same anatomical tissue. The asymmetrical lesion, in which a small lesion was placed at the feeding site while a larger one was produced at the ineffective electrode site, was designed to bilaterally destroy the homologous tissue around the effective electrode. In both of these cases the lesions successfully abolished the elicited feeding but did not disrupt the daily intakes of food and water. It would seem, therefore, that the same neural tissue is not necessary for both elicited

feeding and spontaneous feeding: in other words, these lesions have dissociated the two phenomena suggesting that their neural mechanisms are not identical. Part of the reason for this dissociation probably involves the localized area of the neural tissue activated by electrical stimulation (Doty, 1969) as compared to the diversity of pathways apparently involved in feeding (Grossman, 1972). Moreover, the measure of natural, or spontaneous feeding, is relatively crude in that no attempt has been made to break down this complex event we call feeding into its components. Nevertheless, this dissociation of elicited feeding and spontaneous feeding suggested that a closer comparison of some of the characteristics of these phenomena might be warranted.

EXPERIMENT 2

The previous experiment showed that it was possible to dissociate feeding induced electrically and spontaneous feeding (as measured by daily intake) by lesions at the tips of the stimulating electrodes. It was pointed out, however, that such a dissociation could simply be an artifact associated with brain stimulation since only a limited area of the brain is being activated (Roberts, 1969). However, there are other studies in the literature which also suggest that electrically elicited behavior is not identical to spontaneous ingestion in some critical ways (see review by Valenstein et al., 1970). It is important, however, to our understanding of the essential nature of both phenomena to clearly delineate the similarities and differences between electrically induced feeding and feeding as it naturally occurs. It is extremely difficult, nevertheless, to meaningfully compare these phenomena since the so-called "spontaneous" or "natural" feeding is a complex event which appears to be under multifactor control (Stevenson, 1969). Accordingly, "spontaneous" feeding must be placed under more rigorous control to provide a reasonable standard for comparison with electrically elicited feeding. A relative simple answer to this problem - but by no means a perfect one - is to induce feeding "naturally" by deprivation. The

solution is not perfect because we do not as yet have a clear understanding of the mechanisms behind the eating induced by short-term deprivation, and more importantly, perhaps, this technique may not involve the anticipatory mechanisms which also seem important to spontaneous feeding (LeMagnen, 1967; Mogenson, 1977).

In this particular study the preference for various diets was compared when feeding was induced by food deprivation and electrical stimulation. Valenstein had previously reported that animals would not readily switch to eating a new - though familiar - food without considerable experience (Valenstein et al., 1968). There was even one animal which did not show elicited feeding when the form of the food was changed from pellets to powder. Furthermore, Valenstein and Phillips (1970) also found that animals reared on a liquid diet displayed stimulus-bound eating of food pellets but did not show such behaviors with the familiar liquid diet. Valenstein has used these data to argue that this is a serious point of dissociation between spontaneous and electrically-induced feeding. Wise and Erdmann (1973) - although agreeing that there is less switching from pellets to liquid diet under ESB than under deprivation conditions - pointed out that even under deprivation, animals could be inhibited from switching over to a new diet by increased arousal or "emotionality". It is important, therefore, that the order of presentation of the diets be controlled for so as to not bias the results if there is some resistance to displaying elicited feeding to a variety of diets: this was done in the present study.

Method

Subjects

Two series of animals were prepared. Series I animals (N=25) were implanted bilaterally with bipolar electrodes in the lateral hypothalamic-medial forebrain bundle region (P 2.7; L 1.6; V 8.8) using the standard operative procedure. Animals in Series II were similarly implanted bilaterally with bipolar electrodes as well as indwelling cannulae aimed at the noradrenergic bundle (P 7.8; L 1.5; V 6.3; N=10), the substantia nigra (P 5.4; L 2.1; V 6.9; N=7), or the lateral ventricles (P 1.0; L 1.5; V 3.2; N=4). Guide cannulae were 1 mm dorsal to the target site. Animals in Series II were also used in Experiments 4, 6, or 8.

Procedure

Forty-eight hour food deprivation. Twelve animals from Series I were tested for diet preference following 48 hrs deprivation. All the animals were given Purina Lab Chow pellets, HFD, and wet mash in their home cages for one week prior to 48 hrs food deprivation. The wet mash was made fresh daily from finely ground pellets and tap water mixed in a 1:1 ratio. Following the 48 hrs food deprivation a measured amount of each diet was placed in the home cage and the amount consumed in four hours recorded. Three large pellets were placed on the cage floor while the HFD and mash were in small cold cream jars (4 cm in diameter, 4 cm deep) level with the rim. Paper towels were placed beneath each cage to collect any spillage. After recording the amount consumed, the three diets were returned to the home cage for three more days and then all food was removed for 48 hrs. Following this deprivation a measured amount of one of the diets was presented and the amount consumed in four hours recorded. The same schedule (i.e., three days with all the diets and then

48 hrs deprivation) was used to test for the consumption of the remaining two diets. The order of presentation of the diets was controlled for by using incomplete counterbalancing (McGuigan, 1968).

Elicited feeding. Animals from Series I and Series II were randomly assigned to one of three conditions according to which diet (i.e., pellets, mash or HFD) they were first exposed to in the test for electrically elicited ingestive behavior. The order of diet presentation in each of these conditions was controlled for by using incomplete counterbalancing. The animals were connected to the stimulator and allowed at least three minutes to adapt before testing began. The test chamber contained the appropriate diet, either on the floor (pellets) or in a cold cream jar secured to the front corner of the chamber (HFD or mash), as well as tap water in a graduated cylinder. The current level of the ESB was initially set at 20 μA and was administered for five 30 sec. stimulation intervals alternating with 30 sec. intervals of no stimulation. If elicited feeding occurred, as defined by clear ingestion during ESB, on three out of five stimulation intervals the current was lowered by 2.5 or 5 μA. If no elicited eating was observed at 20 μA, the current was increased in 5 μA steps until the animal displayed elicited feeding, showed violent jumping, or the maximum output of the stimulator (100 μA) was reached. Each diet was tested twice with at least one day of no stimulation between tests.

Results

Forty-eight Hour Deprivation

The amount of food consumed in four hours was calculated for each of the single diet tests as well as for the combined test in which all three diets were available. Since pilot work indicated that the daily intake of the three diets differed, it was decided that a ratio would provide a more accurate measure of preference than would absolute amounts.

Accordingly, Figure 2-1 presents the intake of each diet during the combined test expressed as a percentage of the intake when only one diet was available. A one-way ANOVA indicated a significant difference among these mean values, $F(2,22) = 58.36$, $p < .01$. Furthermore, a Newman-Keuls test showed significant differences ($p < .01$) for all the pairwise comparisons. Accordingly the diets could be hierarchically ordered from least preferred to most preferred as: pellets, mash, HFD.

Elicited Eating

Figure 2-2 indicates the percentage of electrode placements which displayed elicited feeding to each of the diets. Electrode placements which did not show any elicited feeding were not included in this study. Less than 50% of the effective electrode placements showed elicited eating to the pellets whereas these same placements readily showed elicited eating to both the mash and HFD.

A similar pattern of results emerged when the thresholds for elicited feeding were analyzed (see Figure 2-3). If an electrode placement did not show elicited feeding the maximum current value of 100 μA was assigned. A 3 x 3 ANOVA indicated a significant main effect of the diets, $F(2,78) = 47.38$, $p < .01$. Further analysis with the Newman-Keuls procedure showed that the mean threshold of elicited feeding was significantly lower for the mash and HFD as compared to the pellets ($p < .01$); the thresholds for the mash and HFD did not differ significantly. There was no significant effect for the order of diet presentation.

Histology

The sites of the stimulating electrodes which supported electrically elicited feeding can be found in Appendix 1, Figures A1, A2, A5, A6, & A9.

Figure 2-1. Mean percentage intake on single diet test consumed during the combined diet test (all diets available). The standard error of the mean of each diet is indicated by the bars.

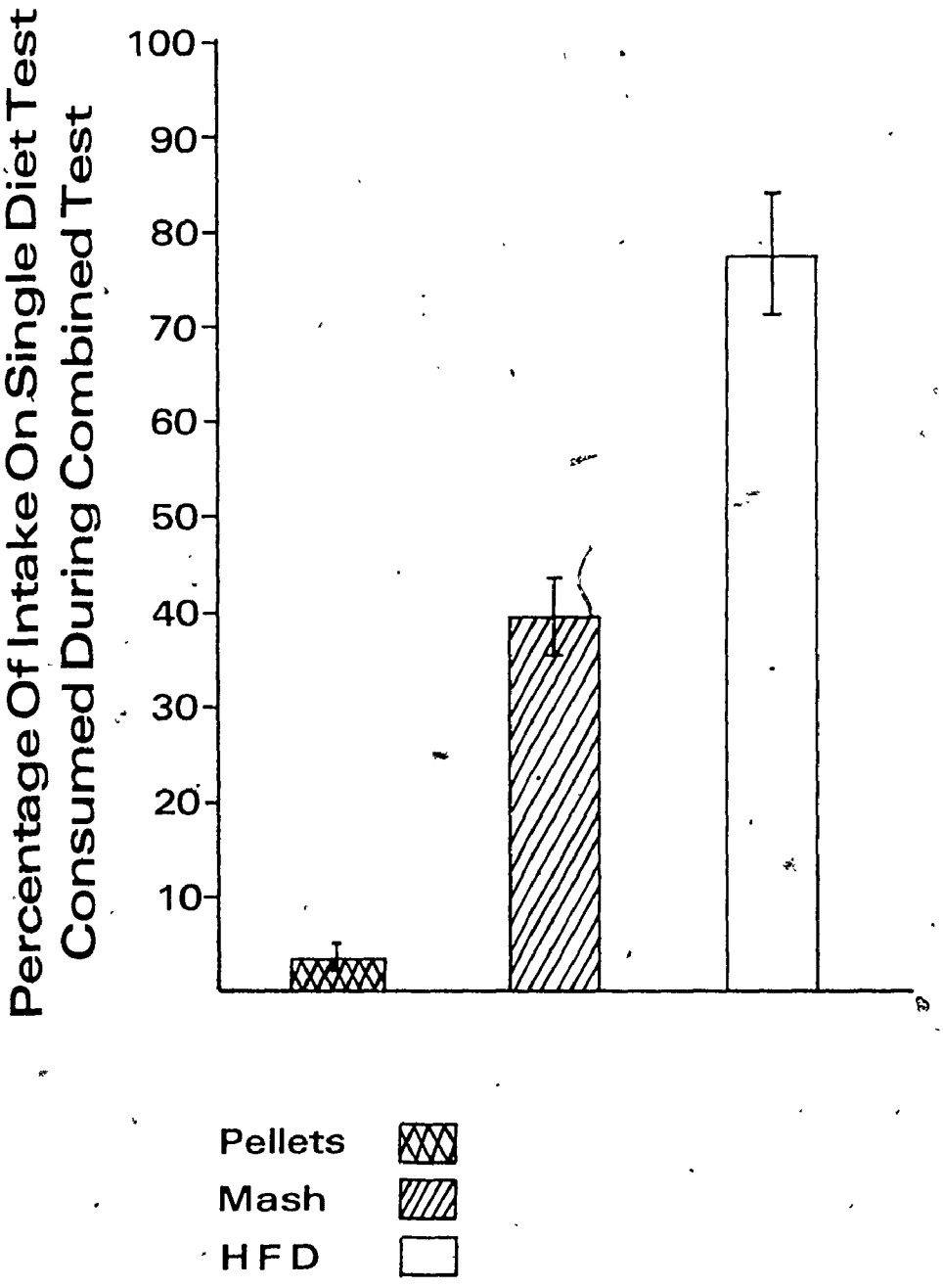

Percentage Of Intake On Single Diet Test
Consumed During Combined Test
100
90
80
70
60
50
40
30
20
10
Pellets
Mash
HFD

Figure 2-2. The percentage of electrode placements displaying elicited eating to Purina Chow pellets, mash and HFD. Electrode placements which did not support elicited eating to any of the diets were not included.

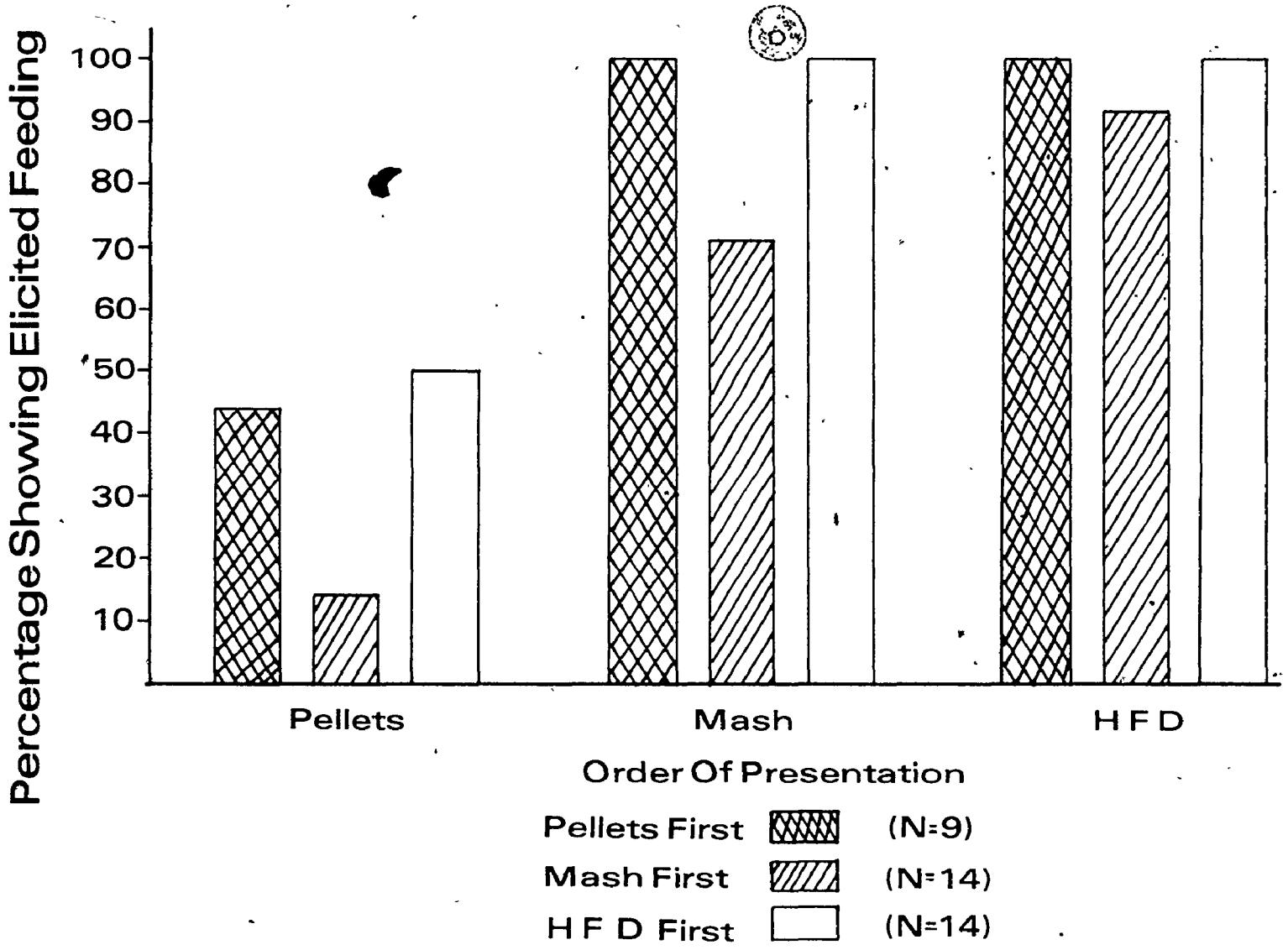
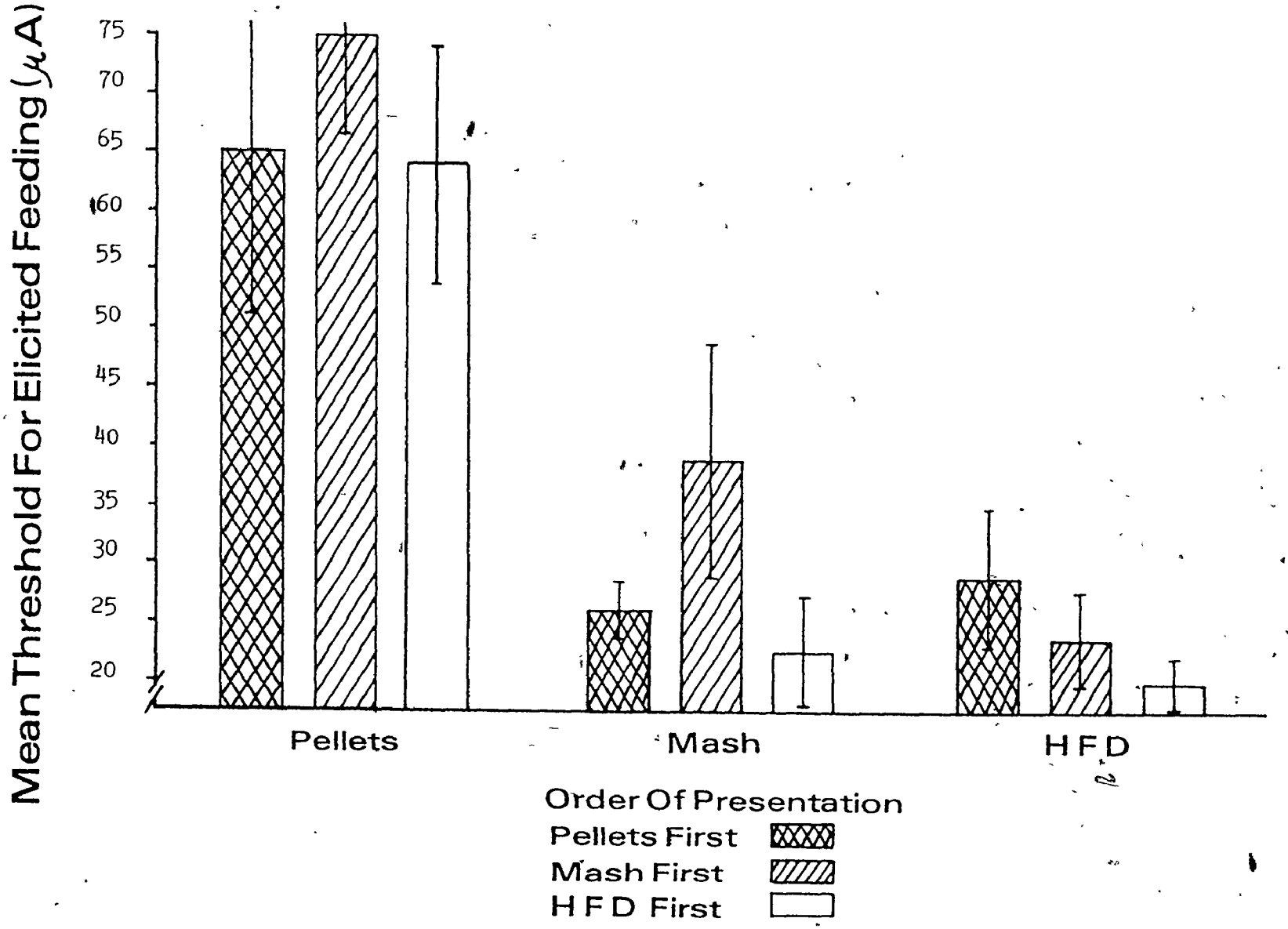
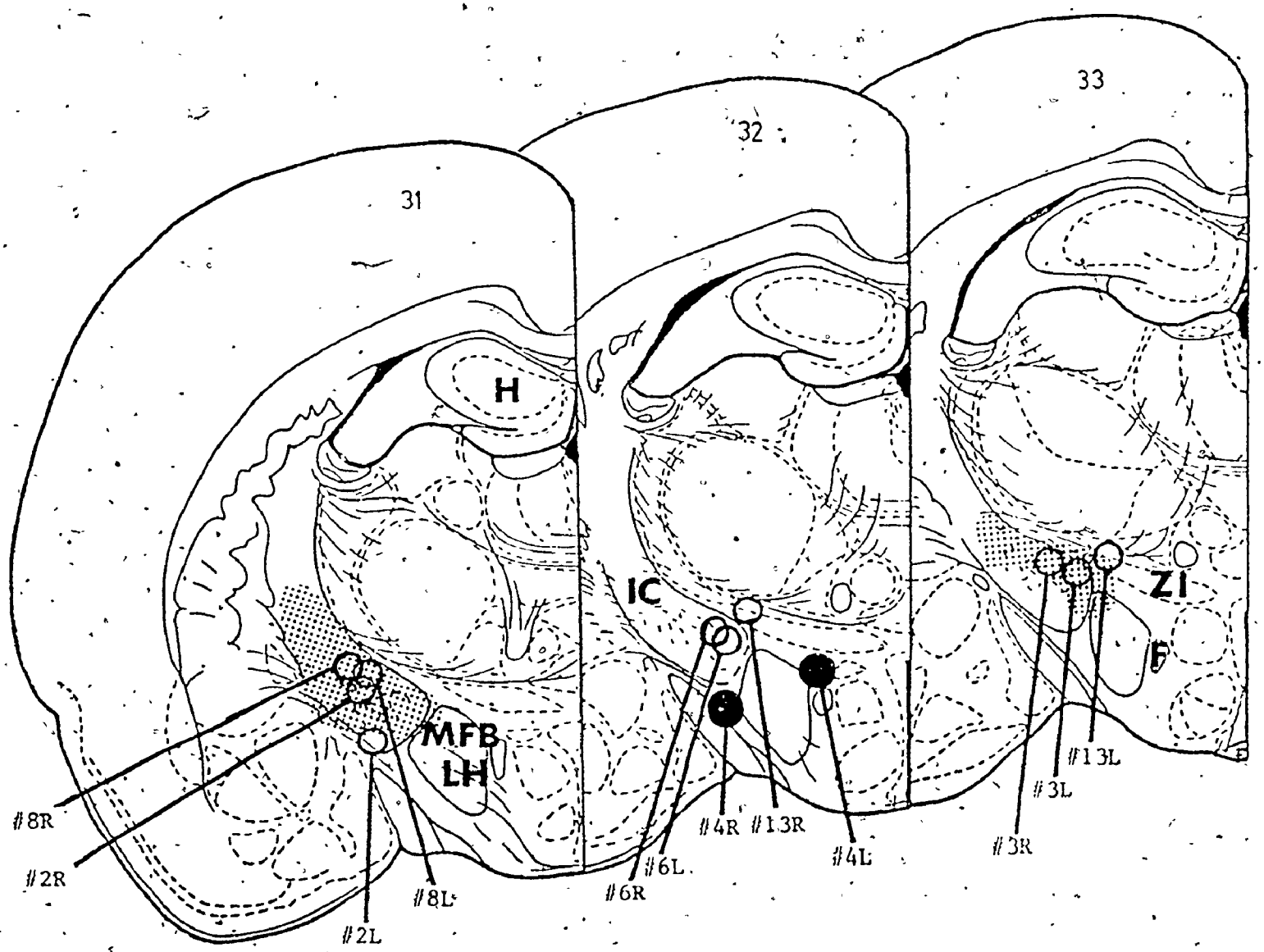

Percentage Showing Elicited Feeding
100
90
80
70
60
50
40
30
20
10
Pellets
Mash
H F D
Order Of Presentation
Pellets First (N=9)
Mash First (N=14)
H F D First (N=14)

Figure 2-3. Mean threshold levels for elicited feeding to pellets, mash and HFD. Electrode placements which did not show elicited eating to a particular diet were assigned the maximum value of 100 μA. The bars indicate the standard error of the mean.


Mean Threshold For Elicited Feeding (μA)
75
70
65
60
55
50
45
40
35
30
25
20
Pellets
Mash
HFD
Order Of Presentation
Pellets First
Mash First
HFD First


31
32
33
H
IC
ZI
F
MFB
LH
#8R
#2R
#2L
#8L
#6R
#6L
#4R
#13R
#4L
#3R
#3L
#13L

the problem of locking of the animal into one response mode, which would occur if all the diets were simultaneously available (Valenstein, 1971). It was, of course, not practical to reverse the procedure by trying to obtain "threshold" values under a deprivation condition.

The observed differences in preference under these two conditions are interesting inasmuch as they suggest different factors may be important in controlling feeding. Gustatory factors cannot be the only ones involved in this selection process since under both conditions the mash - i.e., ground-up pellets and water - was preferred over the solid pellets. Since it is unlikely that the water itself provided any gustatory cues, it seems that the differentiation was probably made on the consistency of the food. Barnett (1963), in fact, notes that wild rats appear to prefer soft, mushy food since they will soak hard grain in water if given the opportunity. It is noteworthy that with the ESB the two foods which had the same general consistency - HFD and mash - were not differentiated.

It is possible, however, that under ESB the animal is less reactive to taste than it is under deprivation conditions. Tenen and Miller (1964) reported that quinine-adulteration is more effective in reducing eating produced by deprivation than by electrical stimulation. Smith (1972) also found ESB did not make the animals more reactive to taste. This relative insensitivity to taste may account for the differences between conditions, but there are other alternatives. For instance, since both the HFD and mash have the same consistency the pattern of ingestion would be the same. This is not true, however, for the pellets. A different sequence of responses is required to ingest the pellets as opposed to a soft, mushy food. It is interesting that Valenstein and

Phillips (1970) could get their animals to chew up and swallow pellets but not lick to ingest a liquid diet under the initial test with ESB. Perhaps the ESB is specific in the sense that it predisposes the animal to engage in a particular type of ingestive sequence which may have some intrinsic species value as suggested by Glickman and Schiff (1967).

The findings of this study tend not to support the contention of Valenstein et al. (1968) that animals fail to show elicited feeding when a different diet is used. Under the present test conditions, where each diet was tested separately, almost all of the animals that showed elicited feeding to the HFD diet also displayed it to the mash. There was support, however, for Valenstein's observation on the single animal that would not eat once the form of the food was altered from pellets to powder. Animals in the present study often would not eat the pellets although they readily consumed the wet mash. Valenstein, moreover, pointed out that under deprivation this animal readily ate the altered form of food.

In conclusion - although one must be cautious - it appears once again that elicited feeding can be dissociated from natural feeding (48 hrs food deprivation) this time with respect to the preference shown for diets of different consistency, and presumably taste (i.e. pellet-based diets vs. HFD).

EXPERIMENT 3

Ungerstedt (1971a), as well as others (eg. Oltmans & Harvey, 1972; Stricker & Zigmond, 1976), has suggested the LH syndrome is primarily a result of damage to the dopaminergic nigrostriatal bundle since damage to this system reproduces much of the LH syndrome. Consequently in order to determine whether elicited feeding is a result of the same mechanisms which subserve spontaneous feeding, stimulating electrodes were aimed at the NSB at that point where electrolytic lesions produce feeding deficits (Oltmans & Harvey, 1972). If elicited feeding were obtained from the NSB, then the view that elicited feeding and spontaneous feeding share the same mechanisms would be supported; however, failure to obtain such behavior cannot be used against this view because of the complex properties of electrical stimulation (Roberts, 1969).

Method

Subjects

Fifteen rats were implanted bilaterally with bipolar electrodes aimed at the nigrostriatal bundle (P 2.7 - 2.8, L 2.8, V 8.8 - 8.9). One animal (#11) was not tested since his electrode assembly was prematurely dislodged. All animals were maintained exclusively on the HFD and water for at least one week prior to testing for elicited behavior; small blocks of pine (3 x 3 x 3 cm) were placed in the home cage.

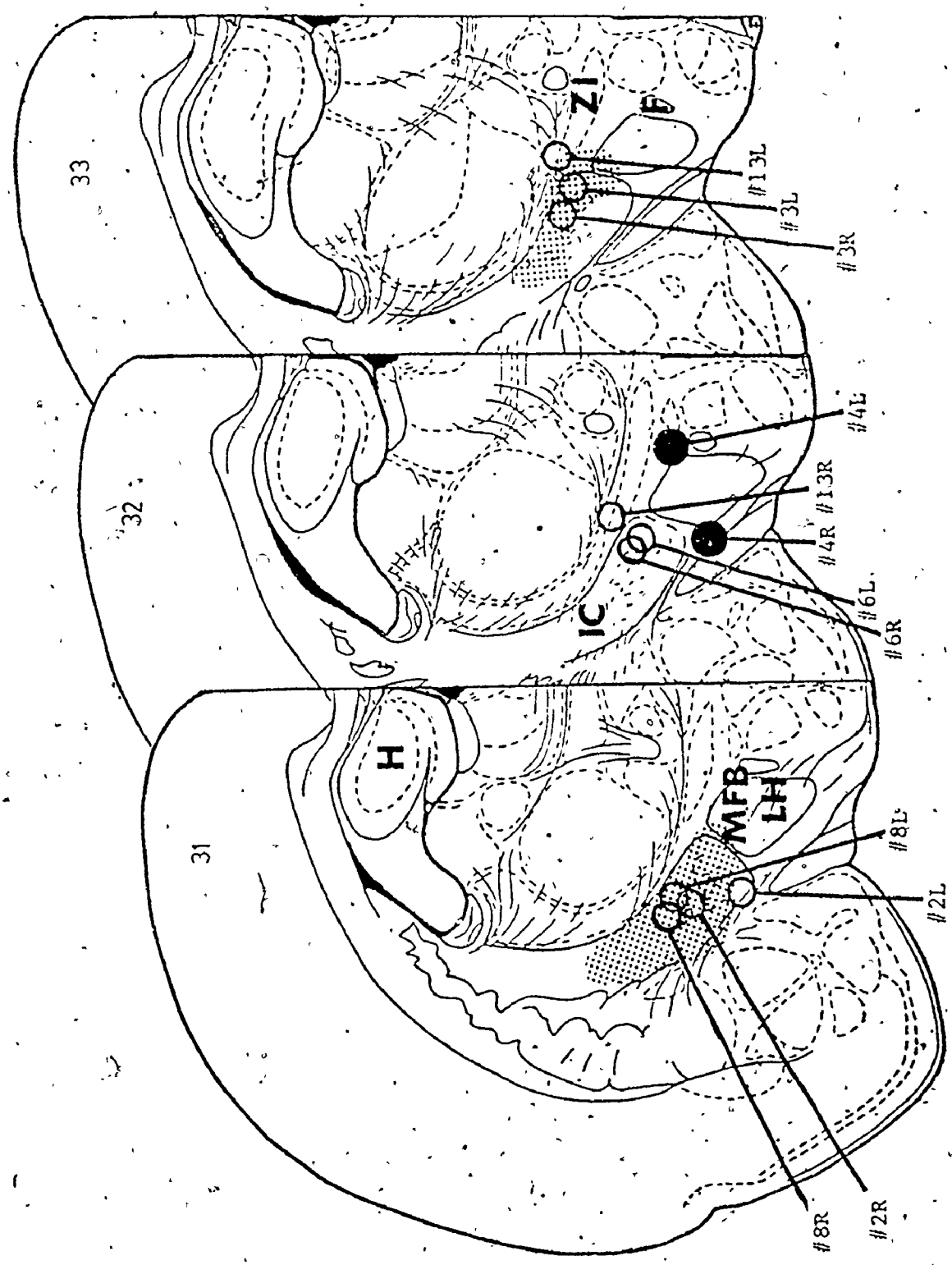
Procedure

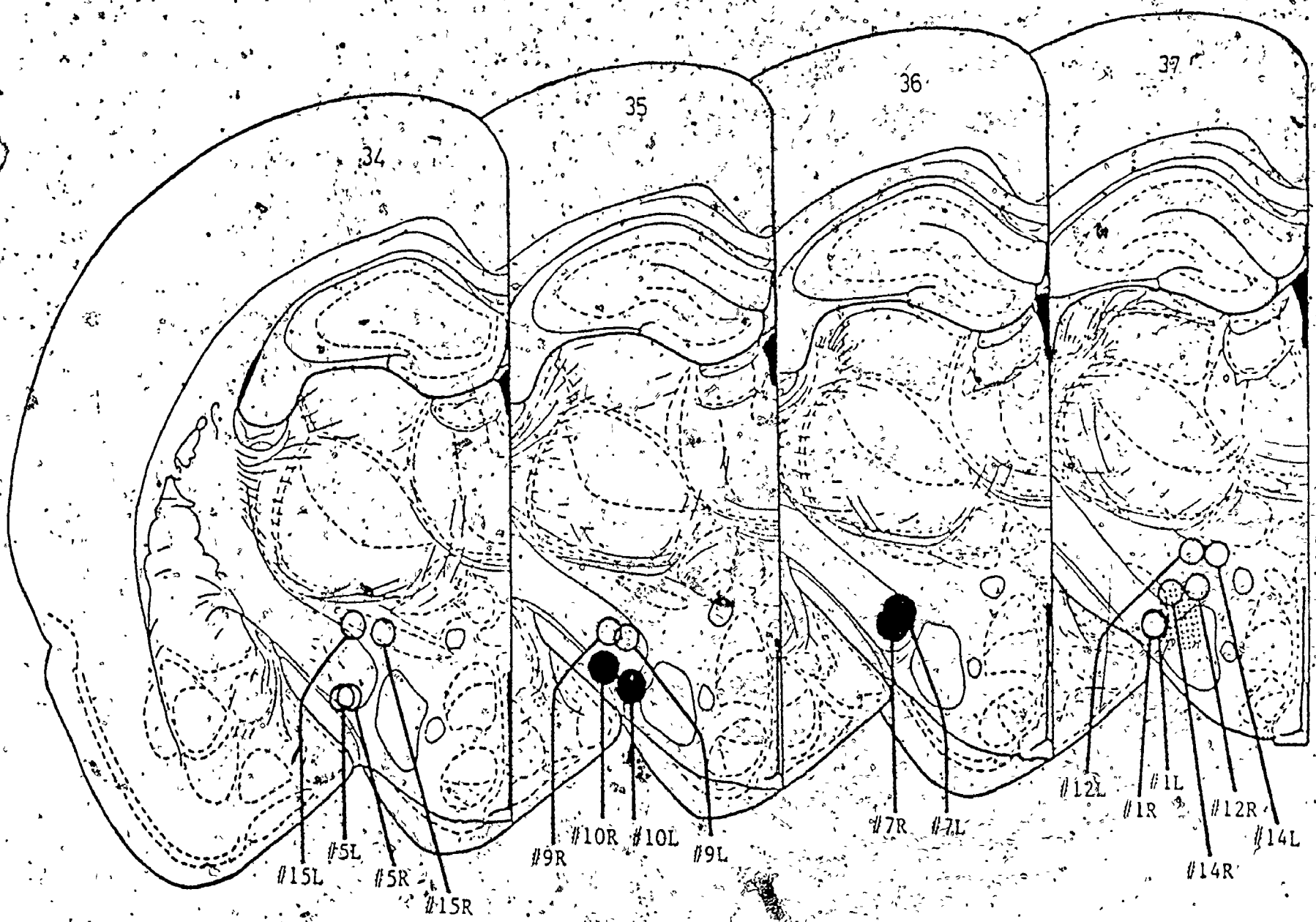
The animals were tested for electrically elicited behavior in clear Plexiglas chambers containing the food dish from the home cage (HFD), tap water via a Richter spout, and three small blocks of pine (3 x 3 x 3 cm). Following a three-minute adaptation period, the current was set at 10 μA and was administered for five 30 sec. stimulation intervals alternating with 30 sec. intervals of no ESB. The current was increased in 5 μA steps every five minutes to a maximum current level of 100 μA or until the animal was incapacitated by the ESB. The behavior of the animal during each interval was noted: the behaviors of interest included feeding, drinking, gnawing, carrying, and forced movements.

Results

Of the 28 electrodes tested for elicited behavior 21 were judged from histological evidence to be stimulating the NSB (see Figure 3-1). Electrical sitmulation of the NSB failed to elicit feeding, drinking, gnawing, or carrying under the conditions tested. Forced movement was the only category of elicited behavior observed from the NSB and involved either forced turning or circling in a direction contralateral to the electrode placement (i.e., electrodes on the right side of the brain induced

Figure 3-1. Electrode sites aimed at the nigrostriatal bundle (NSB). Open circles indicate sites which elicited contralateral turning or circling; closed circles indicate sites which did not elicit contralateral turning or circling. The stipled area outlines the NSB after Ungerstedt (1971a). The serial sections are from König and Klippel (1963), their Figures 31b - 37b. (F - fornix; H - hippocampus; IC - internal capsule; LH - lateral hypothalamus; MFB - medial forebrain bundle; ZI - zona incerta).


33
32
31
ZI
IC
H
MFB
LH
#13L
#3L
#3R
#4L
#4R
#13R
#6L
#6R
#8L
#2L
#8R
#2R


34
35
36
37
#15L
#5L
#5R
#15R
#9R
#10R
#10L
#9L
#7R
#7L
#12L
#1L
#1R
#12R
#14L
#14R

counter-clockwise circling or turning, whereas left electrodes produced clockwise movement). Forced turning involved the animal's arching its body to the right or left, whereas forced circling involved the animal's walking in a complete circle. Forced movements were reliably observed during three or more stimulation intervals out of five from 19 of the 21 placements in the NSB (90.5%). These forced movements were restricted to the period of ESB and usually commenced with the onset of the stimulation. The vigor of these movements, as judged by the speed and control of the animal's behavior, increased with increased current such that at the higher current levels (e.g., 40 μA) the animal would be walking briskly or running in circles for the duration of the stimulation. At the higher currents animals who displayed forced turning would be so contorted that occasionally they would flip over and get entangled in their leads; stimulation was terminated at this point. All of these "forced" movements had a "mechanical" quality to them. The current threshold ranged from 10 - 30 μA.

Three of the seven sites not in the NSB also elicited forced movement but with these placements the vigor of these movements decreased over time if the current level was kept constant; this effect was not observed for the NSB placements. Electrically elicited eating was obtained from electrode #4L which was located on the edge of the medial forebrain bundle outside of the NSB. Eating was observed on 9 out of 10 stimulation periods with a total intake of 7.51 g. None of the other predetermined categories of elicited behavior were observed from these placements.

Discussion

Electrical stimulation of the NSB at the level of the lateral

hypothalamus produced only forced movements which involved either body contortions or circling toward the unstimulated side. Such observations are consistent with the view of Andén (1966) and others (eg. Ungerstedt & Arbuthnott, 1970) that turning behavior results from excess release of dopamine from the striatal terminals. When electrolytic lesions were made through electrodes in the substantia nigra (which produced contraversive turning when stimulated) pharmacological activation of the remaining NSB resulted in turning towards the side of the lesion (Arbuthnott & Crow, 1971). Apparently the ESB involves a similar asymmetrical activation of the NSB. Turning behavior has also been reported by Arbuthnott and Ungerstedt (1975) from stimulation of the NSB at the level of postero-lateral hypothalamus; the action of pharmacological agents supported the idea that DA was involved in this behavior.

The failure to obtain elicited ingestive behavior - although suggested by the lesion studies - does not mean that the NSB plays no part in ingestion. As Roberts (1969) points out, it is difficult to draw such a conclusion from ESB since often the stimulation only activates a small portion of brain. Moreover, the gross nature of the pattern of activation produced makes it quite likely that the ESB could "jam" the system. This latter point gains support from the observation of Phillips and Fibiger (1973a) that rebound-feeding can be produced by electrical stimulation of the substantia nigra (the cell bodies of the NSB).

EXPERIMENT 4

As was already pointed out, catecholaminergic neurons have long been implicated in feeding behavior. For example, Grossman (1962) found that intracerebral injections of NA into the hypothalamus elicited feeding from satiated rats. More recently it has been shown that CA damage produced by electrolytic lesions (Oltmans & Harvey, 1972, 1976) and the neurotoxin 6-OHDA administered both intraventricularly (eg. Zigmond & Stricker, 1972; Fibiger et al., 1973) and intracerebrally (Ungerstedt, 1971b; Smith, Strohymayer & Reis, 1972; Fibiger, Phillips & Clouston, 1973) result in disruption of feeding and drinking (as well as other deficits).

In an attempt to understand the nature of elicited feeding and its relationship to natural feeding it is important to examine the involvement of the catecholamine system in these phenomena to uncover points of similarity and dissimilarity. A number of anorectic agents which operate by interfering with CA have also been shown to disrupt or raise the threshold for elicited feeding (Miller, 1960; Stark & Totty, 1967; Wishart & Wall, 1974) suggesting a common CA involvement in both phenomena. Even anorectic drugs which have little of the psychomotor stimulation effects of amphetamine can inhibit elicited feeding (Hoebel

et al., 1975). More to the point, perhaps, Phillips and Fibiger (1973b, 1976) have examined the effects of intraventricular 6-OHDA plus a monoamine oxidase inhibitor (MAOI) on elicited feeding. They have observed that even after an animal has recovered its abilities to regulate its daily food and water intakes the elicited feeding is still almost completely depressed. The present study is designed as a replication of this work and is aimed at determining whether in fact central CA damage can dissociate elicited feeding from spontaneous feeding.

Method

Subjects

Sixteen animals were implanted bilaterally with stimulating electrodes in the lateral hypothalamic - medial forebrain bundle region (P 2.7, L 1.6, V 8.8) and with chronic guide cannulae aimed at the lateral ventricles (P 1.0, L 1.5, V 3.2). The guide cannulae were positioned 0.5 mm above the ventricles while the injection cannulae (30 gauge stainless steel tubing) projected 1.0 ($\pm$ 0.1) mm beyond the end of the guide cannulae.

Procedure

The animals were subjected to the screening procedure for elicited ingestive behavior at least twice. Those animals which displayed elicited feeding from at least one electrode were randomly divided into an experimental (N=7) and a control group (N=6). A current level which would produce stable elicited feeding was selected for each electrode placement. Each animal was tested for electrically elicited feeding on three consecutive days to establish the pre-injection performance level. A test session consisted of a 3 min. adaption period followed by 10 min. of alternating brain stimulation (30 sec. ON - 30 sec. OFF). The presence or absence of an elicited ingestive response was recorded as was the total amount of food (HFD) and water consumed during the entire test session (13 min.).

All subjects were pretreated with intraperitoneal injections of tranylcypromine sulfate (5 mg/kg in a concentration of 5 mg/ml dissolved in isotonic saline). Thirty minutes later they were lightly anaesthetized with ether and prepared for intraventricular injections of 250 µg of 6-OHDA in 25 µl of 0.9% NaCl containing ascorbic acid (.2 mg/ml) or 25 µl of vehicle. The inner stylus pin was removed and the 30 gauge inner cannula was inserted into the guide cannula. The inner cannula was connected

with a tight seal to PE 10 (7401) Intramedic Polyethylene Tubing (Clay Adams - I.D. = 0.254 mm; O.D. = 0.610 mm) and then to a 25 µl Hamilton syringe with a Chaney adaptor. The injection was infused into the lateral ventricle with a syringe pump (Sage Syringe Pump #237-2) at a rate of 5 µl/min. The patency of the injection cannulae was previously verified by elevating the polyethylene tubing about 10 cm above the rat's skull and observing the rapid inflow of artificial cerebral spinal fluid (Myers, 1972).

Following the infusion, all animals were returned to their home cages where their daily food and water intakes, as well as body weight, were monitored. Animals were maintained by intragastric intubation of 10 cc of Carnation Vanilla Instant Breakfast mixed with 2% milk and Kao-pectate (Upjohn) in the morning and afternoon every other day using a #5 French feeding tube for premature babies. On alternate days only a morning feeding was given to determine whether the rat was eating the HFD in the home cage. When each animal was able to maintain himself, intragastric feeding was terminated. After the pre-lesion food intake was reached the animals were retested for electrically elicited feeding for three consecutive days.

Results

Intraventricular injections of 6-OHDA with a pretreatment of tranylcypromine sulfate produced a severe reduction in daily food and water intake. Water intake was reduced to a mean of 4.8 ml as compared to a pre-lesion level of 21.3 ml; food intake was reduced to a mean of 7.4, from 19.8 g.

By the end of the sixth day post-lesion both food and water intake had recovered sufficiently so that body weight had stabilized at 82% of

the pre-lesion level. Daily food and water intakes, as well as body weight, returned to the pre-lesion levels by the tenth day post-lesion, at which time the animals were tested for elicited behavior. Control animals showed only a slight decrease in food and water consumption during the 24 hrs following the control injection of the vehicle but returned to their pre-lesion levels after that.

Elicited feeding was strongly suppressed by the injection of 6-OHDA and tranylcypromine sulfate. A 2 x 2 ANOVA, using the lesion condition and "pre vs post" as factors, showed significant main effects as well as a significant interaction for the frequency of elicited feeding (F (1,11) = 181.24, 278.30, and 219.75 respectively; $p < .01$). As Figure 4-1 illustrates, the experimental treatment produced a significant decrease in the frequency of elicited feeding both with respect to the pre-lesion levels as well as in comparison to the control animals. There was virtually no difference, however, in the frequency of elicited feeding following the control procedure. A similar analysis on the amount of food consumed during brain stimulation indicated significant effects for the "pre vs post" factor and the interaction term (F (1,11) = 44.89, and 31.03 respectively; $p < .01$). Figure 4-2 illustrates that the amount of food consumed remained relatively constant following the control procedure but that there was a significant decline after the 6-OHDA was administered. The failure to obtain a significant main effect of the lesion condition can be attributed to the lower intake of the control animals prior to the administration of the treatments. In both analyses, however, it is the interaction term which is most informative since it indicated that the control and experimental groups differed following the treatment.

Figure 4-1. The effect of 6-OHDA and tranylcypromine sulfate on the mean frequency of elicited feeding. Each point is a mean score averaged over the three days prior to the treatment or three days after the return to baseline intakes of food and water.

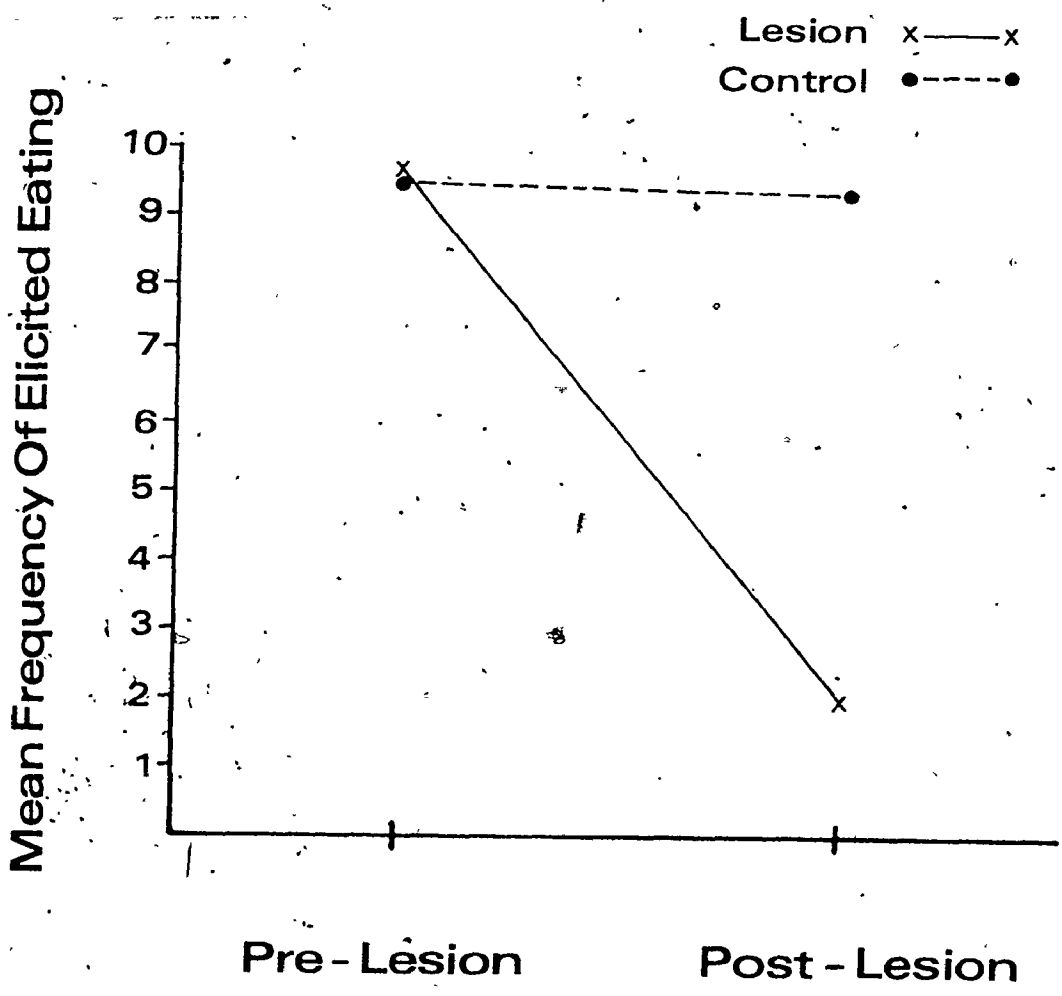
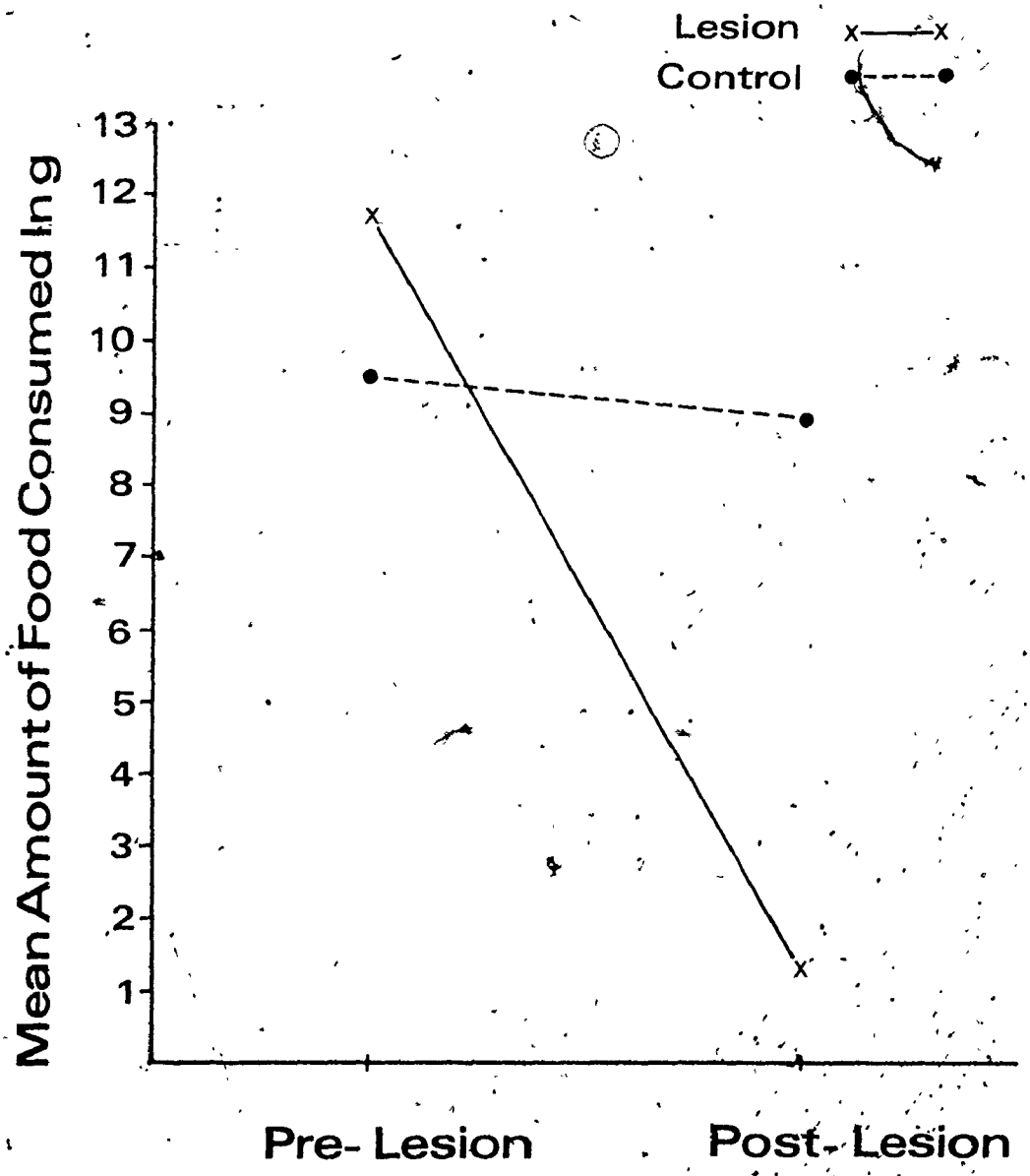


Figure 4-2. The effect of 6-OHDA and tranylcypromine sulfate on the mean amount of food intake during elicited eating. Each point is a mean score over the three days prior to the treatment or three days after the return to baseline intakes of food and water.



Histology

The sites of the stimulating electrodes which supported electrically elicited feeding can be found in Appendix 1, Figure A2. The placements of the ventricular cannulae were histologically verified.

Discussion

The results of this study are in complete agreement with the findings reported by Phillips and Fibiger (1973b, 1976). Intraventricular injections of 6-OHDA following a MAOI pretreatment disrupted elicited feeding even after the animals had recovered from the temporary aphagia and adipsia produced by the lesion. Phillips and Fibiger (1976) have demonstrated that this suppression, in addition to being almost total, is also a long-term effect inasmuch as the disruption continued for the entire 56-day postinjection test period. Moreover, this effect was not the result of an increase in the threshold required to elicit feeding since increases in current failed to reinstate the elicited behavior. A similar long-term disruption occurred with other elicited oral behaviors, i.e. drinking and gnawing.

What is important, however, is that these deficits in elicited behavior remain despite a recovery of spontaneous intake. Such a dissociation of elicited feeding from spontaneous intake brings into question the view that these two phenomena share a common neural mechanism. As was pointed out in the discussion of the factors which can induce an animal to eat, there is reasonable evidence to suggest that spontaneous feeding is under multifactor control (Stevenson, 1969). It is also likely that there are different neural subsystems involved in the control of these factors (Blass & Kraly, 1974). Mogenson (1974), for example, has suggested that some of these subsystems may be involved in integrating

deficit signals and their control of feeding, while others may initiate feeding in response to the external incentive stimuli suggested by LeMagnen (1967). Failure to obtain elicited feeding while the animal can still eat spontaneously may indicate that the ESB is activating only one subsystem which has been damaged by the lesion; spontaneous feeding recovers and carries on because it utilizes alternate systems. Such a possibility is examined further in Experiment 7 where the feeding deficits of animals with various CA lesions are considered.

Nevertheless, this is probably not a simple motor problem inasmuch as the animal can make the appropriate response sequence in its home cage but not when the ESB is applied. It is possible, however, that elicited feeding is not displayed because there are subtle deficits in feeding efficiency which prevent the animal from eating during the relatively short test intervals used for elicited behavior. Some support for this possibility is provided by the recent observation by Stricker (1976) that some of the long-term deficits following electrolytically induced LH damage can be reversed if the animal is given sufficient time to respond. However, there is evidence that these animals could eat under time constraints inasmuch as they consistently commenced eating the HFD when it was freshened each day.

The technique employed in this study (i.e. intraventricular administration of 6-OHDA) does not, however, permit a conclusion about the relative contribution of the NA or DA systems in this dissociation since it produces significant depletion in both systems (eg. Uretsky & Iversen, 1970; Fibiger et al., 1973). One way to determine the involvement of these systems in this phenomenon would be to selectively disrupt the

various catecholamine pathways and observe the effects on elicited feeding. The following studies represent an attempt to do this using electrolytic lesions, intracerebral injections of 6-OHDA, and pharmacological agents.

EXPERIMENT 5

The involvement of the dorsal noradrenergic pathway in elicited feeding was examined by destroying the locus coeruleus with a unilateral electrolytic lesion, and by an intracerebral injection of 6-OHDA into the pathway. The cell bodies for the dorsal noradrenergic pathway are located in the locus coeruleus (Ungerstedt, 1971a; Palkovits & Jacobowitz, 1974) so that destruction of this area would disrupt this system. According to Ungerstedt (1971a, 1973) and others (Arbuthnott, Christie, Crow, Eccleston & Walter, 1973), this system is uncrossed so that if elicited feeding was a result of activation of this pathway unilateral destruction ought to disrupt elicited feeding. The use of a unilateral lesion provides an excellent control for any nonspecific effects of the lesion when used with animals which have bilaterally effective stimulating electrodes. In such a preparation destruction of the pathway should disrupt elicited feeding only from the electrode ipsilateral to the lesion site. If elicited feeding is suppressed at both electrode placements it must be concluded that the effect is not the direct result of damage to the tissue underlying the electrode but rather to a general debilitation of the animal's performance.

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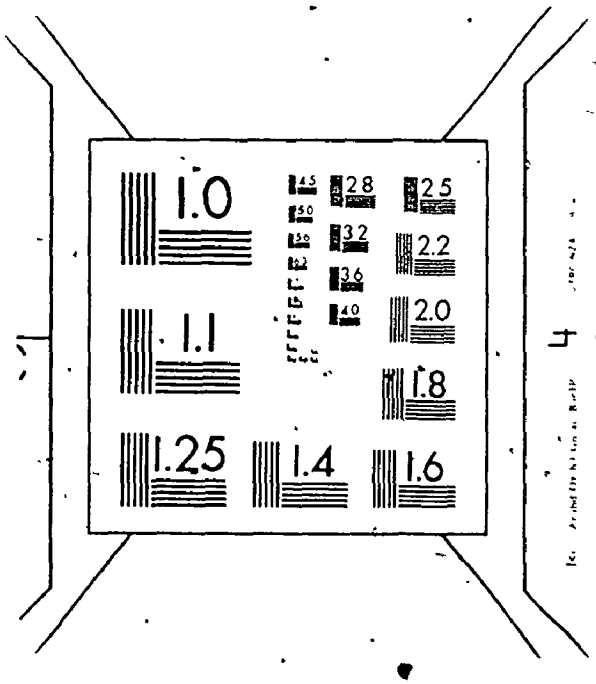


An electrolytic lesion, however, is not very selective and could possibly damage adjacent structures. This is an important concern since Zeigler and Karten (1974) have suggested that damage to the trigemenal fibres might be involved in some of the components of the LH syndrome. Intracerebral injections of 6-OHDA provide a means of selectively damaging the catecholamine system (Breese & Traylor, 1970; Ungerstedt, 1971a). In order to limit damage to the dorsal NA system an injection of the 6-OHDA must be made into the axons at the level of the interpeduncular nucleus where the system is running as a separate bundle (Ungerstedt, 1973). Such a lesion denervates parts of the diencephalon, the cortex, and the hippocampus of their NA terminals, while the cerebellum is left intact. Moreover, this lesion will cause degeneration which is limited to the side ipsilateral to the lesion. Injections directly into the region of the NA cell bodies produce little damage since the cells in the locus coeruleus are relatively insensitive to 6-OHDA.

Method

Subjects

Sixteen animals were implanted bilaterally with stimulating electrodes in the lateral hypothalamic - medial forebrain bundle region (P 2.7, L 1.6, V 8.8) and with chronic indwelling lesion wires aimed at the locus coeruleus (2.1 mm posterior to lambda; 0.5 mm lateral to the midline; 7.4 mm ventral to the surface of the skull at lambda; skull level between lambda and bregma). The lesion wires were insulated except at the cross-section of the tip. The upper portion of the lesion wires were protected from damage by a thin layer of acrylic cement after they had been bent so as to lie flat on the head.

Another seventeen animals were implanted bilaterally with stimulating electrodes in the lateral hypothalamic region (P 2.7, L 1.6, V 8.8) and with chronic guide cannulae aimed at the dorsal noradrenergic bundle anterior to the locus coeruleus (P 4.45, L 0.8, V 5.6). The guide cannulae were 1.0 mm above the target area for injection.

Procedure

Electrolytic lesion. All electrode sites were screened for electrically elicited ingestive behavior at least twice; only elicited feeding was observed. Of the 16 animals tested, 6 showed elicited feeding from only one electrode placement and 4 showed it from both electrode placements. Suitable current levels which supported elicited behavior were selected and checked the following day. Each animal was tested for elicited feeding on three consecutive days; a test session consisted of a 3 min. adaptation period followed by 10 min. of alternating brain stimulation (30 sec. ON - 30 sec. OFF). The food dish from the home cage (HFD) and water were available during the testing. On the fourth day the same testing procedure was followed except that the ESB was turned off; this acted

as a baseline for eating without ESB. The descending threshold for elicited eating was determined by starting with the pre-selected current level and reducing the current in 2.5 μA steps until no elicited feeding (i.e., eating on less than 3/5 stimulation intervals) was observed on two consecutive levels. Each current level was presented for five 30 sec. stimulation intervals. The ascending threshold was determined by starting at 5 μA below the last current level in the descending series. The current was increased in 2.5 μA steps until elicited feeding (i.e., eating during 3 or more of the 5 stimulation intervals) was observed on two consecutive levels. A retest using the pre-selected current level was run on the seventh test day to assure a stable response. Immediately following this test, the animal was lightly anaesthetized with ether while the chronic lesion wire ipsilateral to the effective stimulating electrode was exposed and the insulation scraped away. A unilateral anodal lesion (1 mA for 10 sec.) was performed through this exposed wire. Following the lesion all the electrode placements were tested at their pre-selected current levels for three consecutive days, given one day of the control procedure, and then subjected to the descending and the ascending threshold determinations. Two weeks later this sequence of testing was repeated.

Animals that displayed elicited feeding from both electrodes (N=4) were tested twice daily. The second electrode was tested approximately two hours after the first one. These animals received only a unilateral lesion ipsilateral to the first placement tested. These preparations acted as controls for the non-specific effects of the lesions.

6-OHDA lesion. The animals with indwelling cannulae aimed at the dorsal noradrenergic bundle were treated to basically the same procedures as the animals with lesion wires in the locus coeruleus. In this group

there were 4 animals who displayed elicited feeding to only one electrode placement and 3 who showed it at both placements. Since the electrolytic lesion in the locus coeruleus had failed to selectively disrupt elicited feeding, an attempt was made to more specifically destroy the dorsal noradrenergic bundle using 6-OHDA injected directly into the pathway. The lesion was performed after the test for elicited feeding on the seventh day. The animal was lightly anaesthetized, the stylus removed and the inner cannula inserted. 6-hydroxydopamine was dissolved in isotonic saline (containing .2 mg/ml ascorbic acid) in the concentration of 8 µg base/µl and injected at the rate of 0.5 µl/min over two minutes using an infusion pump. The injection was unilateral and was ipsilateral to the effective electrode site. The rest of the procedure was the same as for the electrolytically lesioned animals.

Results

Electrolytic Lesions to the Locus Coeruleus

Table 5-1 presents the effects of unilateral electrolytic lesions in the locus coeruleus on three measures of elicited feeding. Each score is a mean value derived from 10 electrode placements averaged over three days. One-way ANOVA's computed for each measure failed to show any significant differences across the lesion conditions; this indicates that the lesion failed to disrupt elicited feeding. It should be noted, however, that on the day immediately following the lesion that there was a significant decrease in both the frequency of elicited feeding (t (9) = 2.01, $p < .05$) and the amount consumed (t (9) = 5.61, $p < .01$) as compared to the test session prior to the lesion. By the third day following the lesion, however, elicited feeding had returned to pre-lesion levels. Such a suppression in elicited feeding does not appear to be the result

Table 5-1

Effects of Unilateral Electrolytic Lesions in the Locus Coeruleus on the Frequency of Elicited Eating, on the Amount Consumed, and on the Threshold for Elicited Eating

Measure	Pre-Lesion	Post-Lesion I	Post-Lesion II[a]
Frequency[b]	9.3 (0.35)[d]	8.0 (0.99)	8.8 (0.54)
Amount (g)	7.23 (1.18)	5.19 (1.14)	6.23 (1.17)
Threshold[c] (μA)	46.5 (4.84)	49.2 (9.60)	59.2 (11.97)

a A retest which occurred two weeks after the lesion

b Maximum score = 10

c Mean total for Ascending and Descending conditions

d The standard error of the mean ($S_m = S/\sqrt{N}$)

of destruction of fibres coursing near the electrode tip since animals with bilaterally effective electrode placements (N=4) showed a similar suppression from the unlesioned side. The frequency of elicited feeding was reduced to 72% of the pre-lesion level for electrodes contralateral to the lesion as compared to 67% for ipsilateral electrodes; the amount consumed went down to 58% of the pre-lesion level for the contralateral electrodes and 53% for ipsilateral electrodes. Furthermore, the total daily food intake immediately following the lesion was significantly reduced to 56% of the pre-lesioned intake, t (9) = 3.40, $p < .01$.

Histology. The sites of the stimulating electrodes which supported electrically elicited feeding can be found in Appendix 1, Figure A3. Figure 5-1 shows the extent of the lesion for each animal. The lesion did completely destroy the locus coeruleus in most of the animals. In some cases there was extensive damage to the radix mesencephalica nervi trigemini and the stratum griseum centrale.

6-hydroxydopamine Lesions to the Dorsal Noradrenergic Bundle

The effects of a unilateral injection of 6-OHDA in the dorsal noradrenergic bundle on elicited feeding are shown in Table 5-2. Each of these scores is a mean derived from 7 electrode placements averaged over three days. Independent ANOVA's on these data indicated a significant effect of the lesion condition in terms of the frequency of elicited feeding, F (2,12) = 4.09, $p < .05$; the other analyses failed to attain significance. Further analysis using the Newman-Keuls procedure showed that the frequency for the post-lesion I condition was significantly reduced ($p < .05$) as compared to the pre-lesion condition. A similar suppression in elicited feeding was also found for the unlesioned side in the three animals which had bilaterally effective electrode placements.

Table 5-2

Effects of Unilateral 6-OHDA Lesion in the Dorsal Noradrenergic Bundle on the Frequency of Elicited Eating, on the Amount Consumed, and on the Threshold for Elicited Eating

Measure	Pre-Lesion	Post-Lesion I	Post-Lesion II[a]
Frequency[b]	9.0 (0.33)[d]	7.7 (0.66)*	8.9 (0.49)
Amount (g)	6.38 (1.04)	5.41 (1.23)	8.13 (0.89)
Threshold[c] (μA)	60.0 (13.15)	61.8 (14.90)	58.2 (11.75)

a A retest which occurred two weeks after the lesion

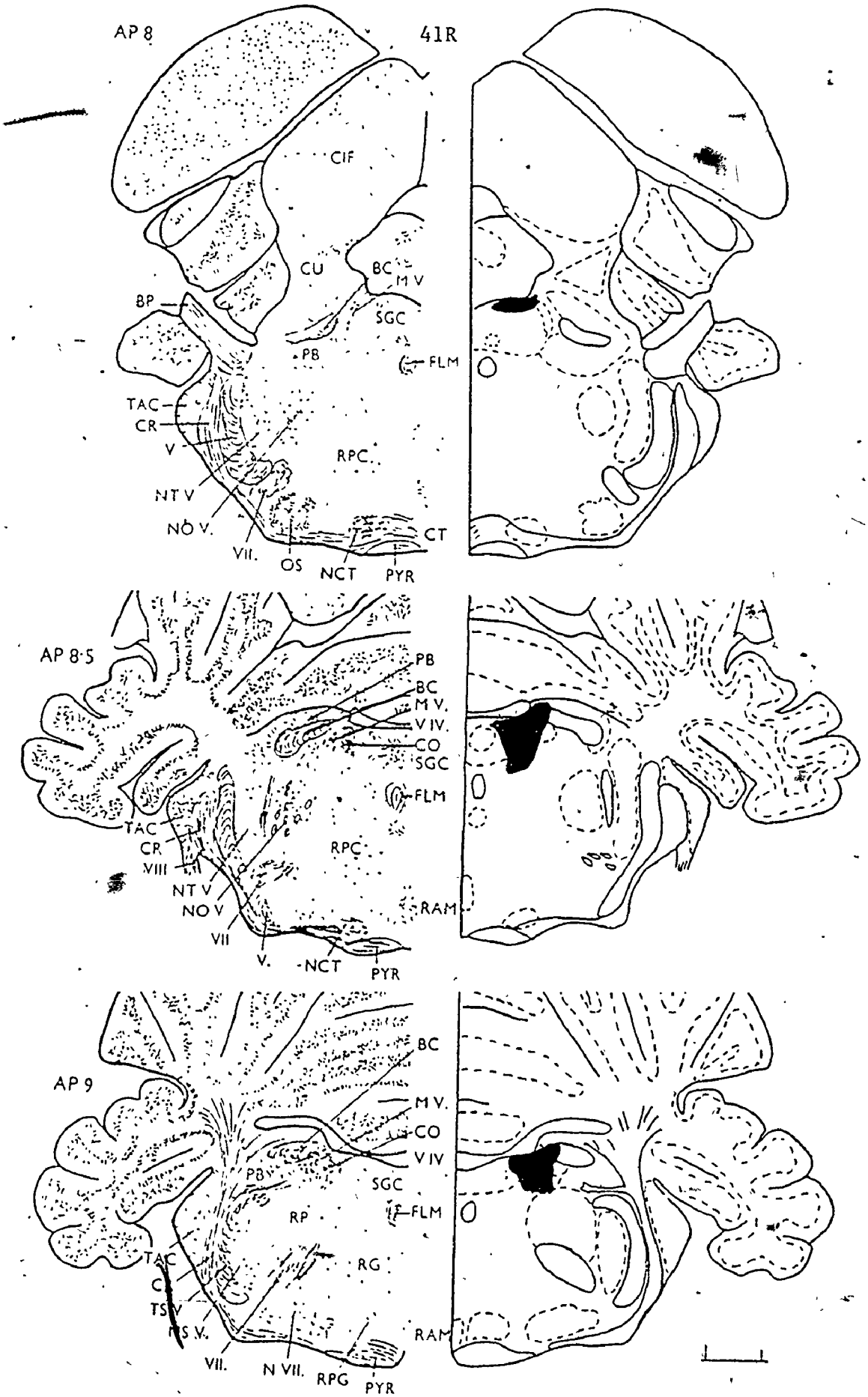
b Maximum score = 10

c Mean total for Ascending and Descending Conditions

d The standard error of the mean ($S_m = S/\sqrt{N}$)

* Significantly ($p < .05$) lower than Pre-lesion

Figure 5-1. The location of the electrolytic lesions to the locus coeruleus is shown in black. The underlining indicates which side was tested first for elicited feeding in a pair of effective electrode placements. The brain section are from Fifková and Marsala (1967). (BC - brachium conjunctivum; C - locus coeruleus; FLM - fasciculus longitudinalis medialis; MV - radix mesencephalica nervi trigemini; PB - nucleus parabrachialis; SGC - stratum griseum centrale; V IV - ventriculus quartus.)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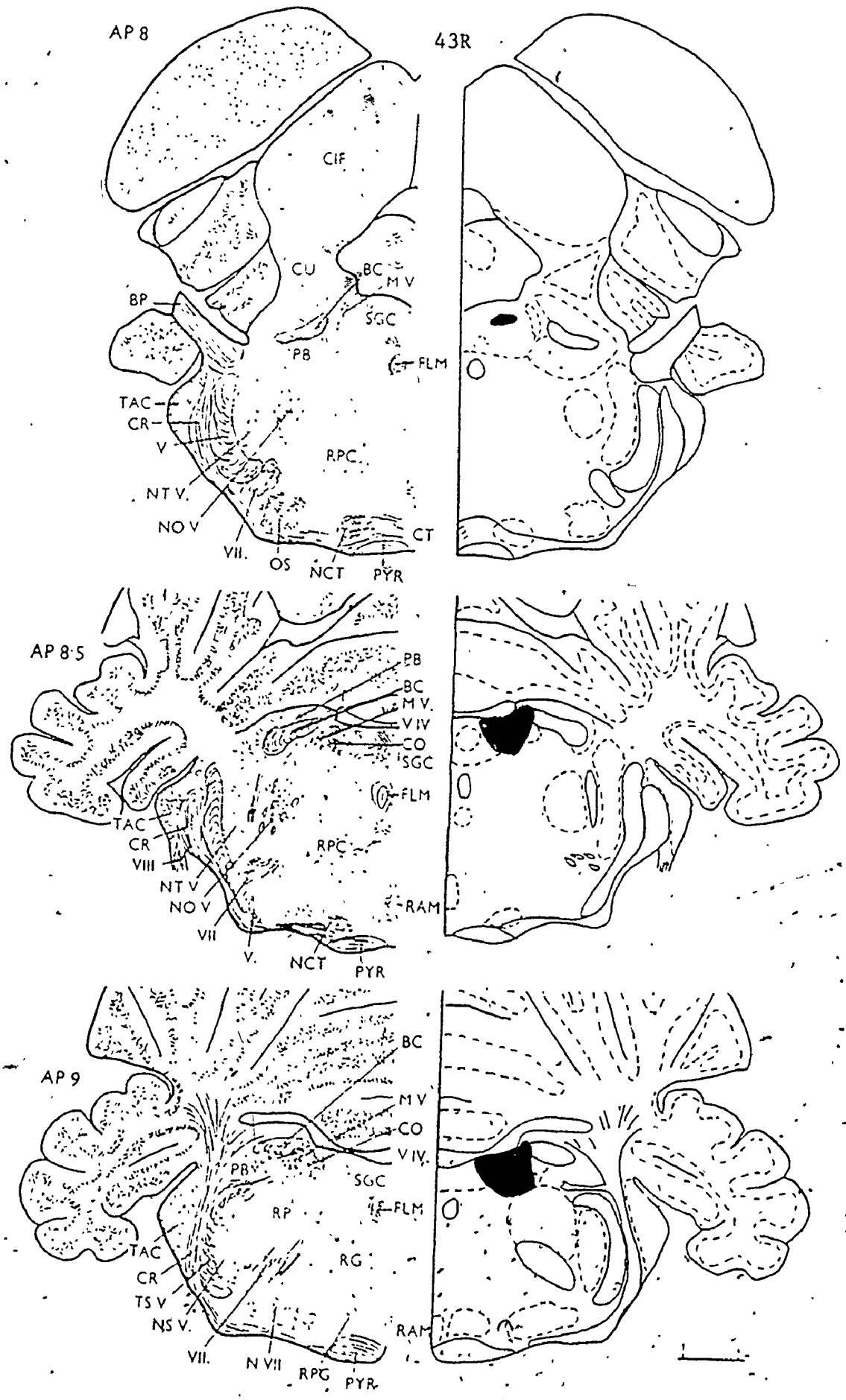
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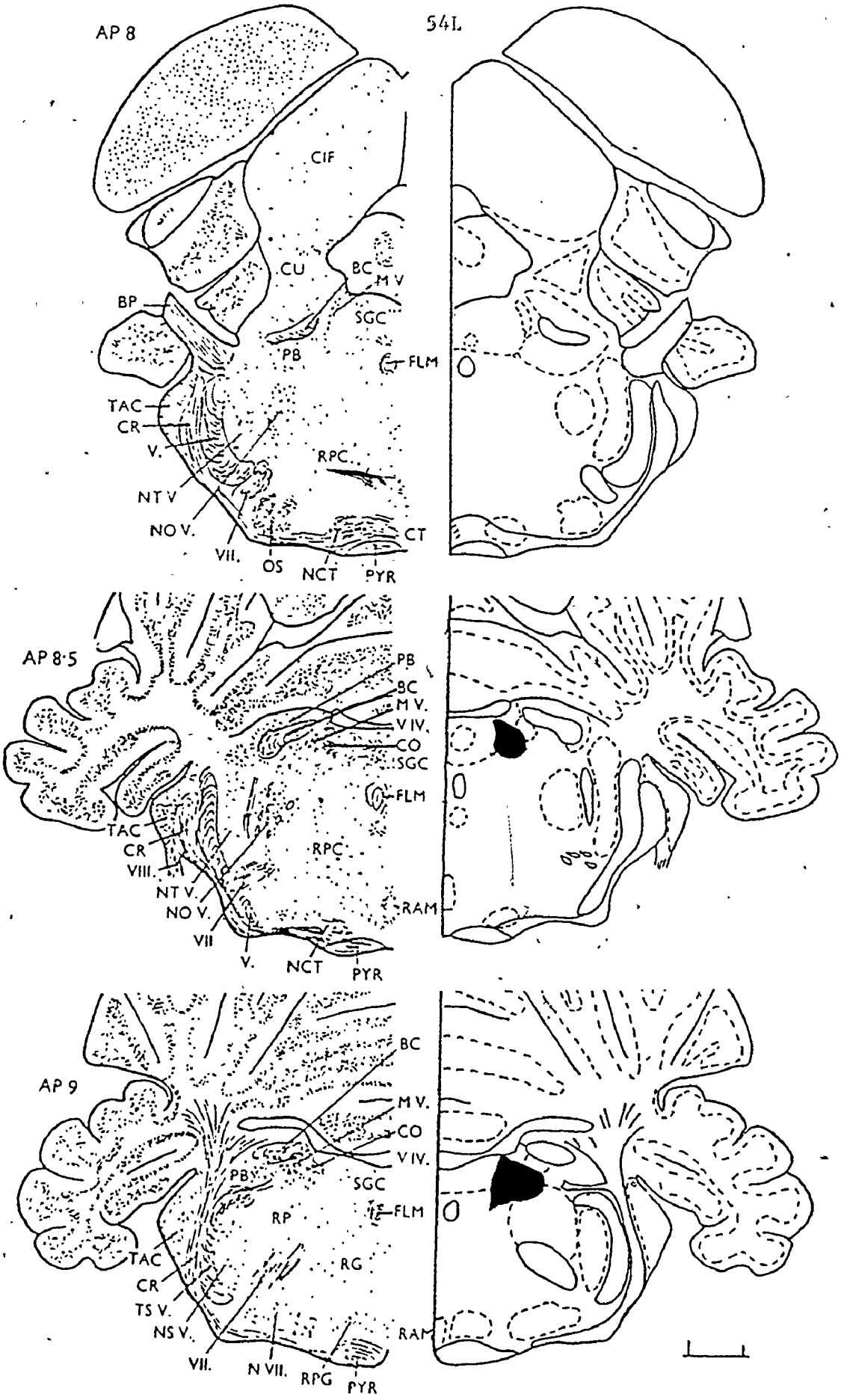
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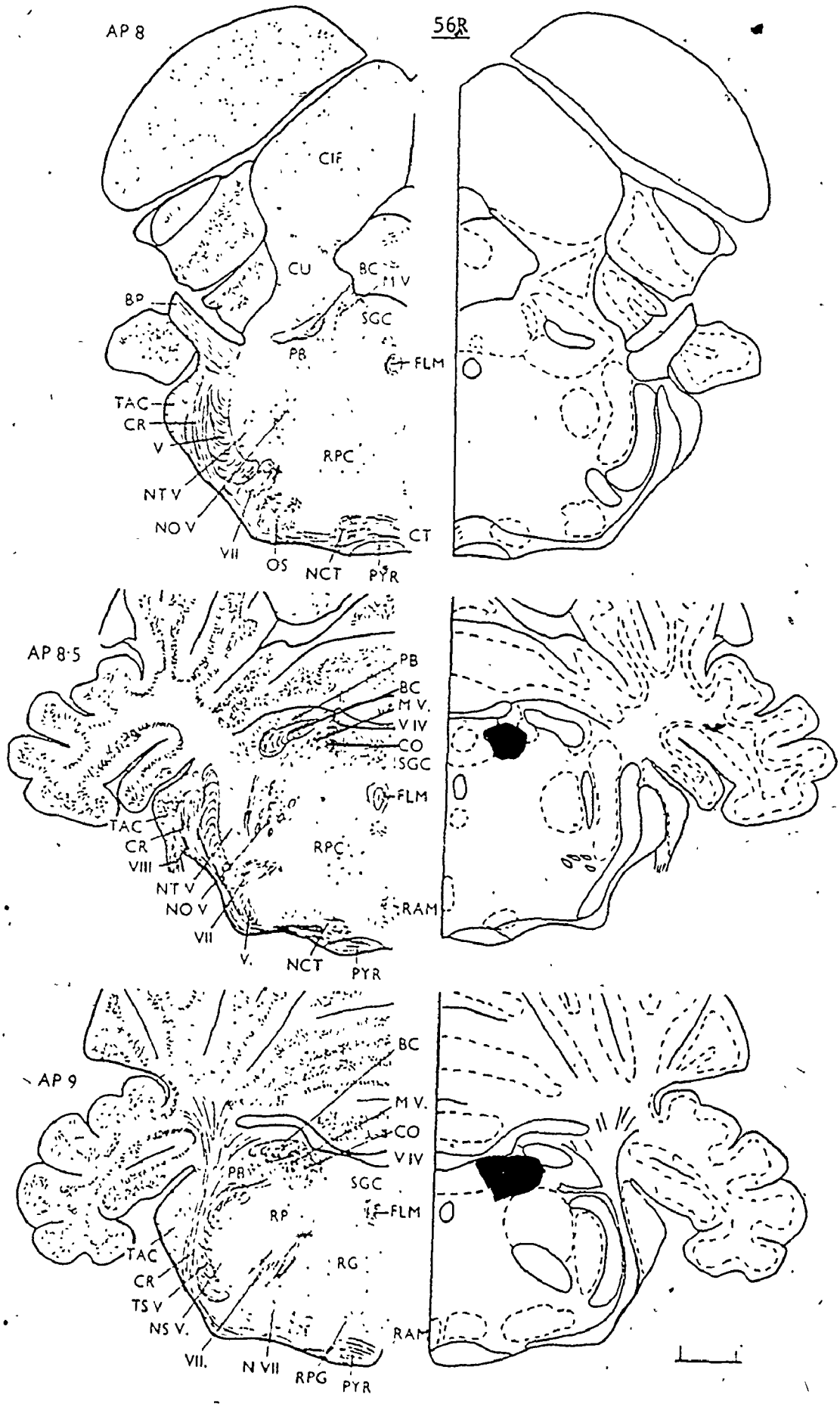
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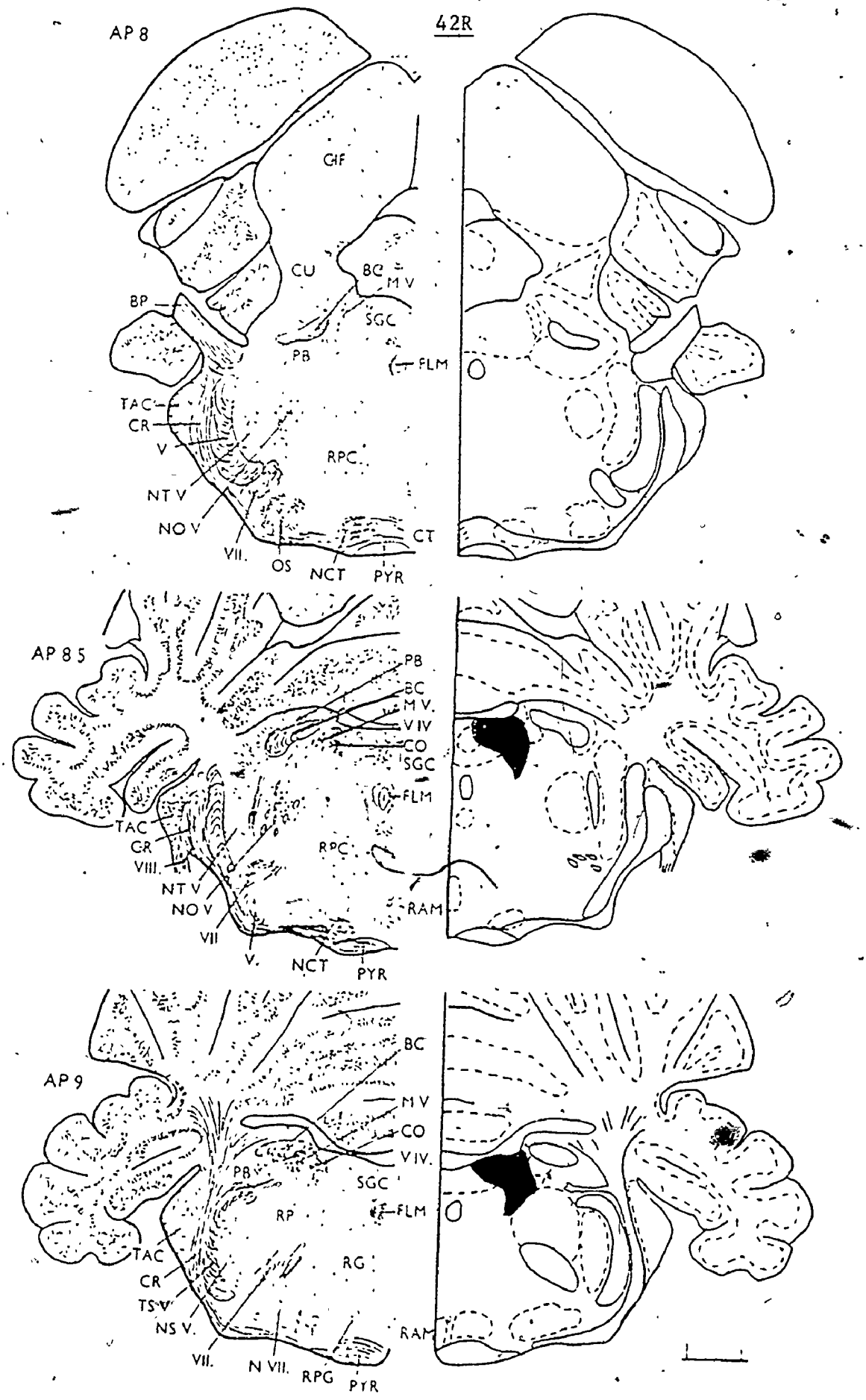
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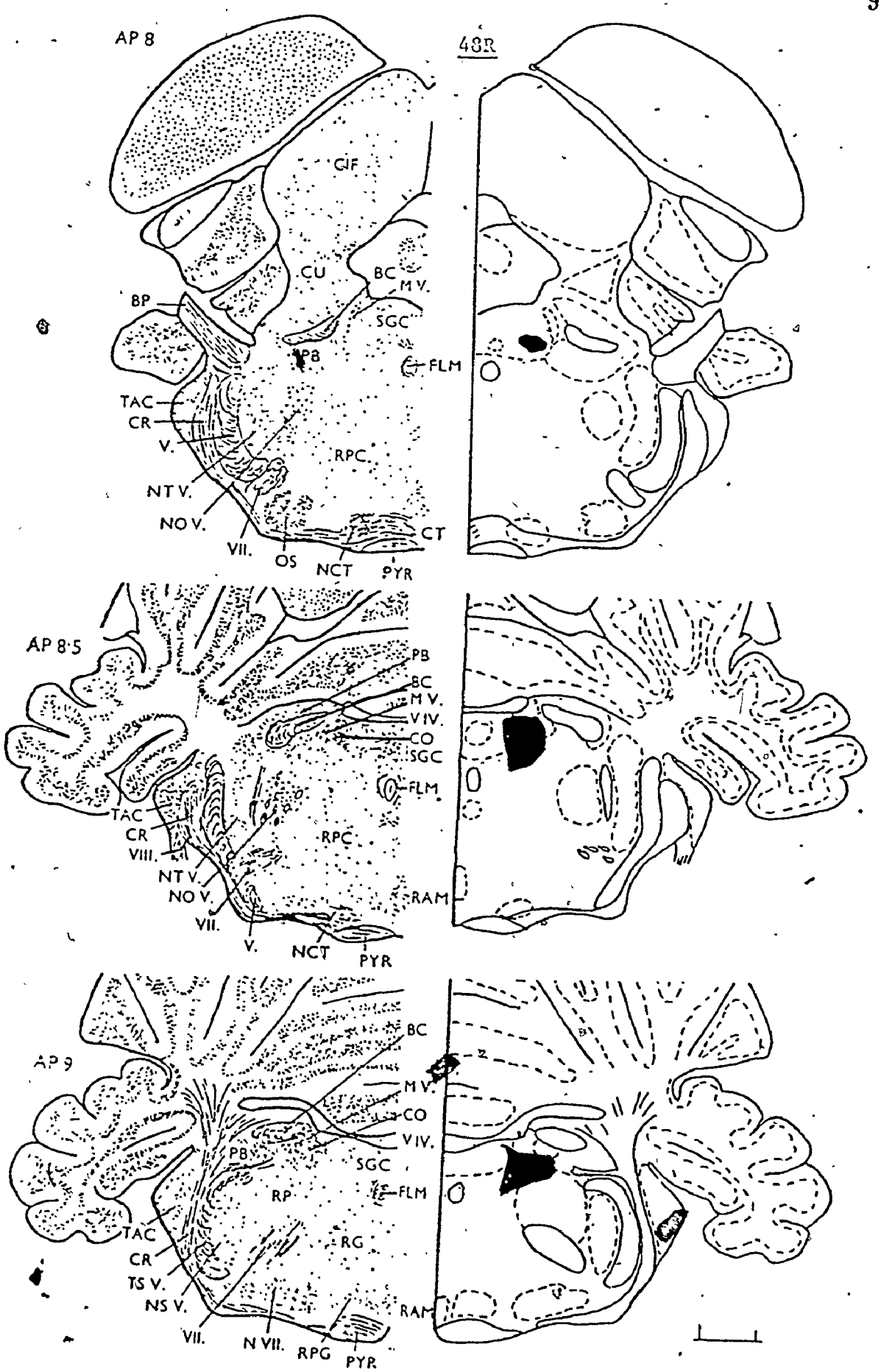
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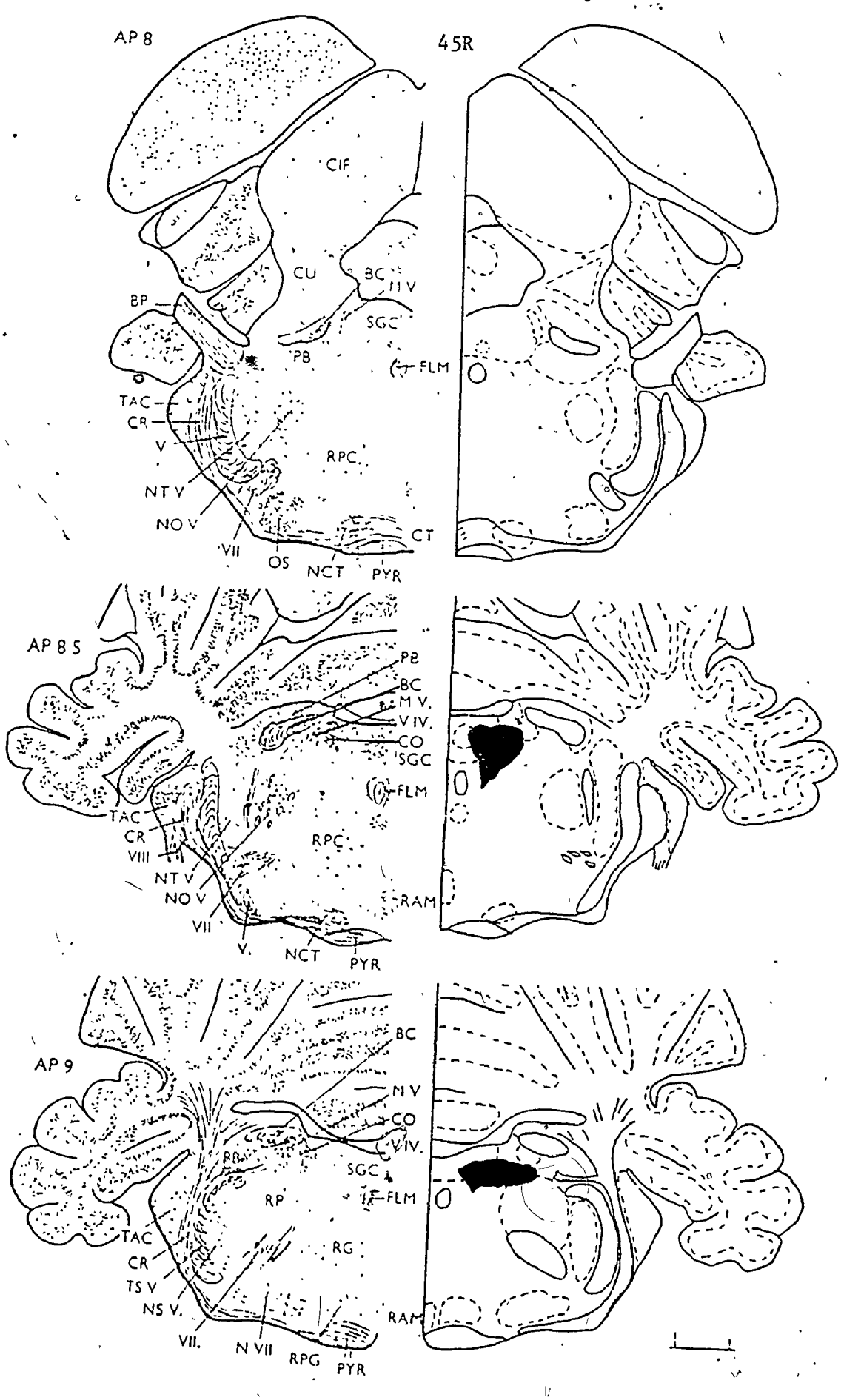
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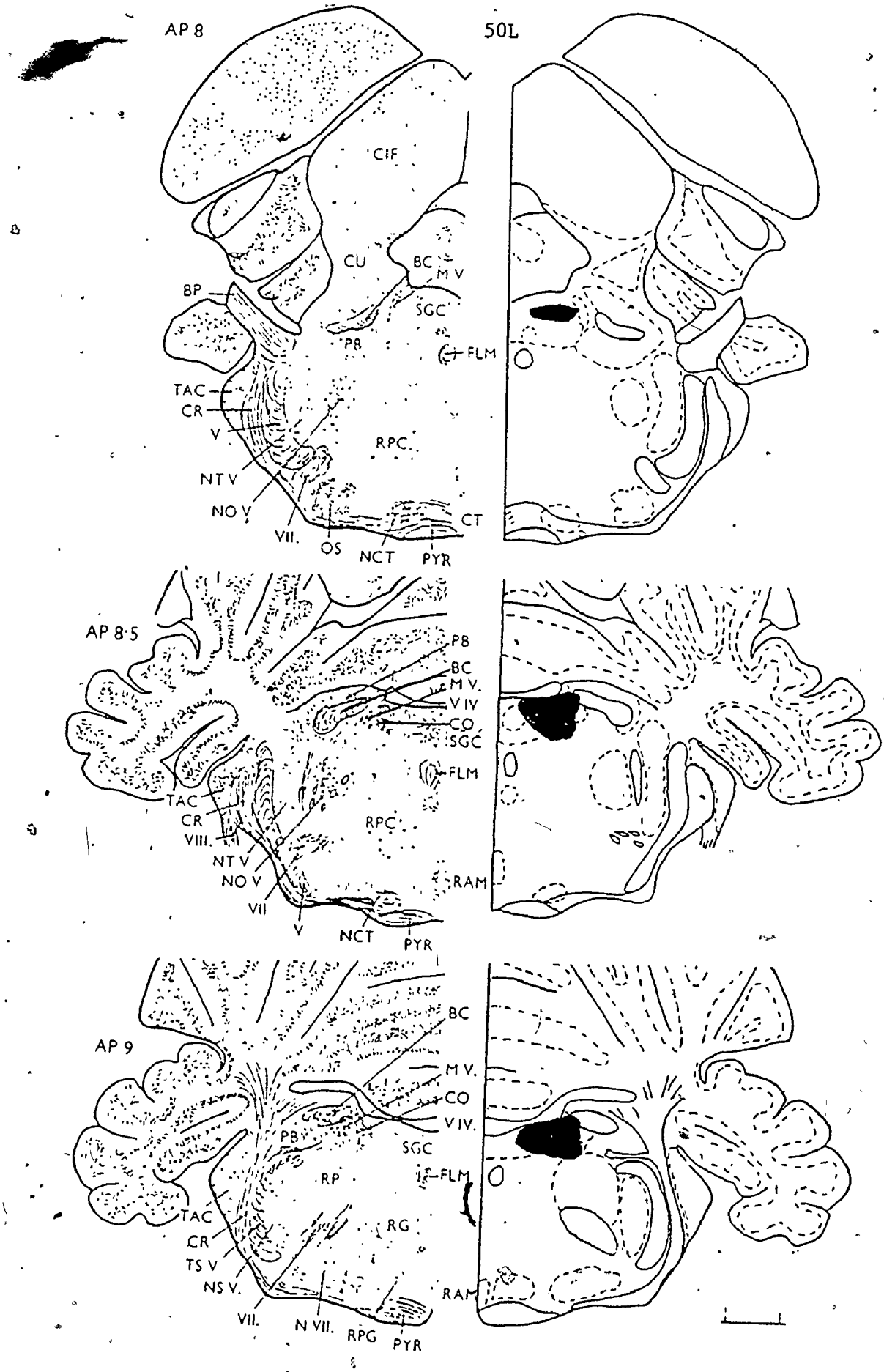
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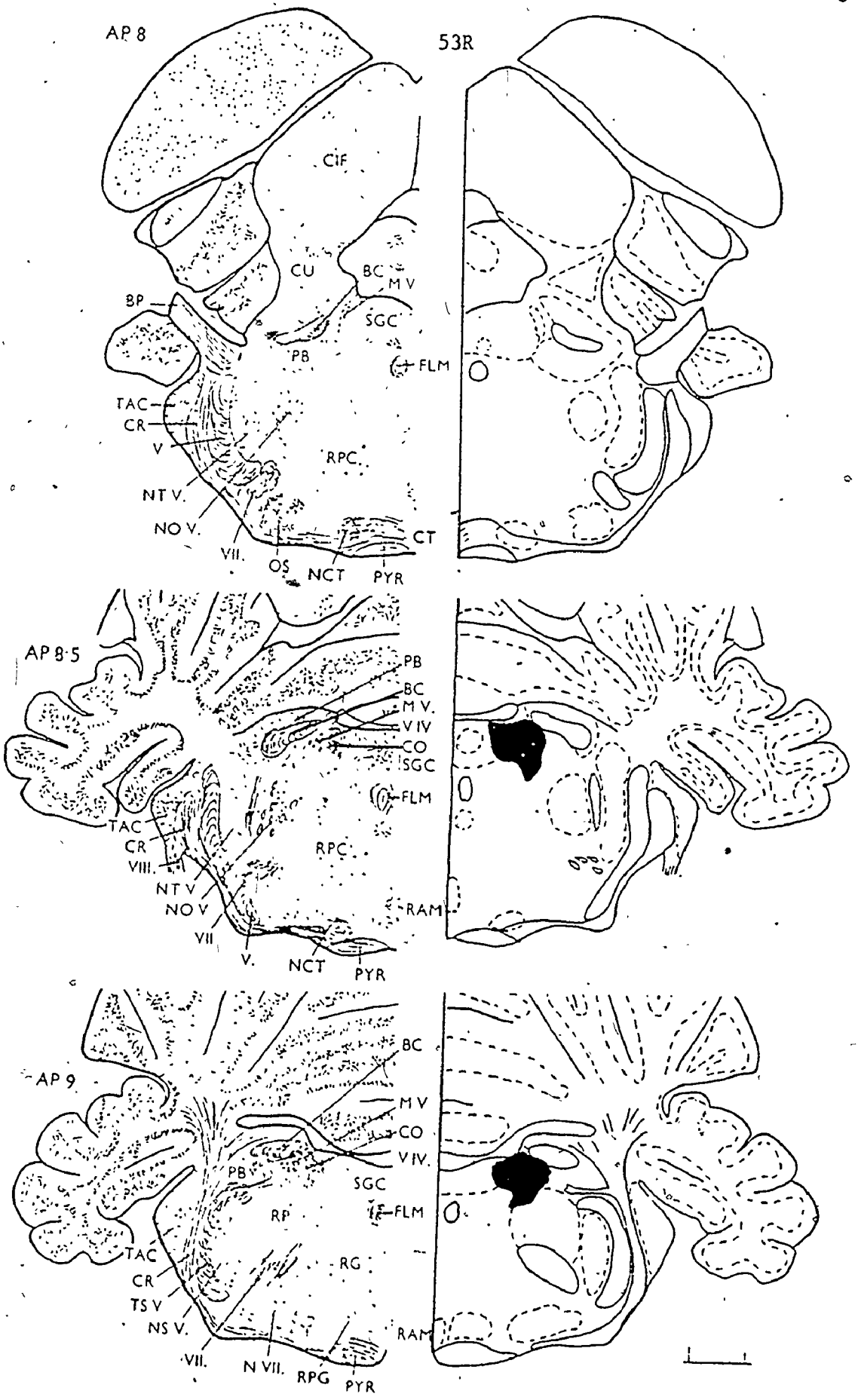
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NT V
NO V
VII
V.
NCT
PYR
RAM
AP 9
BC
M V
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V IV.
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TAC
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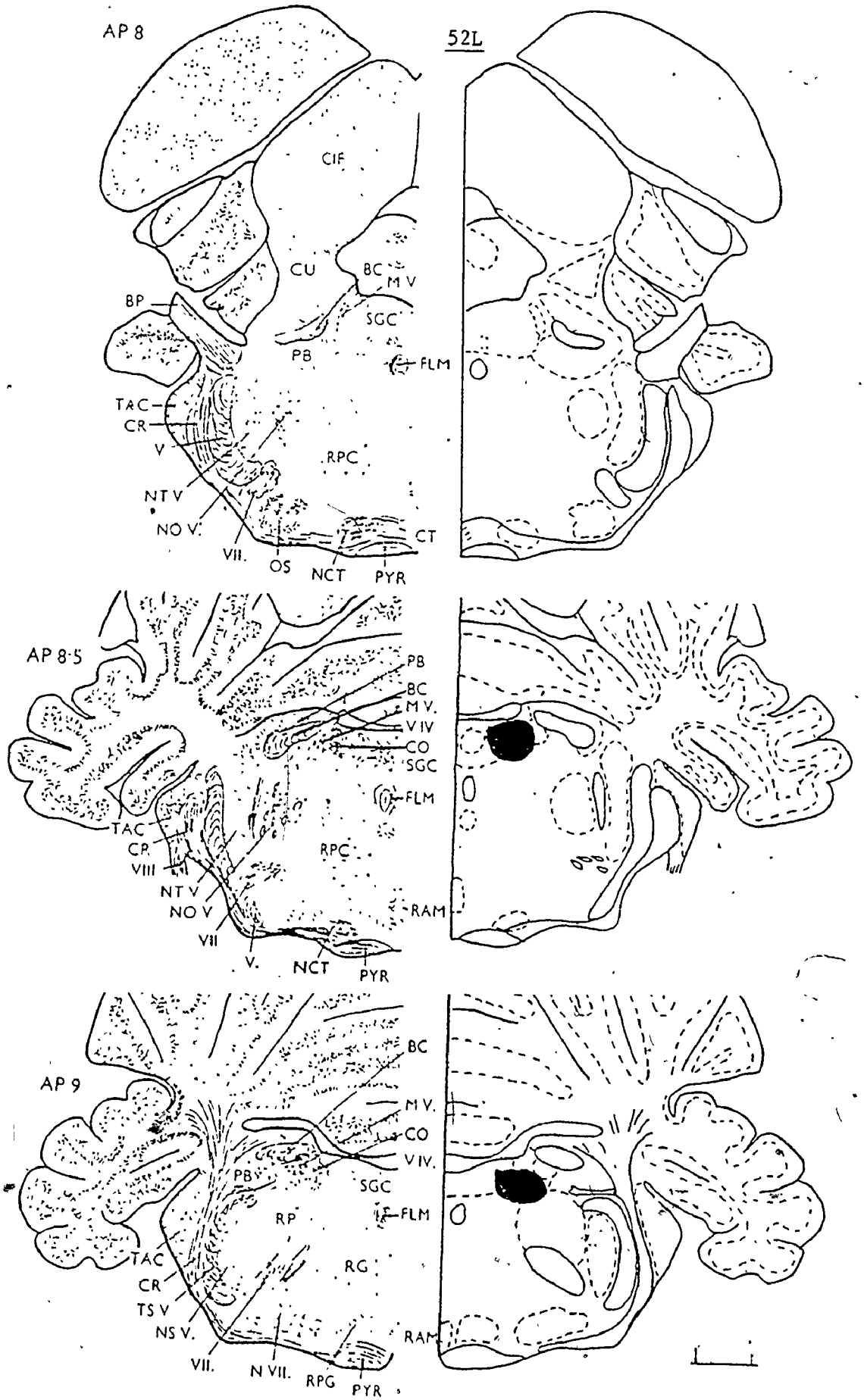
CR
TS V
NS V.
VII.
N VII.
RPG
PYR
RAM


AP 8
52L
CIF
CU
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M V
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NT V
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VII.
OS
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CT
AP 8·5
PB
BC
M V.
V IV
CO
SGC
FLM
TAC
CR
VIII
RPC
NT V
NO V
VII
V.
NCT
PYR
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AP 9
BC
M V.
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SGC
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TS V
NS V.
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N VII.
RPG
PYR
RAM

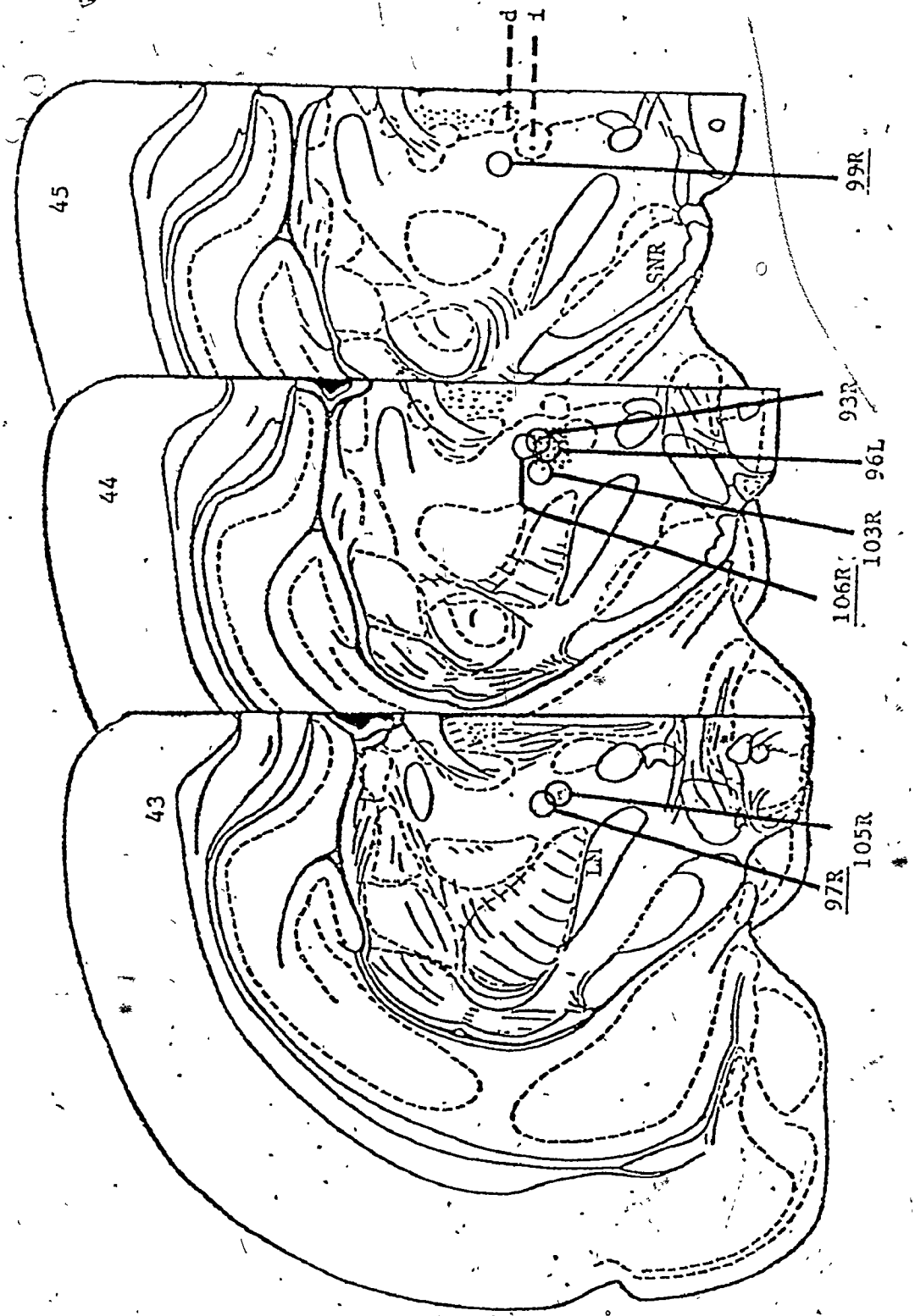
The frequency of elicited feeding was reduced to 83.4% of the pre-lesion level for electrodes contralateral to the lesion as compared to 85.7% for the ipsilateral electrode. Moreover, total daily food intake immediately following the lesion was significantly reduced to 68% of the pre-lesion level, $t(6) = 2.05$, $p < .05$ but returned to pre-lesion levels within two days.

Histology. The sites of the stimulating electrodes which supported electrically elicited feeding can be found in Appendix 1, Figure A4. Figure 5-2 shows the placement of the tips of the injection cannulae. As can be seen all the cannulae were near the dorsal noradrenergic bundle and as such the injection of 6-OHDA probably did extensive damage to this sytem (Ungerstedt, 1973). Similar bilateral lesions by Roberts, Price & Fibiger (1976) produced a 93% reduction in hippocampal-cortical norepinephrine.

Discussion

Unilateral damage to dorsal noradrenergic pathway as a result of electrolytic lesion to the locus coeruleus or intracerebral injections of 6-OHDA directly into the pathway failed to selectively disrupt elicited eating. There was, however, a transitory disruption of elicited feeding which was nonspecific inasmuch as the elicited response was disrupted at electrode sites which were both ipsilateral and contralateral to the lesion. The electrolytic lesion produced a short-term disruption whereas the 6-OHDA injection produced a slightly longer and more severe disruption which accounts for the significant reduction in the frequency of elicited feeding. This measure, however, was taken over three days, and during this period there was a consistent increase in the frequency of elicited feeding. Accordingly, when the animals

Figure 5-2. The tips of the inner injections cannulae aimed at the dorsal noradrenergic bundle (the stippled area dorsal to the nucleus interstitialis: from Ungerstedt, 1971a; p. 35. Figure I; the bundle continues both anterior and posterior to this section). The underlining indicates the electrode site tested first in a pair of effective electrode placements. (d - nucleus Darkschweitsch; i - nucleus interstitialis (Cajal); LM - lemniscus medialis; SNR - substantia nigra, zona reticulata).


d
r
45
44
43
SNR
LN
99R
93R
96L
103R
106R
105R
97R

were retested two weeks after the lesion there was no difference in any of the measures of elicited feeding. Moreover, with both lesions there was also a transitory disruption in daily food intake which paralleled the effects on elicited feeding. When the daily food intake had returned to baseline, elicited feeding was also back at pre-lesion levels. This interference with food intake has also been reported by Osumi, Oishi, Fujiwara and Takaori (1975). These investigators, however, used bilateral lesions and obtained decreased food intake which lasted for about five days until it returned to control levels.

It would seem, therefore, that damage to the dorsal noradrenergic system is not responsible for the long-lasting disruption of elicited feeding following CA destruction by means of intraventricular 6-OHDA.

EXPERIMENT 6

This experiment is concerned with assessing the role of the nigrostriatal DA system, the combined dorsal and ventral NA pathways (Ungerstedt, 1971a; Palkovits & Jacobowitz, 1974; Jacobowitz & Palkovits, 1974) as well as the ventral periventricular NA bundle (Lindvall et al., 1974b) in elicited feeding. These systems were damaged using two-stage injections of 6-OHDA directly into the brain. For the NSB, injections were made into the region of the cell bodies located in the zona compacta of the substantia nigra (Ungerstedt, 1973). The combined dorsal and ventral noradrenergic pathways were reached caudal to the interpeduncular nucleus before the bundles have separated thus affecting the ascending NA axons to the forebrain (Ungerstedt, 1973). These, of course, are the primary catecholamine systems in the brain and as such are the likely targets for a lesion given the involvement of CA in elicited feeding. The NSB has been implicated in the LH syndrome (Ungerstedt, 1971b; Stricker & Zigmond, 1976) although it does not seem entirely possible to exclude a NA contribution (Marshall et al., 1974). The ventral periventricular system was also attacked because the existence of this pathway coincides with some sites from which chemically

elicited feeding had been obtained using alpha-adrenergic agonists (Leibowitz, 1975). Furthermore, given the proximity to the ventricles this system would suffer extensive damage following intraventricular injection of 6-OHDA (Ungerstedt, 1973). This system does not appear to have been previously lesioned selectively using a neurotoxin but Ungerstedt (1973) suggests that NA fibres are sensitive to 6-OHDA and so they should be destroyed by an intracerebral injection into the pathway.

Method

Subjects

Animals were prepared with bilateral stimulating electrodes in the lateral hypothalamic region (P 2.7, L 1.6, V 8.8) and chronic, indwelling guide cannulae in the following locations: the zona compacta of the substantia nigra (P 5.4, L 2.1, V 6.9; N = 12), the noradrenergic system (dorsal and ventral; P 7.8, L 1.5, V 6.3; N = 16), and the periventricular region (P 0.8, L 1.1, V 6.6; N = 5). In all cases the guide cannulae were aimed 1.0 mm dorsal to the target area. Ten additional animals were prepared with bilateral stimulating electrodes in the lateral hypothalamic region to act as controls. All animals were maintained on HFD during testing.

Procedure

All animals were screened for electrically elicited ingestive behavior at least twice; only elicited feeding was observed. Elicited feeding was observed in 8 animals with cannulae in the substantia nigra (6 of these had bilaterally effective placements), 7 animals in the noradrenergic bundle group (5 of these were bilaterally effective), 5 animals in the periventricular group (2 were bilateral) and 8 animals in the control group (4 were bilateral).

Suitable current levels which supported elicited behavior were selected and checked the following day. The spontaneous baseline feeding behavior was determined by measuring the intake and frequency during a control session without ESB. Following this baseline measure, each animal was tested for elicited feeding on two consecutive days during a test session consisting of a 3 min. adaptation period followed by 10 min. of alternating brain stimulation (30 sec. ON - 30 sec. OFF). An

ascending and descending threshold were determined. In the ascending sequence, a current level, which on the basis of the previous screening would not elicit feeding, was selected. The current level was increased in 5 μA steps until elicited feeding occurred in at least three out of five presentations of the ESB. The descending series (conducted the following day) started with the ascending threshold level and lowered the current in 5 μA steps until elicited feeding stopped. Each current level in both series was presented five times. Elicited feeding at the pre-selected current level was determined on the sixth test day.

Immediately following this test session all animals with cannulae received a sham unilateral lesion through the cannula ipsilateral to the effective electrode placement. The animals were lightly anaesthetized with ether, the stylus removed, and the inner cannula inserted. An intracerebral injection of 1 μl of 0.9% saline and ascorbic acid (.2 mg/ml) was delivered at the rate of 0.5 μl/min using a syringe pump. Following the injection, the inner cannula was removed and the stylus re-inserted. The control animals (no cannulae) were simply anaesthetized with ether.

Elicited feeding was measured on two consecutive days, the ascending and descending thresholds were determined, and then the animals were once again tested for elicited feeding at their pre-selected current level. After the last test session the animals were given an intracerebral injection of 8 μg of 6-OHDA, expressed as a free base (67.9% of the compound), dissolved in 1 μl of vehicle (as above). The injection was delivered through the same cannula used for the sham procedure. The same testing sequence was initiated (i.e., elicited feeding test for two days, threshold determination and another test for elicited feeding).

A control for the spontaneous feeding behavior without ESB was

performed, after which a second injection of 6-OHDA (two weeks after the first) was delivered through the other cannula to complete the bilateral lesion. The baseline daily intake of food and water without ESB was measured for two days. The standard testing sequence was then initiated.

Results

Elicited feeding was not significantly disrupted by either unilateral or two-stage bilateral injections of 6-OHDA in the noradrenergic system (both the dorsal and ventral pathways), the nigrostriatal dopamine bundle (substantia nigra), or the periventricular system. Tables 6-1, 6-2, and 6-3, respectively, give the mean values for the frequency of elicited feeding, the amount consumed during elicited feeding, and the threshold for elicited feeding under the various conditions. A 4 x 4 repeated measures ANOVA conducted on each of these measures of elicited feeding failed to detect any significant differences among the means.

Histology

The sites of the stimulating electrodes which supported elicited feeding can be found in Appendix 1, Figures A5, A6, A7, and A8.

Figures 6-1 and 6-2 show the placement of the tips of the cannulae used to make the first and second stage 6-OHDA lesion to the combined dorsal and ventral noradrenergic pathways. Due to the shape of these pathways it is difficult to determine the precise extent of damage done to this system although clearly the cannulae were in a position to do considerable damage.

Figure 6-3 and 6-4 show the cannulae placements in the zone compacta of the substantia nigra. Injections of 6-OHDA at these sites should have produced extensive damage to the nigrostriatal pathway.

Figures 6-5 and 6-6 show the cannulae placements in the periventricular

Table 6-1

Frequency of Elicited Eating Following Unilateral and Two-stage Bilateral Lesions with 6-OHDA

Lesion Site		Pre-Lesion		Sham		Unilateral		Bilateral[a]	
Noradrenergic System	(7)[b]	8.71[c]	(0.38)[d]	8.6	(0.51)	9.5	(0.31)	8.9	(0.62)
Substantia Nigra	(8)	9.4	(0.29)	9.6	(0.78)	8.8	(0.85)	8.0	(1.1)
Periventricular System	(5)	8.4	(0.75)	8.5	(0.82)	8.3	(0.96)	8.9	(0.76)
Control	(8)	9.0	(10.4)	9.2	(0.24)	9.1	(0.35)	9.0	(0.22)

[a] The second stage of the lesion was performed two weeks after the unilateral lesion

[b] The number in parenthesis indicates the number of animals in each group

[c] The mean frequency of elicited eating with a maximum value of 10

[d] The standard error of the mean

Table 6-2

Amount of Food Consumed during Elicited Feeding following Unilateral and Two-stage Bilateral Lesion with 6-OHDA

Lesion		Pre-Lesion		Sham		Unilateral		Bilateral[a]	
Noradrenergic System	(7)[b]	8.07[c]	(1.27)[d]	8.22	(1.58)	8.37	(0.92)	8.32	(0.90)
Substantia Nigra	(8)	8.90	(1.20)	9.08	(1.42)	7.99	(1.68)	6.79	(1.34)
Periventricular System	(5)	7.93	(2.75)	8.05	(3.27)	7.40	(2.75)	7.38	(2.07)
Control	(8)	6.24	(0.90)	6.61	(0.91)	6.54	(1.16)	6.94	(0.82)

[a] The second stage of the lesion was performed two weeks after the unilateral lesion

[b] The number in parenthesis indicates the number of animals in each group

[c] Mean amount of food consumed in grams

[d] Standard error of the mean

Table 6-3

Threshold for Elicited Eating Following Unilateral and Two-stage Bilateral Lesions with 6-OHDA

Lesion Site		Pre-Lesion		Sham		Unilateral		Bilateral[a]	
Noradrenergic System	(7)[b]	38.5[c]	(4.2)[d]	35.7	(2.9)	33.6	(2.8)	36.4	(3.4)
Substantia Nigra	(8)	38.8	(9.1)	36.9	(8.0)	51.2	(21.3)	46.9	(17.8)
Periventricular System	(5)	29.0	(3.3)	29.0	(4.0)	30.0	(3.6)	29.0	(3.3)
Control	(8)	30.6	(2.9)	31.2	(2.2)	31.9	(2.6)	31.2	(3.2)

a The second stage of the lesion was performed two weeks after the unilateral lesion

b The numbers in parentheses indicate the number of animals in each group

c The mean value of the total for the ascending and descending in μA

d The standard error of the mean

Figure 6-1. The location of the tip of the inner injection cannulae aimed at the combined dorsal and ventral noradrenergic pathways. The animals received unilateral injections of 6-OHDA at these sites. Animals with * also participated in Experiment 2 to determine diet preference; underlining indicates the electrode site tested first in a pair of effective electrode placements. The stippled area indicates the extent of the noradrenergic pathway as indicated by Ungerstedt (1971a) p. 177, Figure G: the pathway continues in both the anterior and posterior direction. (dr - nucleus dorsalis raphes; FL - fasciculus longitudinalis; LM - lemniscus medialis; PCS - pedunculus cerebellaris superior)

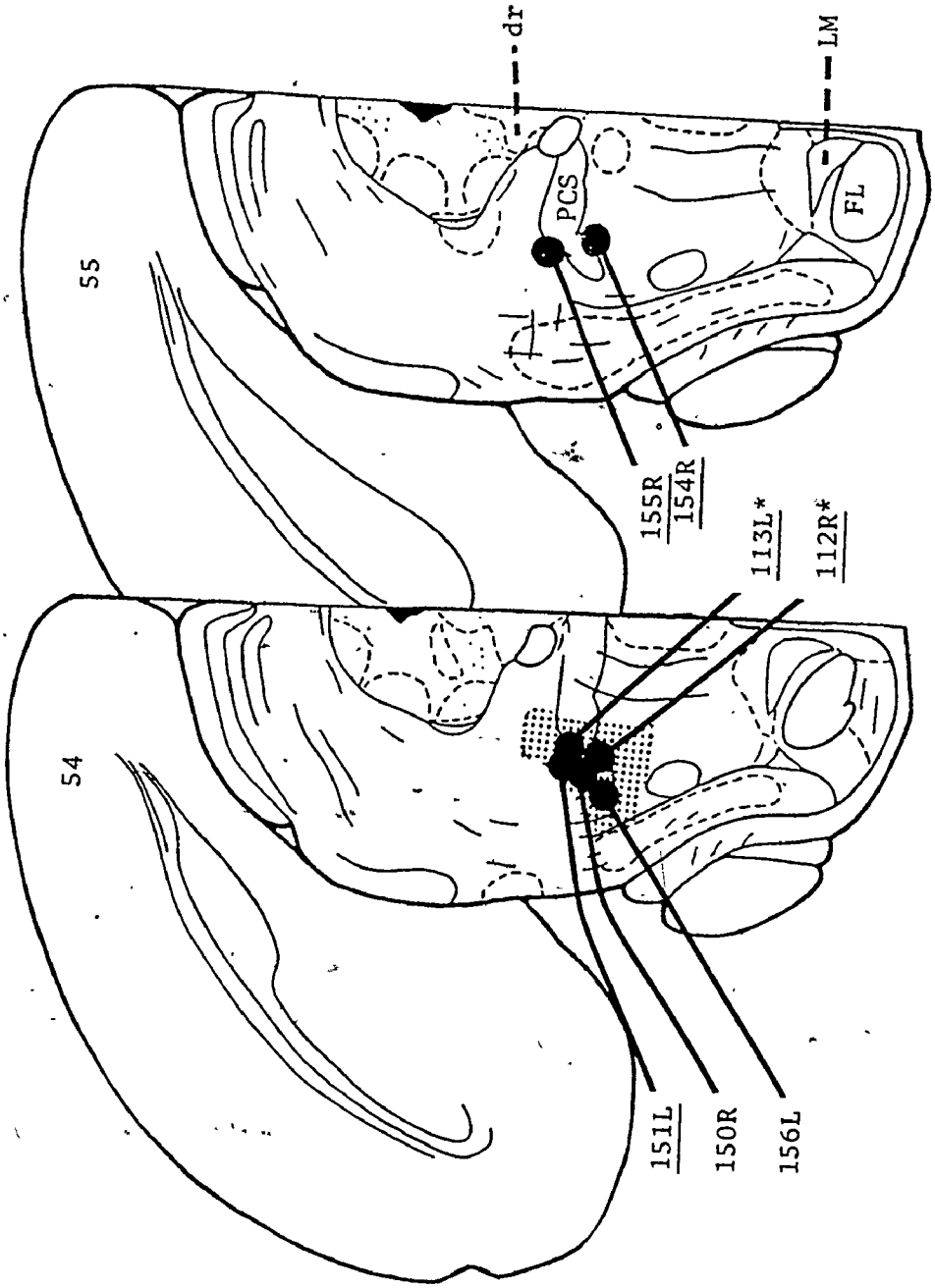

dr
LM
PCS
FL
55
54
155R
154R
113L*
112R*
151L
150R
156L

Figure 6-2. The location of the tip of inner injection cannulae aimed at the combined dorsal and ventral noradrenergic pathways. The animals received the second stage injection of 6-OHDA at these sites. Animals marked with an * were also used in Experiment 2 to test for diet preference. The stippled area indicates the extent of the noradrenergic pathway as indicated by Ungerstedt (1971a) p. 177. Figure G: the pathway continues in both the anterior and posterior direction.

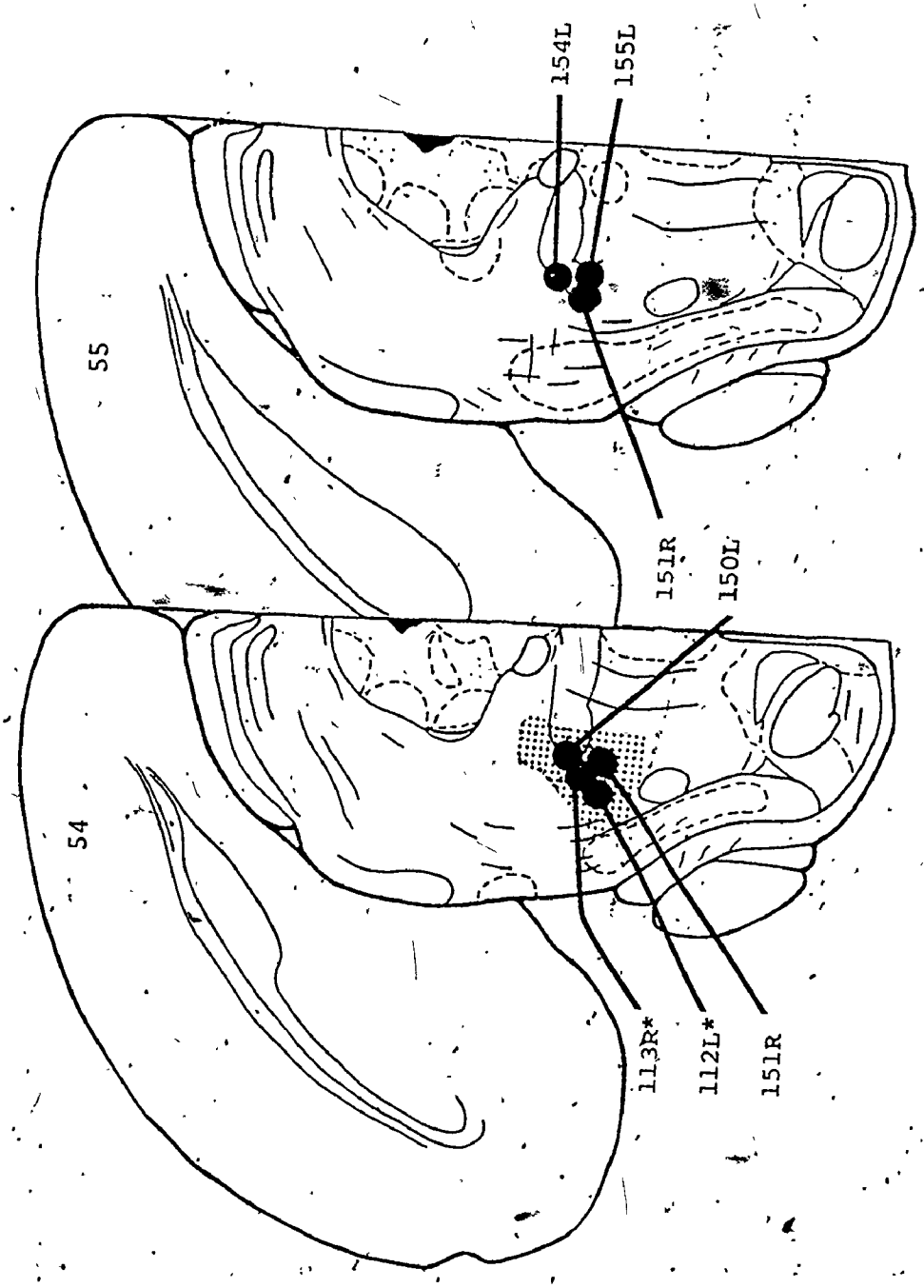

154L
155L
55
151R
150L
54
113R*
112L*
151R

Figure 6-3. The tips of the inner injection cannulae aimed at the zona compacta of the substantia nigra (i.e. the cell bodies of the nigro-striatal bundle; Ungerstedt, 1971a); animals received a unilateral injection of 6-OHDA at this site. The underlining indicates the electrode site tested first in a pair of effective electrode placements; animals marked with an * were also used in Experiment 2 to determine diet preference, (LM - lemniscus medialis; r - nucleus ruber; SNC - substantia nigra, zona compacta; SNR - substantia nigra, zona reticulata)

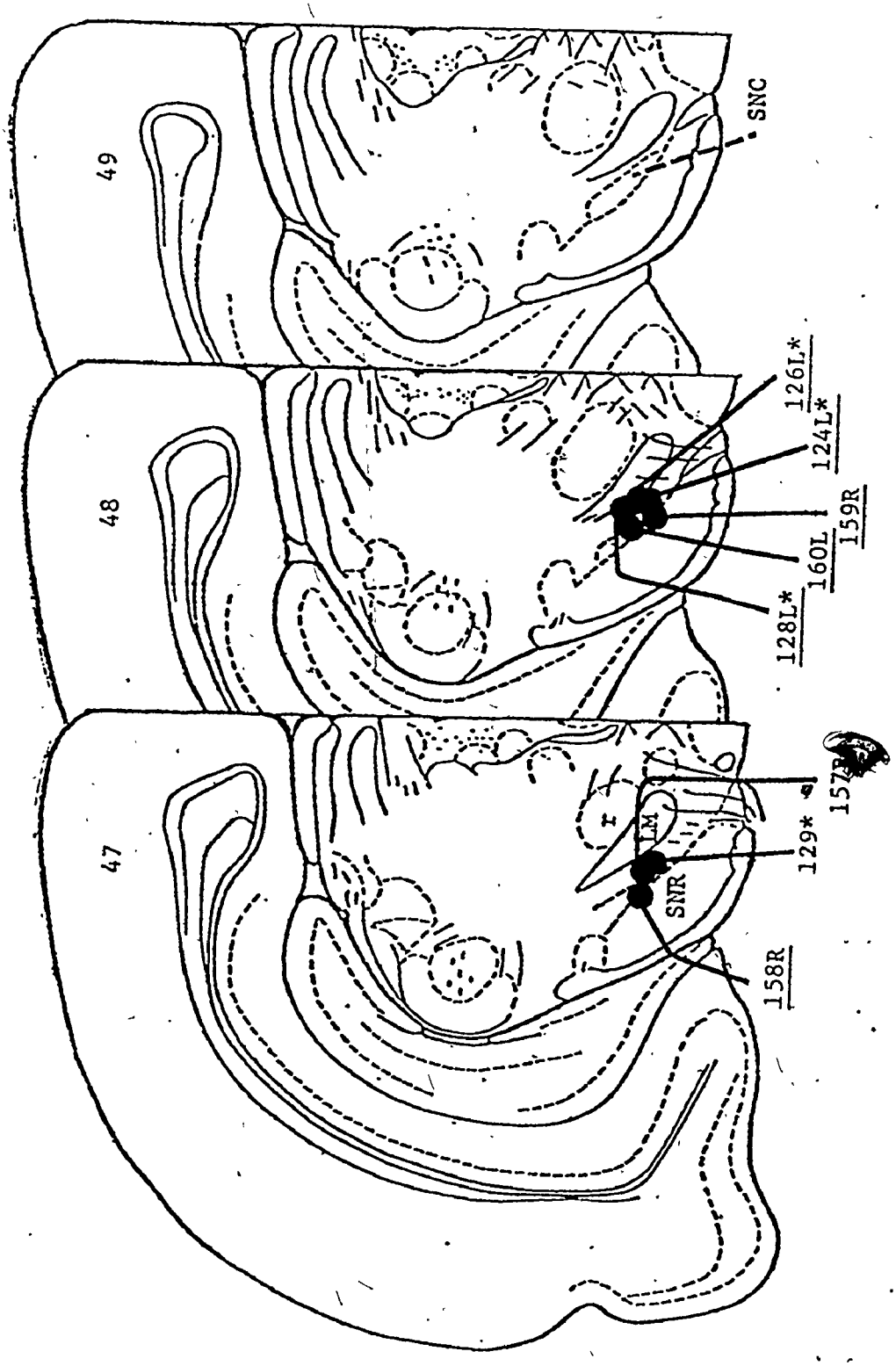

49
48
47
SNC
126L*
124L*
159R
160L
128L*
157R
129*
LM
SNR
158R

Figure 6-4. The tip of the inner cannulae aimed at the zona compacta of the substantia nigra (i.e. the cell bodies of the nigrostriatal bundle, Ungerstedt, 1971a); animals received the second stage of the 6-OHDA lesion at this site. Animals marked with an * were also used in Experiment 2 to determine diet preference.

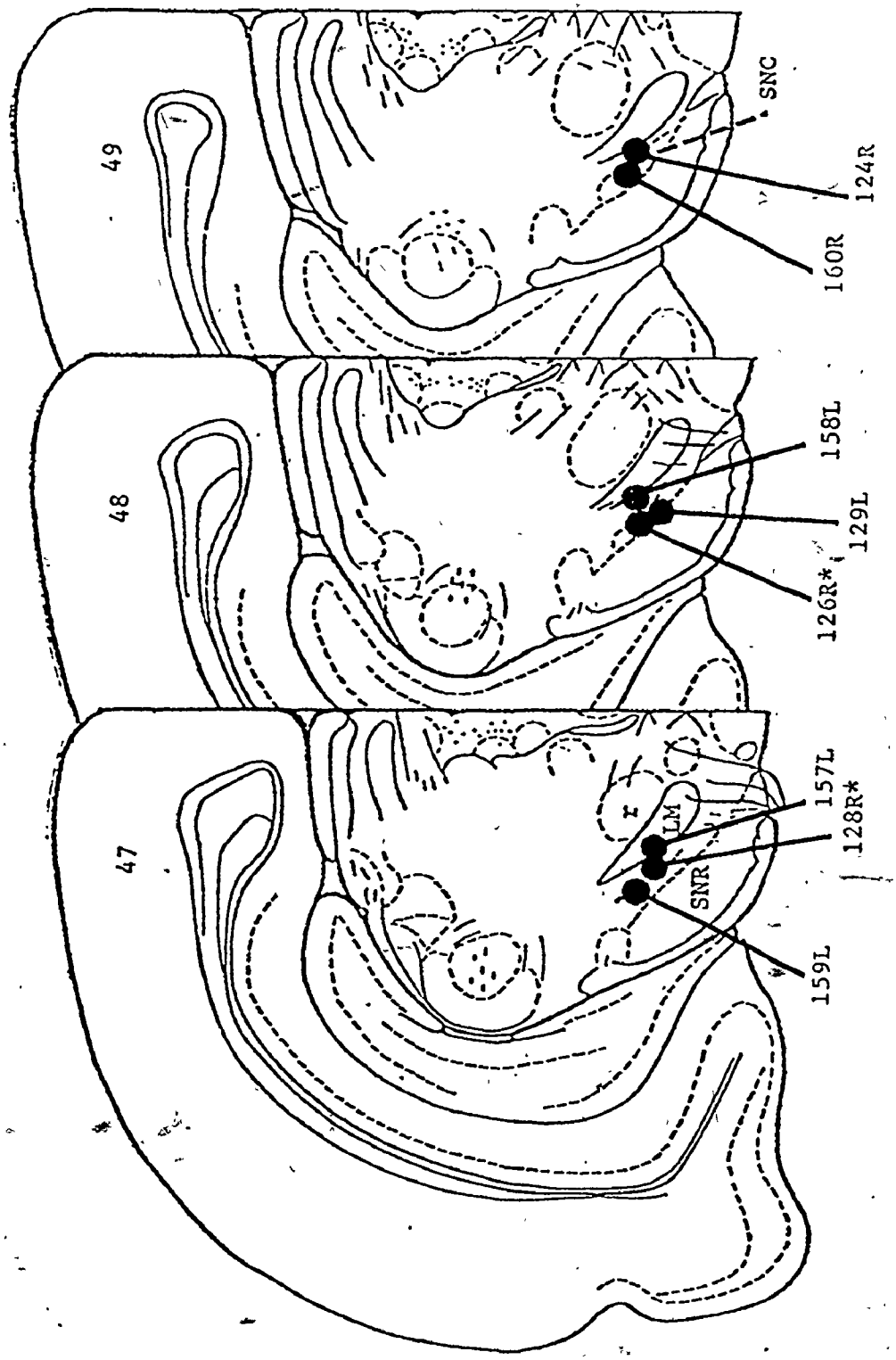

49
48
47
SNC
124R
160R
158L
129L
126R*
157L
128R*
LM
SNR
159L

Figure 6-5. The location of the tip of inner cannulae aimed at the ventral periventricular pathway. The animals received unilateral injections of 6-OHDA at these sites. Underlining indicates the electrode site tested first in a pair of effective placements. The stipled area indicates the extent of the ventral periventricular pathway as indicated by Lindval et al. (1974) p. 329, Figure 6-A: the pathway continues caudally. (CAI - capsula interna; CFV - commissura fornicis ventralis; F - fornix; GP - globus pallidus; ha - anterior hypothalamus; MFB - medial forebrain bundle; SM - stria medullaris thalami.)

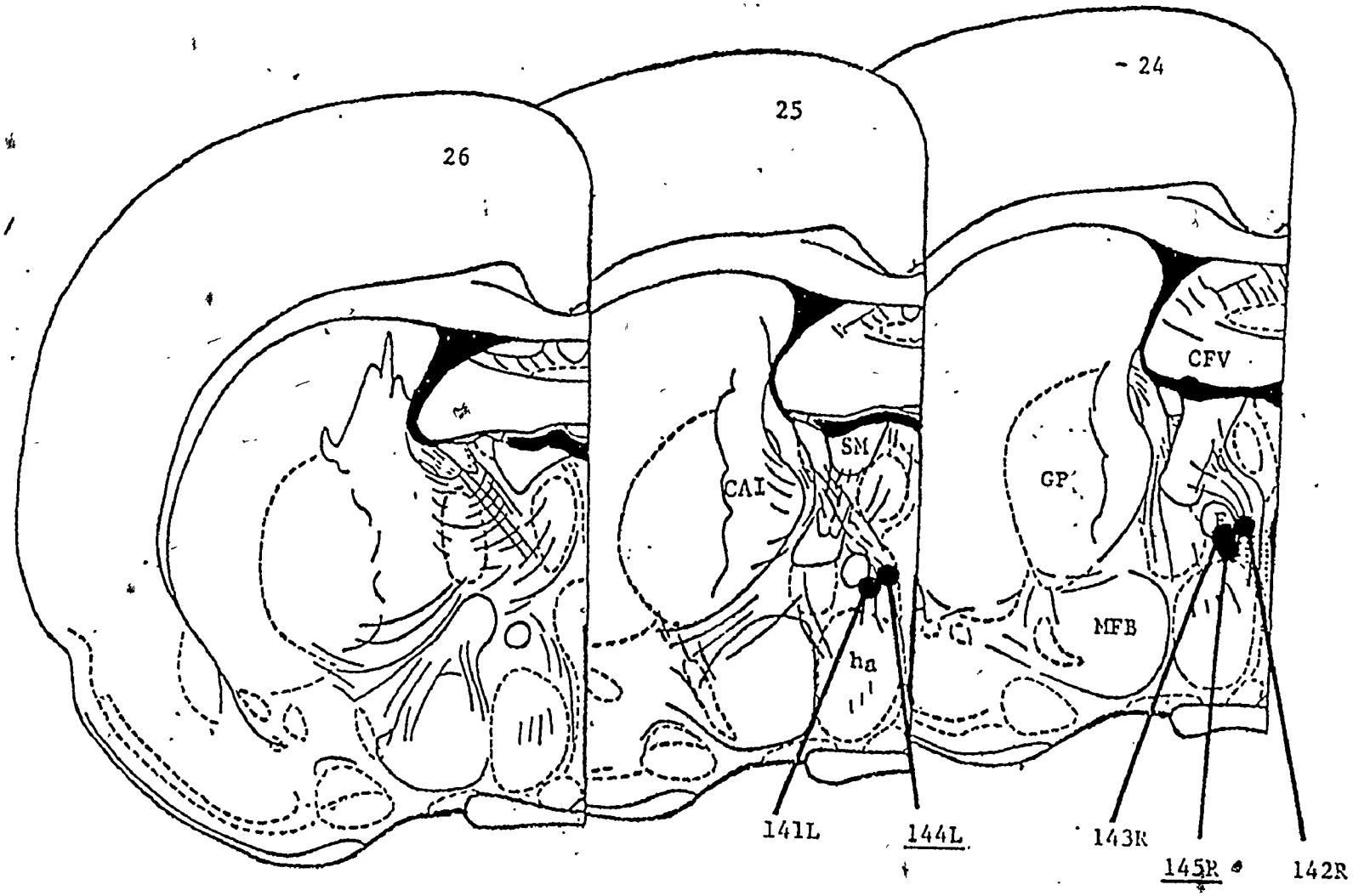
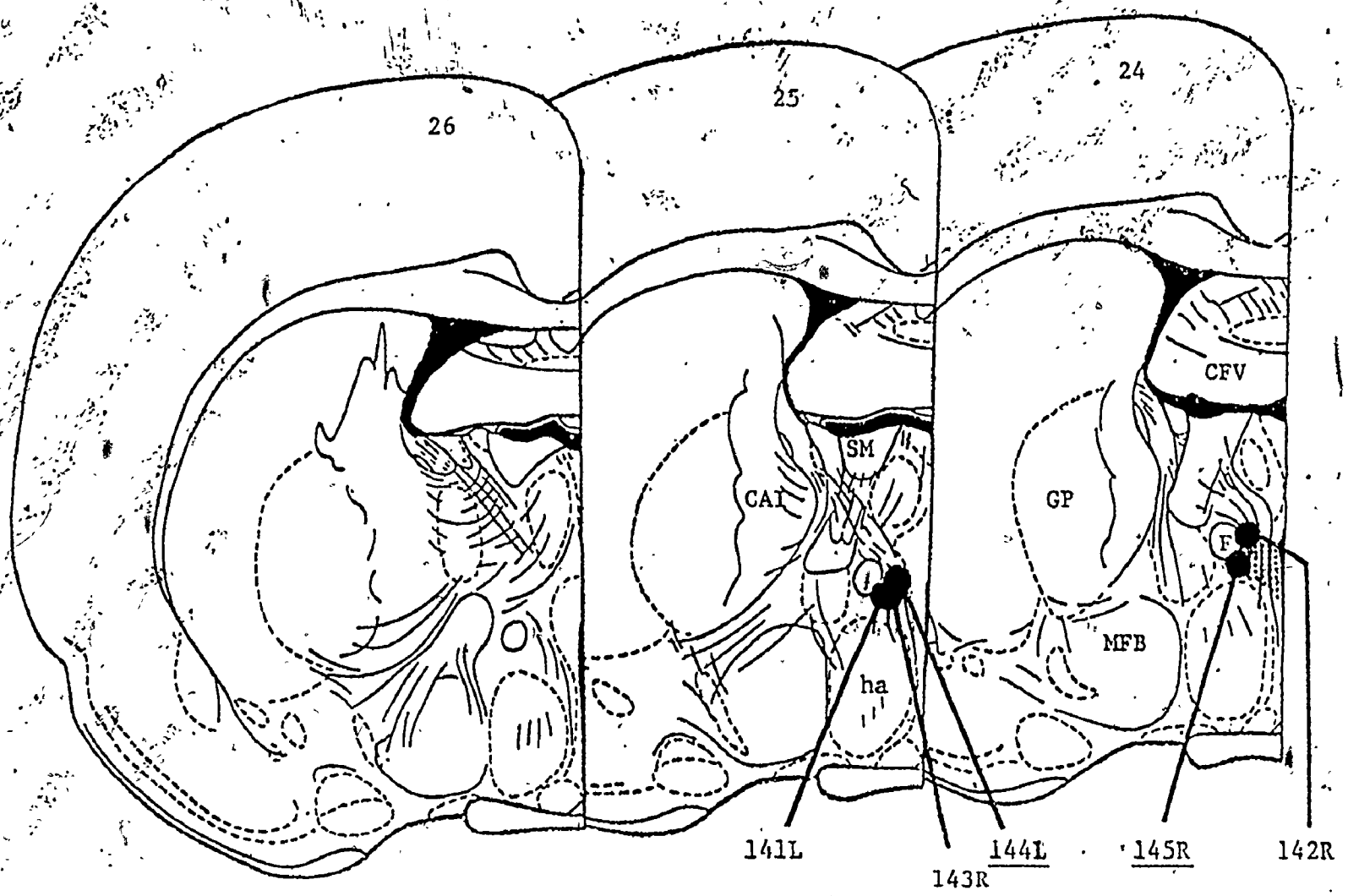

26
25
24
CFV
SM
CAI
GP
MFB
ha
141L
144L
143R
145R
142R

Figure 6-6. The location of the tip of inner cannulae aimed at the ventral periventricular pathway. The animal received the second injection of 6-OHDA at these sites. The stipled area indicates the extent of the ventral periventricular pathway as indicated by Lindval et al. (1974) p. 329, Figure 6-A: the pathway continues caudally.


26
25
24
CFV
SM
CAI
GP
F
MFB
ha
141L
143R
144L
145R
142R

system. The cannulae are all in a position to deliver the 6-OHDA to the fibres of this system.

Discussion

Neither a unilateral nor a two-stage, bilateral lesion in the nigrostriatal DA system, the combined dorsal and ventral NA pathways, or the ventral periventricular NA bundle, selectively disrupted elicited feeding. This inability to suppress elicited feeding by discrete damage to CA pathways despite such a suppression following intraventricular 6-OHDA raises a number of possibilities:

1) There is the possibility that these lesions were ineffective in damaging the desired systems. Although no direct measure of CA levels following the lesions is available, there is reasonable indirect evidence to argue that extensive damage was produced. All the cannula tips were localized within the desired region of the brain. With the concentration of 6-OHDA used, a selective lesion of CA neurons should have been produced in an area of about 2-3 mm in diameter (Ungerstedt, 1971a, 1973). Marshall et al. (1974), for example, observed an 89% reduction in striatal dopamine as compared to that of normal animals after 6-OHDA injections in the zona compacta of the substantia nigra. It is not possible, however, to determine how extensive the present lesions were and this may be an important factor. Fibiger, Phillips and Clouston (1973) produced a 99% reduction in striatal tyrosine hydroxylase activity (an index of CA levels - McGeer, Gibson & McGeer, 1967) and observed behavioral deficits in response to hypertonic saline which were not observed in the present study (see Experiment 7 for a full discussion). This suggests that the present lesions to the NSB may have been subtotal. Consequently one cannot completely discount the

involvement of the nigrostriatal DA system in the suppression of elicited feeding produced by intraventricular 6-OHDA although Ungerstedt (1973) argues that the intraventricular route does not produce a complete reduction in striatal DA. According to the histology the damage to the NA systems ought to have been extensive (Ungerstedt, 1973) since the cannulae were located within the fibre tracts.

2) The use of two-stage lesions may also be important in interpreting the results. According to Stricker and Zigmond (1976) a considerable amount of functional recovery is possible unless the damage to CA neurons is almost total. This recovery appears due in large part to compensatory changes that occur within residual neurons and their post-synaptic receptors. Stricker and Zigmond's (1976) review of the evidence points out that most of the data on recovery come from peripheral adrenergic fibres but that there are reasonable grounds to assume that similar processes are occurring in damaged central CA neurons. The specific processes seem to include increased CA release and synthesis, increased synthesis of tyrosine hydroxylase, and increased receptor sensitivity; collateral sprouting and adjustments within other neuronal systems that are functionally interrelated with the CA-containing neurons (such as serotonergic pathways) also may be important. As might be expected, the rate of recovery appears to depend on the size of the lesion, with more severe depletions generally associated with more prolonged periods of recovery. This recovery process may also be significantly influenced by certain variables which seem to affect the biochemical mechanisms at the synapse. The relevant variable here is the time between lesions (Finger, Walbran & Stein, 1973): the two week interval between completing the bilateral lesion used here falls within the time

frame found in some studies to produce sparing (eg. Stewart & Ades, 1951; Meyer, Issac & Maher, 1958). Moreover, some of the processes considered responsible for recovery of functions in CA systems, such as increased CA release (Fibiger, Lonsbury, Cooper & Lytle, 1972; Longo, 1973) and regenerative sprouting (Björklund, Katzman, Stenevi & West, 1971) occur within this time frame. Such recovery of function might conceivably be responsible for the failure to obtain suppression with lesions to the individual systems. This is probably not the main factor, however, since long-term deficits in elicited feeding were obtained with less than total destruction to the CA system (whole brain NA - 75.4% reduction, DA - 81.3% reduction; Phillips & Fibiger, 1976).

3) The individual systems attacked may not have included the appropriate pathways responsible for this phenomenon. For example, no effort was made to insure total destruction of the mesolimbic DA system whose cell bodies are located close to those of the NSB (Ungerstedt, 1971a). Although injections of 6-OHDA into the substantia nigra also produce some damage to this pathway (Ungerstedt, 1973), intraventricular 6-OHDA would produce considerable damage (Ungerstedt, 1973). This pathway deserves particular attention inasmuch as recent studies have shown that there are DA projections from this system to the frontal cortex (Hökfelt, Ljungdahl, Fuxe & Johansson, 1974). Furthermore, Kolb (Kolb, 1974; Kolb & Nonneman, 1975) has found disruption of feeding from lesions in this area as well as elicited feeding with electrical stimulation (Kolb & Cioé, unpublished observations). Other CA pathways which have yet to be discovered may be differentially influenced by intraventricular administration of 6-OHDA and have not been affected by the methods employed in this study. It is also possible, of course, that

the 6-OHDA may be damaging neurons from a non-catecholamine system which has not been identified. Although this possibility cannot be ruled out the evidence does support the view that 6-OHDA is selective among the suspected neurotransmitters (Ungerstedt, 1971a, 1973).

4) There is at least one other alternative explanation which will also account for the failure to disrupt elicited feeding by individual system damage. It may be that the CA system involved in elicited feeding is diffusely organized and includes more than one of the major pathways. It is possible that the generalized destruction obtained with intraventricular administration can disrupt the underlying system whereas the more specific lesions fail. This hypothesis is, of course, testable by using combined lesions to the various pathways. This study, moreover, partially tested this hypothesis in that both the dorsal and ventral pathways were attacked. Failure to disrupt elicited feeding suggests that this combination is not sufficient. Data considered in Experiments 8 and 9, however, suggest a DA involvement along with NA neurons. The lesion data also tend to support this position since it has not been possible to produce the feeding and drinking deficits associated with the LH syndrome without some damage to both the DA and NA systems (eg. Marshall et al., 1974; Fibiger, et al., 1973).

EXPERIMENT 7

In Experiments 5 and 6 the effects of destruction of various catecholamine systems on elicited feeding were examined. In this study, these animals were further examined to determine whether there were any deficits in other feeding-related situations. First off, all animals were subjected to a hyperosmotic challenge by injecting hypertonic saline intraperitoneally. Such a procedure produces intracellular dehydration which is rectified in intact animals by drinking (Adolph, Barker & Hoy, 1954). By using this challenge it is possible to determine whether there is any disruption of one of the normal homeostatic mechanisms involved in water intake. This particular challenge is also useful in providing a comparison point to the LH syndrome (Epstein & Teitelbaum, 1964). Taste sensitivity or finickiness was assessed by adulteration of the basic HFD with quinine hydrochloride and provides an indication as to whether these structures are necessary for responding to bitter taste. This test has also been found to differentiate intact animals from those with LH damage (Teitelbaum & Epstein, 1962). Two species-typical food-related responses were also examined: hoarding and poison-avoidance. Wild rats will bring food to their nest and store it

(Barnett, 1963) as will laboratory rats after they have experienced deprivation conditions. This behavior then can be considered to be a potential part of an appetitive sequence which precedes food consumption. Herberg and Blundell (1967), moreover, have observed that hypothalamic stimulation which elicited feeding led to immediate and sustained hoarding in satiated animals and even in animals which had never hoarded before (Blundell & Herberg, 1973). It is instructive, therefore, to determine whether hoarding is disrupted by lesions which disrupt elicited feeding. Poison avoidance, or baitshyness, is observed in wild rats (Barnett, 1963) as well as laboratory animals (Garcia, Kimeldorf & Hunt, 1961) when a novel taste is associated with a noxious situation.

These tests - although by no means exhaustive of the animals' behavioral repertoire - provide an opportunity to consider the involvement of the CA systems in a relatively wide range of food-related behaviors and also provide a comparison point with previous lesion studies.

Method

Subjects

The subjects in this series of experiments had all been used in previous experiments to determine the effects of damaging various parts of the catecholamine system on electrically elicited feeding from the hypothalamic region. An additional animal which had received a 6-OHDA lesion to the substantia nigra but did not show elicited feeding was used. Animals which had received ventricular injections of 6-OHDA plus a pretreatment of tranylcypromine (ventricular 6-OHDA, N=7) and those which had a ventricular injection of the vehicle plus tranylcypromine (ventricular vehicle, N=6) were from Experiment 4. The remaining animals (i.e. animals with intracerebral injections of 6-OHDA into the noradrenergic system, N=12; nigrostriatal bundle, N=9; and the periventricular system, N=4, as well as the unlesioned controls, N=9) came from Experiment 6. One animal in the periventricular group had dislodged his electrode assembly following the lesion and so did not complete the challenges.

Procedure

At least two weeks following the lesion, all animals were tested for various deficits in feeding related behaviors. The tests were administered in the order they are described in and there was at least three days between tests. Between tests the animal received both HFD and Purina Lab Chow pellets in their home cages.

Hyperosmotic stress. The animals were placed on an exclusive diet of HFD and water for two days. On Day 3 the animals were rapidly injected with 0.9% saline intraperitoneally (20 ml/kg) and their water intake recorded after 3 hrs and then again after 24 hrs. The following day, hypertonic saline (1 M NaCl) was injected following the same procedure.

Hoarding. To test for overnight hoarding of food pellets the animals were given food pellets in their home cage for three days. Standard hoarding alleys were used (Kolb, 1974). The alleys were constructed of unpainted plywood, with a 127 x 180 cm section forming the floor. Each half of this area was divided into six alleys, each measuring approximately 20 x 88 x 30 cm. Covered cages similar to those in which the animals were normally housed were attached to the alleys, and a guillotine door at the back of each cage was raised in order to allow the animals access to the alleys. Ten food pellets were evenly spaced along each wall extending from about 5 cm from the cage to the end for a total of 20 pellets; there was water in the cage but no food. In the early afternoon (1330) the animals were placed at the end of the alleyway so that they had to enter the cage through the open guillotine door. Twenty-four hours later the number of pellets out of 20 still remaining in the alleyway was recorded. Sufficient pellets were added to those in the alleyway to bring the number up to 20 and they were spaced out as before. The number of pellets remaining on the second day was recorded.

Quinine adulteration. The daily intake of HFD was recorded for two consecutive days. On Day 3 a mixture of 0.1% w/w quinine hydrochloride and HFD was given to the animals. The amount of adulterated diet consumed in 24 hrs was recorded. Water was available throughout the test.

Poison avoidance. Only the ventricular 6-OHDA and the ventricular sham groups were given the test for poison avoidance. The animals were given HFD in their home cage and were placed on a 23½ hrs water deprivation schedule. During that ½ hr they had access to either tap water or the test solution from a Richter tube. The first three days were used to establish a baseline for water intake under the deprivation condition.

On Day 4 the test solution (0.1 M solution of NaCl) was presented during the ½ hr drinking period. Immediately after completion of the ½ hr access to the test solution the animals were injected intraperitoneally with a 0.65 M solution of LiCl dissolved in physiological saline at a dose of 4.61 cc/kg. All food was removed for 3 hrs in order not to confound the aversive cues as the LiCl-induced sickness developed. For the next three days baseline water intake was determined but on the fourth day post-injection the test solution (i.e. 0.1 M NaCl) was re-introduced. The amount of the test solution consumed relative to the first presentation is taken as an index of the extent to which baitshyness had developed to the test solution.

Results

Hyperosmotic Stress

The difference between the water intake following hypertonic saline and physiological saline was calculated. A one-way ANOVA based on these difference scores showed no difference among the groups after 24 hrs but there were significant differences found after 3 hrs, F (5, 41) = 3.48, $p < .05$. Table 7-1 gives the mean difference scores for the various lesioned groups. Scheffé comparisons revealed that the intake was significantly lower ($p < .05$) for the animals receiving 6-OHDA intraventricularly plus tranylcypromine than for the vehicle control group. The vehicle control group did not differ significantly from the unlesioned control group.

Hoarding

A one-way ANOVA based on the number of pellets remaining in the alleyway the following morning of the second day (Table 7-2), failed to reveal any significant differences in the performance of the various groups. Almost all the animals removed the entire 20 pellets from the

Table 7-1

The Mean Difference in Water Intake with Hypertonic Saline Versus Physiological Saline for the Various Lesion Groups

Unlesioned controls (9)[a]	21.61	(3.48)[b]
Noradrenergic system (12)	22.54	(3.11)
Nigrostriatal bundle (9)	22.50	(2.85)
Periventricular system (4)	22.00	(7.40)
Ventricular 6-OHDA + tranylcypromine (7)	7.71 *	(0.72)
Ventricular vehicle + tranylcypromine (6)	28.50	(3.77)

[a] Number in parenthesis indicates the number of animals in each group

[b] The standard error of the mean

* Significantly different at $p < .05$ from the ventricular vehicle + tranylcypromine control group

Table 7-2

The Mean Number of Pellets (out of 20) Remaining in the Alleyway after 24 hrs of the Second Day for the Various Lesioned Groups

Unlesioned controls (9)[a]	0.11	(0.11)[b]
Noradrenergic system (12)	4.75	(1.93)
Nigrostriatal bundle (9)	4.22	(2.36)
Periventricular system (4)	1.75	(1.44)
Ventricular 6-OHDA + tranylcypromine (7)	6.07	(3.34)
Ventricular vehicle + tranylcypromine (6)	3.87	(1.90)

[a] Number in parenthesis indicates the number of animals in each group

[b] The standard error of the mean

alleyway to their home cage.

Quinine Adulteration

The difference between the food intake before (baseline) and after quinine adulteration was calculated. A one-way ANOVA based on these differences scores indicated a significant effect (F (5,41) = 5.35, p < .05) and a Scheffé comparison revealed that animals with 6-OHDA intraventricularly consumed significantly less (p < .05) food following the quinine adulteration than did the vehicle control group (Table 7-3).

Poison Avoidance

There was a significant reduction in the intake of the sodium chloride following the injection of lithium chloride for both the animals receiving 6-OHDA intraventricularly plus tranylcypromine, as well as the vehicle control, t (5) = 9.88 and 6.53 respectively, p < .01. A comparison of these two groups based on the difference scores between pre- and post-treatment intakes failed to reveal any difference in the degree of poison avoidance.

Discussion

The only lesion condition which produced a deficit in response to hypertonic saline was the intraventricular injection of 6-OHDA with a pretreatment of a MAOI. These animals showed a reduced water intake over 3 hrs, but not over 24 hrs, when compared to vehicle control animals. Fibiger, Zis and McGeer (1973) using similar procedures also found a reduction in water intake for the intraventricular group after 2 hrs; Stricker and Zigmond (1974) reported no differences after a 3 hr interval although there was some delay in drinking among a few animals. Their procedure, however, probably involved a relatively weaker stimulus in that they did not consider the animal's body weight

Table 7-3

The Mean Difference in Food Intake for the Various Lesion Groups following Quinine Adulteration (in g)

Unlesioned control (9)[a]	7.60	(0.90)[b]
Noradrenergic system (12)	9.98	(1.11)
Nigrostriatal bundle (9)	9.40	(1.21)
Periventricular (4)	9.25	(2.12)
Ventricular 6-OHDA + tranylcypromine (7)	16.11*	(1.12)
Ventricular vehicle + tranylcypromine (6)	8.73	(1.43)

[a] Number in parenthesis indicates number of animals in each group

[b] The standard error of the mean

* Significantly different at $p < .05$ from the ventricular vehicle + tranylcypromine control group

but simply delivered a fixed volume (i.e., 5 ml of 1 M NaCl). In a more recent report, however, Stricker and Zigmond (1976) noted that animals which were slow to recover feeding - and presumably had more complete CA depletions - showed virtually no drinking to the hypertonic saline after 3 hrs but animals which recovered quickly showed no reduction as compared to the control animals. Apparently this deficit is related to the severity of damage to the CA system. Moreover, Stricker and Zigmond (1976) also confirmed the observation that these animals are impaired only in the short-term (1-3 hrs) since they do not differ from control animals after a 24 hr interval. Stricker (1976) has also found a similar effect with electrolytic LH lesions.

The failure of the nigrostriatal bundle lesion to produce a deficit does not coincide with other reports. Both chemical (Marshall et al., 1974; Fibiger, Phillips & Clouston, 1973; Fibiger, Zis & McGeer, 1973) and electrolytic lesions (Oltmans & Harvey, 1976) to the dopaminergic NSB produced a deficit in the animal's short-term drinking response to hypertonic saline. It is possible, however, that the lack of deficit here may be partly explained on the basis of a functional recovery of CA neurons following a two-stage lesion as was discussed in Experiment 6. Finger et al. (1973) pointed out that a two week interval between lesions (as used here) has been shown to produce sparing, while Stricker and Zigmond (1976) have concluded that there is good evidence for a considerable amount of functional recovery in the CA neuronal system. It must be acknowledged, nevertheless, that Fibiger, Phillips and Clouston (1973) found this regulatory deficit with a unilateral 6-OHDA injection into the substantia nigra. They did not, however, wait two weeks after the lesion before testing but apparently tested for hyper-

tonic-saline induced drinking shortly after the lesion so that it is not possible to make a direct comparison.

The intraventricular 6-OHDA group showed an increased sensitivity to food adulteration in that its intake was reduced as compared to its control group; this was the only group to show such an effect. These results confirm the observations of Fibiger, Zis and McGeer (1973) with respect to the intraventricular group but do not correspond with data on bilateral destruction of the NSB (one-stage lesion). Moreover, one would have expected that the combined dorsal and ventral noradrenergic lesion would not have produced finickiness inasmuch as Ahlskog (as cited in Hoebel, 1976) found no differences between control animals and norepinephrine-depleted rats (only the ventral system was destroyed).

There was, however, no disruption of either hoarding or poison avoidance. The failure to obtain disruption with the intraventricular or the substantia nigra lesions reduces the likelihood that the CA projections to the medial cortex (Hökfelt, Ljungdahl, Fuxe & Johansson, 1974) are important in hoarding. Kolb (1974) has been able to dissociate eating and hoarding deficits by lesions to the orbital pre-frontal cortex and to the medial cortex - both of which receive DA projections. The failure to obtain a deficit in poison avoidance from the intraventricular group is in line with the observations of Stricker and Zigmond (1974). These observations, of course, run counter to the finding of Roth, Schwartz and Teitelbaum (1973) who found that animals who had recovered from LH lesions failed to learn specific food aversions. This difference - and others - suggests the LH syndrome is not identical to the syndrome which follows destruction of CA neurons (or the NSB in particular) (Stricker & Zigmond, 1974).

EXPERIMENT 8

The following two studies are designed to examine the involvement of the CA system in elicited feeding by pharmacological blockade. In this study, the role of DA neurons was examined with the use of intraperitoneal injection of the blocking agent Haloperidol (Andén, Butcher, Corrodi, Fuxe & Ungerstedt, 1970). This experiment is essentially a replication and extension of work done by Dr. A. Phillips who provided the details of his study during its execution (Phillips & Nikaido, as cited in Phillips & Fibiger, 1976). A dose response curve was generated for the effects of this blocking agent on elicited feeding. In addition, curves were generated for deprivation-induced feeding (23 hrs) as well as for deprivation-induced drinking. These latter conditions provided a comparison point for a generalized disruption of ingestive behavior as well as an opportunity to determine whether elicited feeding was dissociable from deprivation-induced feeding by pharmacological means.

Method

Subjects

Six animals which had previously been used to establish diet preference (Experiment 2) when electrically induced to eat were selected. These animals had bilateral stimulating electrodes in the lateral hypothalamic area (P 2.7, L 1.6, V 8.8). All animals were maintained on HFD and water ad libitum during the brain stimulation tests.

Procedure

The animals were tested for electrically elicited feeding during a 13 min. test session (3 min. adaptation followed by 10 min. of alternating ESB) at a current level which had reliably induced elicited feeding. The effects of haloperidol on elicited feeding were determined by injecting the animals 45 min. before testing with either haloperidol (Haldol, McNeil Laboratory; diluted to a concentration of 0.5 mg/ml in 0.9% saline) or 0.9% saline solution. Three different dosages of haloperidol were used: 0.05, 0.10 and 0.15 mg/kg. To control for order effects the order of administration of these dosages was completely counterbalanced; each animal was injected once per day. The haloperidol was injected first, and on the following day the same volume of 0.9% saline was injected so that there was an alternation between the haloperidol and saline over a six day test sequence.

These animals were also tested for deprivation-induced feeding under comparable conditions. All animals were subjected to a 23 hrs deprivation schedule with food (HFD) available for a 1 hr period in the home cage. After a week's exposure to this schedule, the animals were injected with the three dosages of haloperidol using the procedure outlined above. The amount of food consumed during a 10 min. exposure to the HFD in the stimulation test boxes was recorded; following this the animals were returned

to their home cages and allowed access to the food for another 50 min. Half of the animals received the elicited feeding test first whereas the other half were first tested for the effects of haloperidol on deprivation-induced feeding.

Following these tests the animals were placed on a 23 hrs water deprivation schedule for one week before being tested for the effects of the various dosages of haloperidol on deprivation-induced drinking in the test boxes. The same procedures as had been used for deprivation-induced feeding were employed.

Results

Intraperitoneal injections of haloperidol suppressed the frequency of elicited feeding as well as the amount of food consumed during such feeding. A 2 x 3 repeated measures ANOVA on the frequency of elicited feeding revealed significant main effects of the drug and dosage as well as a significant interaction term ($F(1,25) = 97.87$, $F(2,25) = 14.03$ and 12.34 respectively, $p < .01$). Examination of the simple main effects (Figure 8-1) revealed that haloperidol significantly reduced ($p < .01$) the frequency of elicited feeding for the 0.10 and 0.15 mg/kg dosages as compared to the saline. Moreover, the two higher dosages produced a significant reduction ($p < .01$) as compared to the 0.05 mg/kg dosage. A similar ANOVA on the amount of food consumed during elicited feeding produced a similar pattern of significant effects ($F(1,25) = 23.37$, $F(2,25) = 5.41$ and 5.66, $p < .01$). Further analysis of the simple main effects (Figure 8-2), however, showed that the haloperidol significantly ($p < .01$) reduced intake only at the 0.10-mg/kg dosage. The two higher dosages did, nevertheless, significantly reduce ($p < .05$) food intake as compared to the 0.05 mg/kg level.

The parallel study conducted on the effects of haloperidol on eating

Figure 8-1. The effects of intraperitoneal injections of haloperidol and saline on the frequency of elicited feeding.

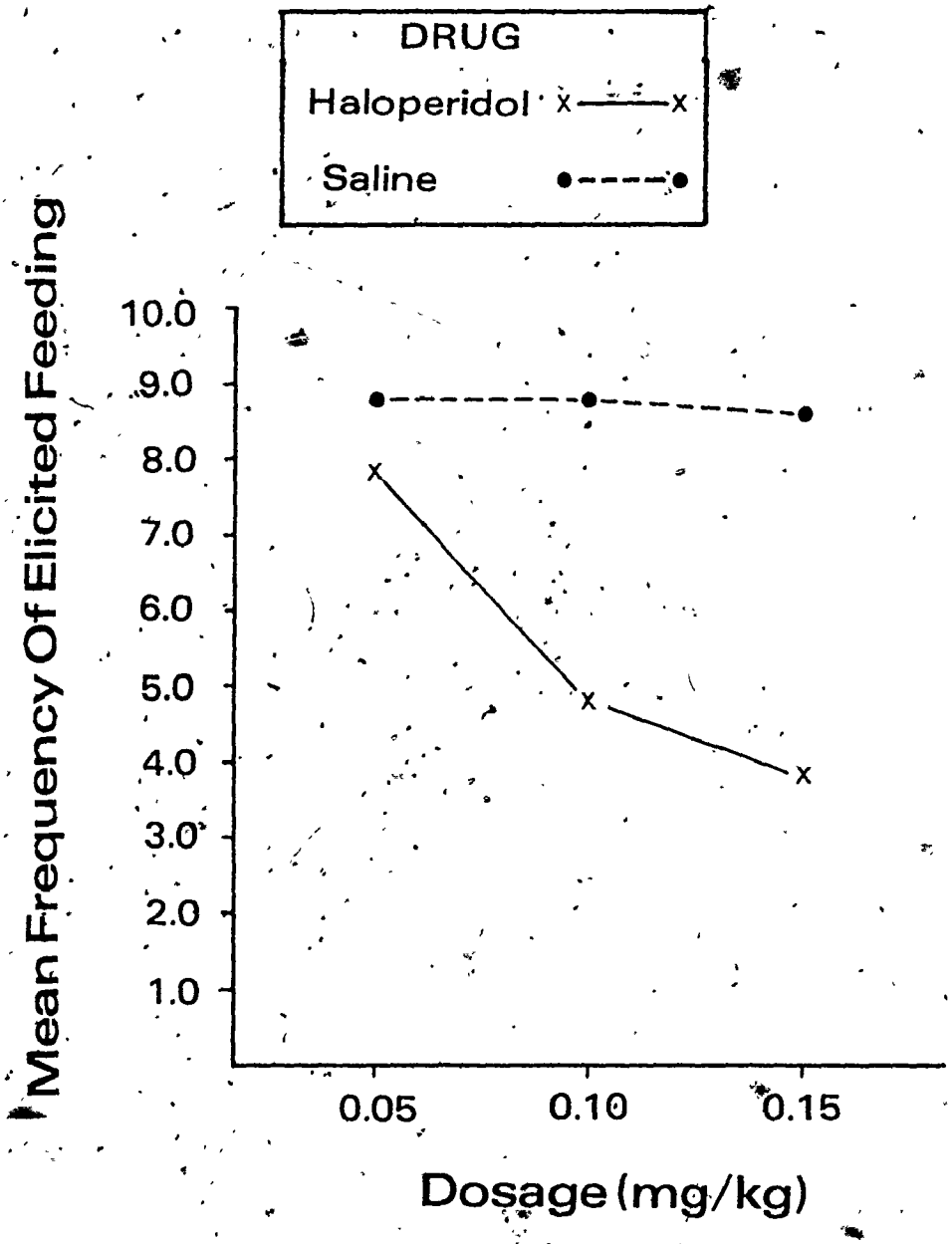
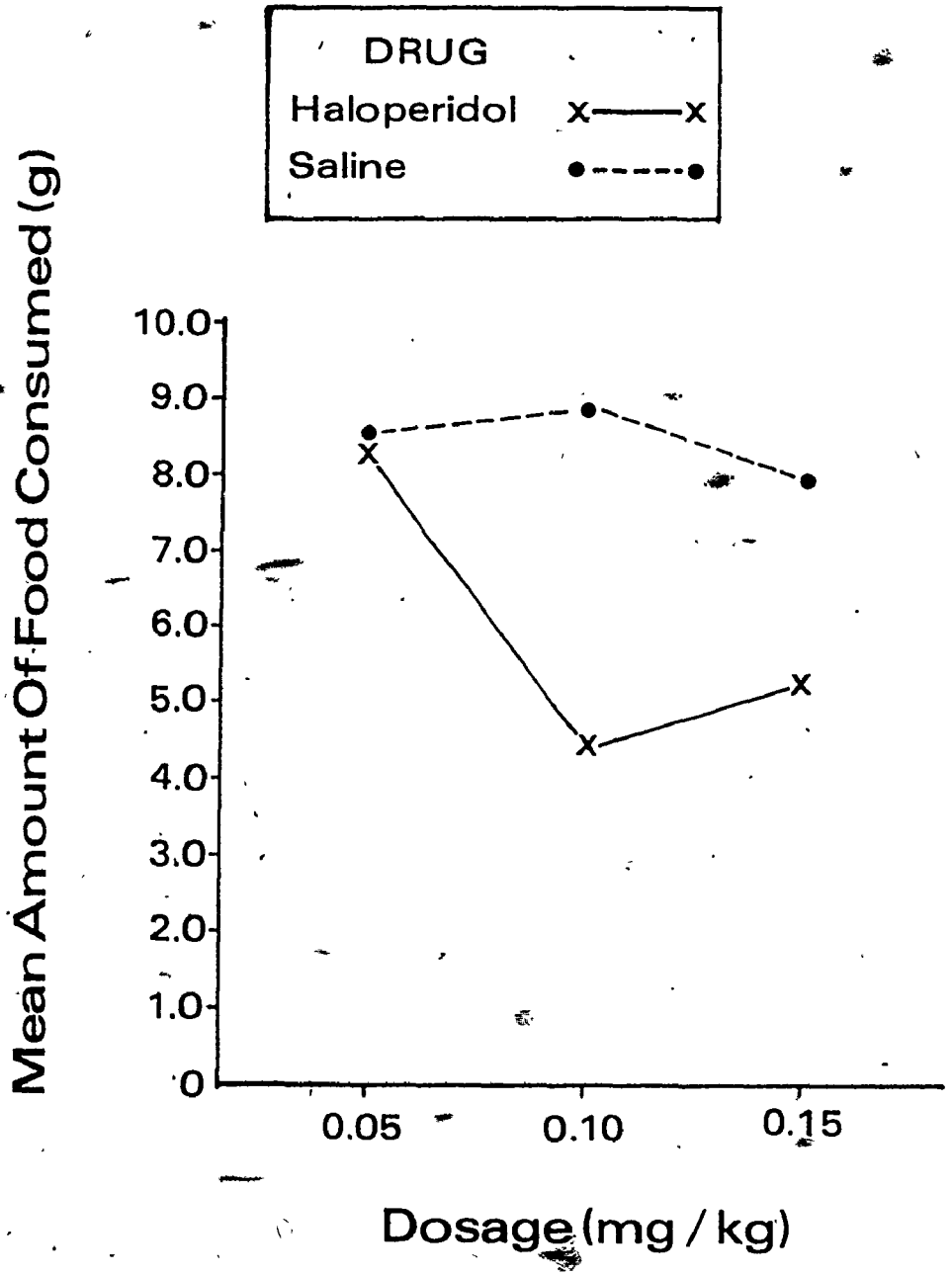


Figure 8-2. - The effects of intraperitoneal injections of haloperidol and saline on the amount of food consumed during elicited feeding.



induced by 23 hrs of food deprivation showed no disruption in eating by the haloperidol. Figure 8-3 presents the dose-response curves for both haloperidol and saline.

There was, however, a significant suppression of drinking induced by a similar period of water deprivation, F (1,25) = 4.78, $p < .05$. As Figure 8-4 indicates, the effect of haloperidol is not dependent on the dosage.

The electrode sites which supported elicited feeding are in Appendix 1, Figure A9.

Discussion

Haloperidol at the higher dosages (0.10 and 0.15 mg/kg) suppressed both the frequency of elicited feeding as well as the amount of food consumed during the ESB when compared to the lowest dosages used (0.05 mg/kg). This, of course, suggests that dopamine is necessary for electrically elicited feeding since at these dosages haloperidol is primarily a dopamine blocker (Andén et al., 1970). Taken in conjunction with the 6-OHDA lesions it also suggests that the lesions designed to disrupt DA fibres did not adequately reduce DA levels. As was pointed out in Experiment 6, however, the lesions in the substantia nigra were primarily aimed at the nigrostriatal bundle and probably did not completely destroy the DA neurons in the mesolimbic system (Ungerstedt, 1973). It is possible, therefore, that the haloperidol (as well as the intraventricular 6-OHDA) disrupted the overall levels of brain DA while the intracerebral injections into the cell bodies of the NSB did not, and that such a general disruption is necessary to produce a suppression of elicited feeding.

Haloperidol did not disrupt feeding induced by 23 hrs deprivation

Figure 8-3. The effects of intraperitoneal injection of haloperidol and saline on the mean food intake in 10 min. following 23 hrs of food deprivation.

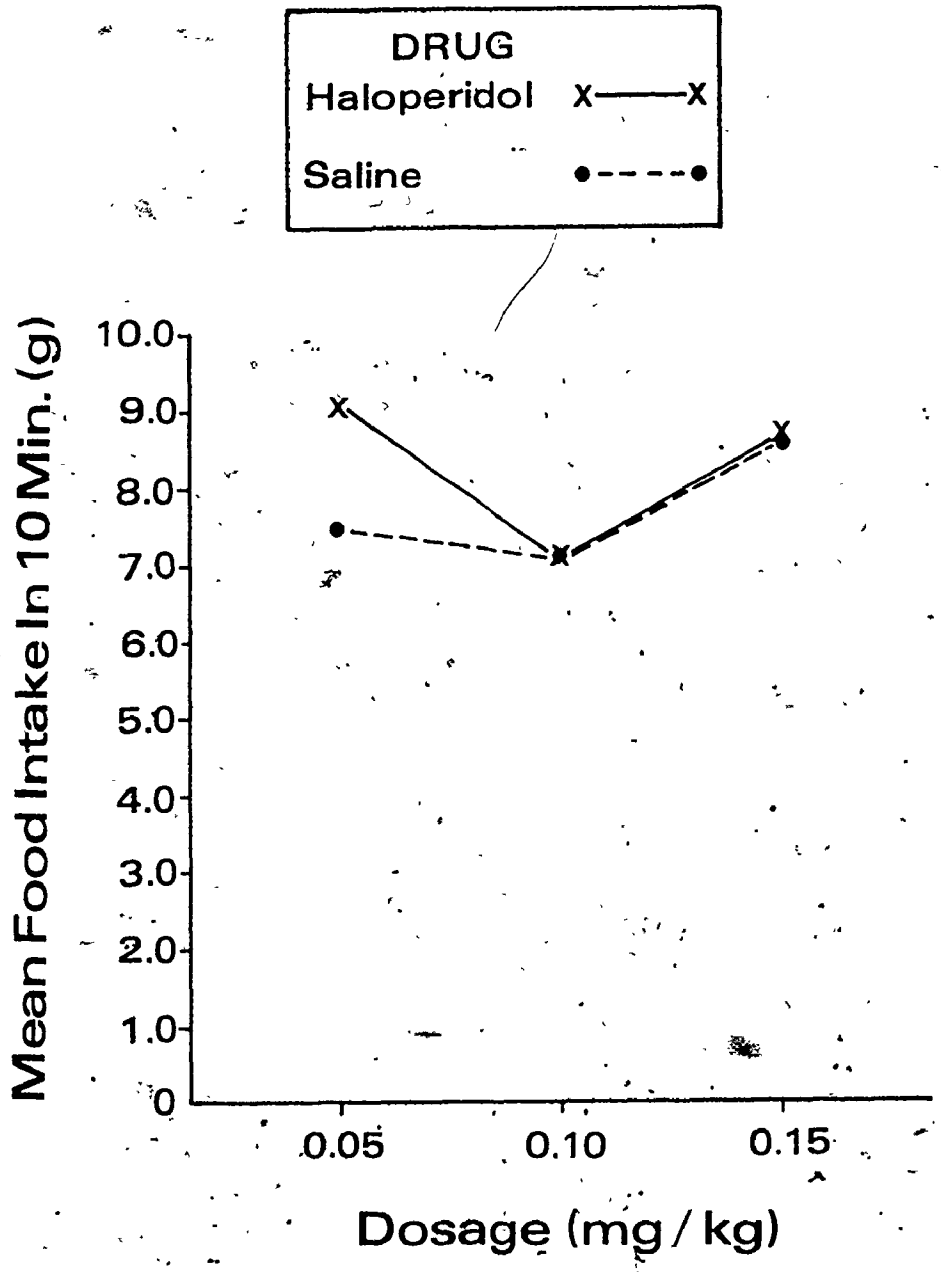
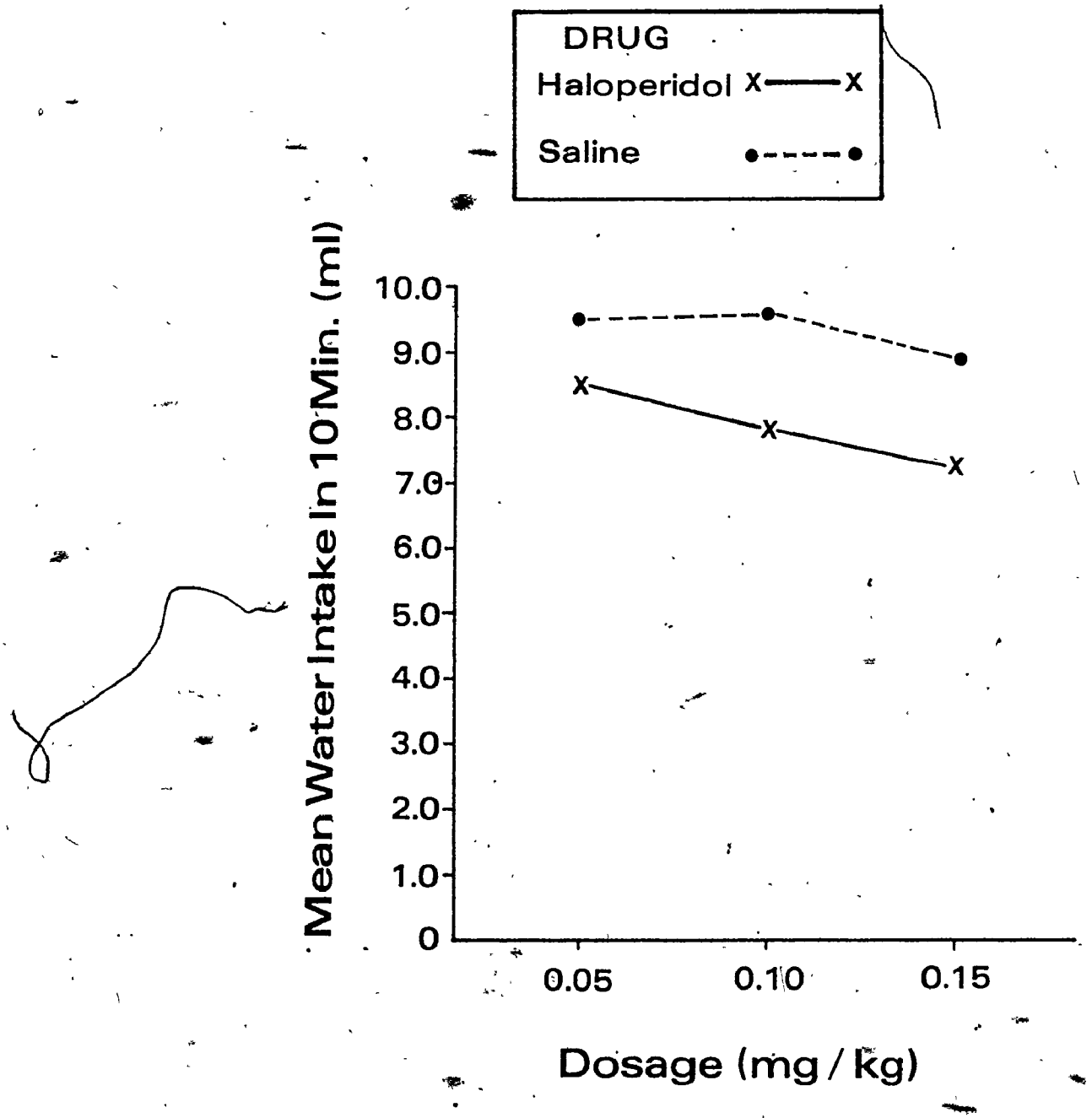


Figure 8-4. The effects of intraperitoneal injections of haloperidol and saline on the mean water intake in 10 min. following 23 hrs of water deprivation.



which suggests that electrically elicited feeding and deprivation-induced feeding do not require the same degree of neural integrity. It is not possible, of course, to discount the involvement of DA neurons in deprivation-induced feeding since the degree of disruption to this system seems to be important. Stricker and Zigmond (1976), for example, claim that in order to get severe aphagia and adipsia from intraventricular injections of 6-OHDA (which depletes DA as well as other CA) it is necessary to reduce brain DA by 90% or more; less destruction does not produce aphagia and adipsia. It is also possible to argue that 23 hrs deprivation is a more potent stimulus to eat than is the ESB used here. In this case we may be simply dealing with a relatively weak stimulus (ESB) which is readily disrupted by haloperidol as opposed to a more powerful stimulus that is not: it is a quantitative rather than a qualitative difference. Such an argument, however, is not very convincing given that these animals consumed the same amount of food when stimulated as they did following 23 hrs deprivation under the saline conditions. The failure to disrupt deprivation-induced eating also indicates that the suppression observed with elicited feeding is not simply a general suppression of behavior, or more specifically the ability to engage in the motor sequence required to ingest the HFD. Behaviorally these animals - at the dosages used - did not appear to be generally debilitated inasmuch as they were responsive to being held and did not show any obvious locomotor problems.

Deprivation-induced water intake, however, was suppressed at all levels of haloperidol. This effect is somewhat perplexing in that Zis and Fibiger (1975) did not find such a suppression using a larger dosage (0.2 mg/kg) with animals who were water deprived for 24 hrs. The differ-

ing effects may be accounted for by the test procedures since Zis and Fibiger measured water intake over 1 hr whereas in this study 10 min. was used. This suggests that the haloperidol may have delayed the drinking rather than suppressing it. Such an interpretation is consistent with the observation made in Experiment 7, and confirmed by Stricker and Zigmond (1974), that animals recovered from CA damage can respond to hypertonic saline injections if given sufficient time. This would suggest that the deficit produced by the haloperidol is not specific to feeding and drinking but may be more general in nature. Stricker and Zigmond (1976) argue that the long-term homeostatic deficits shown by animals suffering damage to DA neurons reflects their inability to behave appropriately after acute and profound stress rather than the ineffectiveness of specific regulatory stimuli involved in eating and drinking. The haloperidol might produce a similar situation but on a temporary basis by interfering with the DA system. If one accepts this analysis then it suggests that 23 hrs of water deprivation is a more "stressful" situation than is 23 hrs of food deprivation.

EXPERIMENT 9

In the previous experiment haloperidol injected intraperitoneally suppressed elicited feeding but did not affect deprivation-induced feeding. It is possible, however, that this effect may be the result of peripheral effects rather than just its central action. Accordingly, this study involves the intraventricular administration of haloperidol as a dopamine blocker in an attempt to minimize peripheral effects. Since it is not possible to exclude the involvement of NA neurons in the disruption of elicited feeding produced by intraventricular 6-OHDA (Experiment 4), this system was also interrupted pharmacologically. Both α-adrenergic and β-adrenergic blockers were administered intraventricularly. Once again, to determine whether the same neural systems are necessary for both elicited and deprivation-induced feeding, the effects of these blockers on 23 hr deprivation-induced feeding was also examined.

Method

Subjects

Fifteen rats were prepared with bilateral stimulating electrodes in the lateral hypothalamic area (P 2.7, L 1.6, V 8.8) as well as chronic indwelling guide cannulae aimed at the lateral ventricles (P 1.0, L 1.5, V 3.2; guide cannulae end 1 mm above the target site). The animals were screened for electrically elicited ingestive behavior using HFD; 12 animals displayed elicited feeding from at least one electrode site.

Procedure

The 12 animals which displayed elicited feeding were randomly divided into two equal groups. One group was induced to eat by electrical stimulation of the brain (elicited) whereas the other was put on a 23 hrs food deprivation schedule (deprivation).

The animals in the elicited group were given three days of testing for elicited feeding using the standard testing procedure to ensure stable responding. Three blocking agents were administered intraventricularly via the cannula ipsilateral to the stimulating electrode 10 min. before testing; the order of presentation was completely counterbalanced. Haloperidol (a dopamine blocker) was given at a dose of 25 µg in 5 µl of 0.6% lactic acid; phentolamine methanesulphonate (an α-adrengeric blocker; Regitin, Ciba) was given at a dose of 50 µg in 5 µl of 0.9% saline; and MJ-1999 (4'-(2- isopropylamin o-1- hydroxyethyl) methanesulphonanilid, Mead Johnson; a β-adrenergic blocker) was given at a dose of 50 µg in 5 µl of 0.9% saline. The sequence of testing was as follows: Drug A, Control, Vehicle A, Control, Drug B, Control, Vehicle B, etc. On the control days there was no injection. All injections were given at a rate of 5 µl/min using a syringe pump.

The animals in the deprivation group were exposed to a 23 hr food deprivation schedule for a week before being given the drug treatments. The same procedures for administering the drugs, as described above, were used. The amount of feeding which occurred in the stimulation test boxes during the 10 min. of access to the food was recorded. The animals were returned to their home cage for an additional 50 min. exposure to the food.

Results

A one-way repeated measures design ANOVA based on the mean frequency of elicited feeding failed to show a difference among the drugs administered intraventricularly. There was, however, a significant effect using the amount of food consumed during the elicited feeding, F (5,30) = 9.86, $p < .01$. Figure 9-1 presents the mean frequency of elicited feeding for the various conditions whereas Figure 9-2 presents the mean food intakes. The intake for the haloperidol condition was significantly lower ($p < .01$) than the haloperidol vehicle condition as well as the control baseline levels.

The parallel study in which feeding was elicited by 23 hr food deprivation did not indicate any differences among the conditions for food intake during the first ten minutes of the access period.

Histology

The sites of the stimulating electrodes which showed elicited feeding and which were used in the course of this study can be found in Appendix 1, Figure A10.

The placements of the cannulae in the ventricles were confirmed histologically but more importantly they were verified using the gravity flow technique described in Experiment 2 (Myers, 1972).

Figure 9-1. The mean frequency of elicited feeding after intraventricular injection of blocking agents. The bars indicate the standard error of the mean. The baseline measures are an average over three days for each subject.

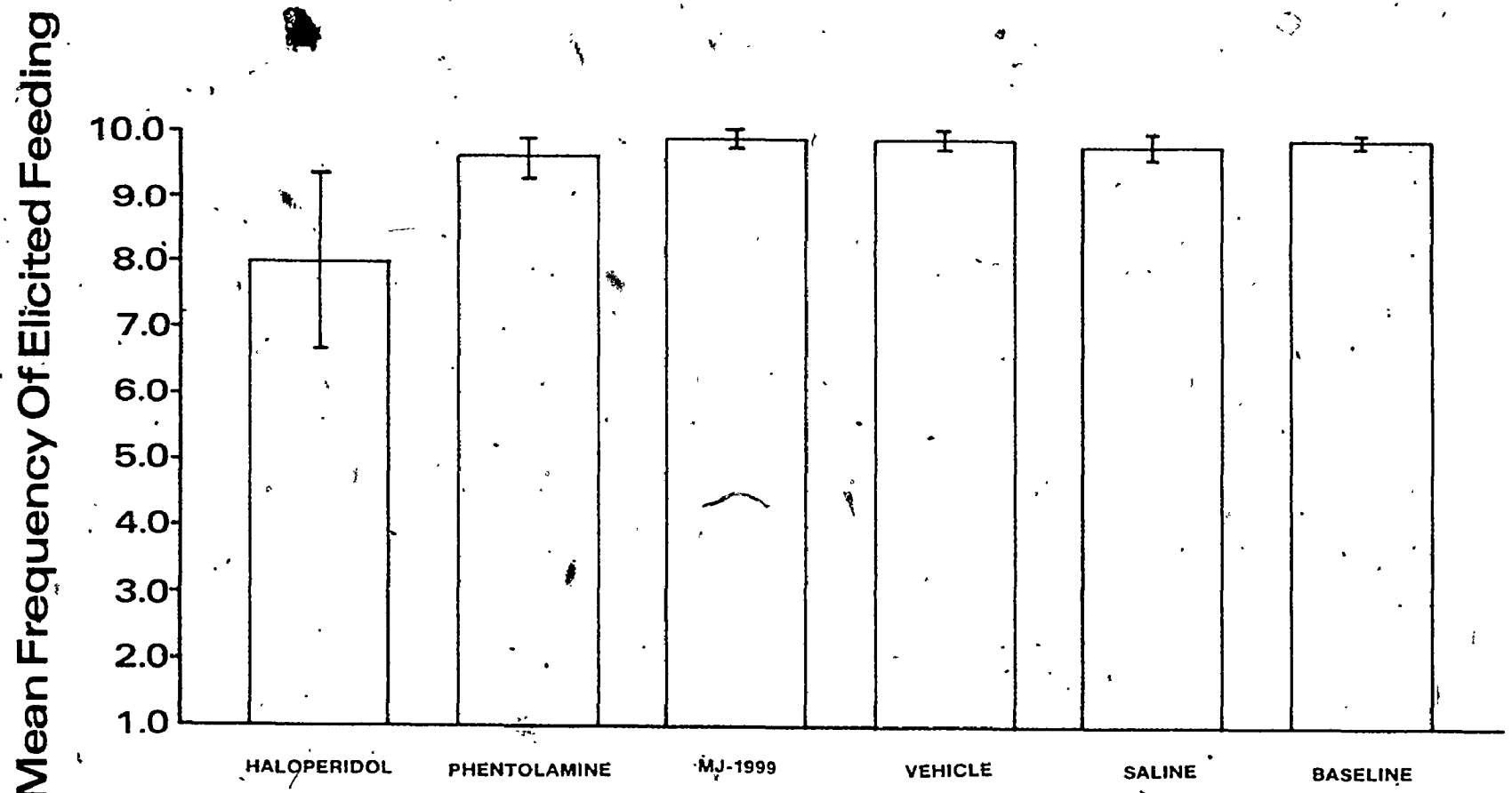
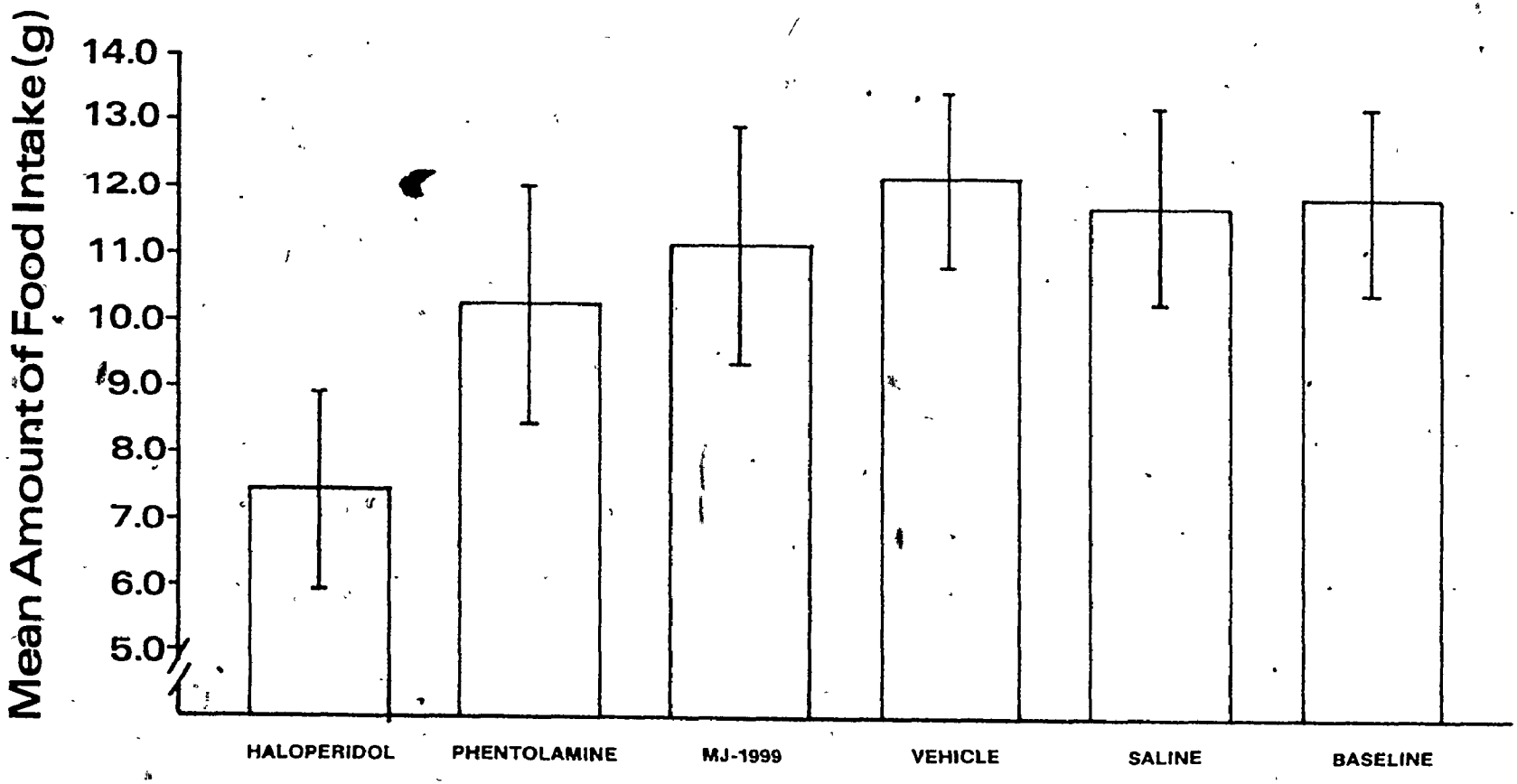

Mean Frequency Of Elicited Feeding
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
HALOPERIDOL
PHENTOLAMINE
MJ-1999
VEHICLE
SALINE
BASELINE

Figure 9-2. The mean amount of food consumed during elicited feeding after intraventricular injection of blocking agents. The bars indicate the standard error of the mean. The baseline measures are an average over three days for each subject.


Mean Amount of Food Intake (g)
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
HALOPERIDOL
PHENTOLAMINE
MJ-1999
VEHICLE
SALINE
BASELINE

Discussion

The only drug to produce a statistically significant suppression of elicited feeding was haloperidol, and it did so primarily by reducing the amount of food consumed during ESB. The failure to disrupt the frequency of elicited feeding is interesting in that it suggests that haloperidol may be interfering with processes related to the maintenance of feeding rather than its initiation (LeMagnen, 1971). Too much should not be made of this difference, however, since intraperitoneal injections of haloperidol disrupted both measures and there is some indication that haloperidol did affect the frequency of elicited feeding in that there was an increase in variability with this drug along with a slight reduction. The effectiveness of haloperidol would suggest that DA neurons are important for elicited feeding. It would be unwise, however, to exclude the involvement of NA in elicited feeding since haloperidol is known to also interfere with NA although to a lesser degree (Andén et al., 1970; Janssen, 1967). Furthermore - although it is usually dangerous to draw conclusions about statistically nonsignificant differences - phentolamine did produce a slight reduction in intake during ESB which suggests that there may be some contribution by NA neurons. The same amount of phentolamine (50 µg) delivered intraventricularly, moreover, did reduce feeding elicited by a systemic injection of 2-DG whereas the MJ-1999 did not (Müller, Cocchi & Mantegazza, 1972). At this point, then, the safest conclusion would be that DA is involved in elicited feeding but a contribution to this phenomenon by NA neurons cannot be excluded.

There was, however, no comparable disruption of deprivation-induced feeding measured under the same time restrictions as the elicited feeding. Müller et al. (1972) also reported that neither phentolamine nor MJ-1999

disrupted food consumption measured over six hours. It would seem, therefore, that elicited feeding is also dissociable from deprivation-induced feeding with this pharmacological manipulation and this strengthens the conclusion reached in Experiment 8 that the two phenomena do not require the same degree of neural integrity to be obtained.

GENERAL DISCUSSION

Perhaps the most impressive aspect of electrically elicited feeding in its highly integrated form is that it occurs at all! Judging simply on the basis of the characteristics of electrical stimulation of neural tissue it does not seem very likely that a complex pattern of responses which can be influenced by environmental factors would be produced. For one thing, the electrical excitation around the electrode tip acts relatively indiscriminantly on afferent axons, short-axon interneurons and efferent neurons which have both excitatory and inhibitory synapses. Although there is some indication that axons are more sensitive to electrical stimulation than dendrites or somas (Porter, 1963), at the suprathreshold levels commonly used this difference is relatively meaningless. Add to this the fact that the spatiotemporal pattern of activation produced by the ESB is not likely to match the precise phasing of natural inputs and it would seem that the neural tissue activated by the electrode must be driven in bizarre and nonsensical synchrony. This means that the ESB can tell us nothing about the normal input of the stimulated zone or the type of information processing normally going on there. It can only indicate the effects of

a general increase in the output of the zone. The subtle, highly integrated neural effects resulting from the ESB must occur because the neural systems downstream (post-synaptic) are able to transform this nonsense signal into an effective neural code. ESB, moreover, activates a very limited portion of the response mechanism. For one thing, stimulation is applied unilaterally leaving the paired structure on the other side to be excited by any commissural input which may exist. In addition, only one component of a number of structures which appear to make up a system is stimulated. Even within the structure the ESB is probably only exciting a small fraction of the neurons in that structure (Roberts, Steinberg & Means, 1967). Despite all these potential difficulties, complex integrated responses are elicited..

As was pointed out in the Introduction, electrically elicited feeding appears to be quite similar in many ways to normal feeding in that the animal will learn and perform an operant response which delivers food when electrically stimulated (Miller, 1957; Coons et al., 1965). Although on occasion it is possible to obtain "eating" without the appropriate goal object (eg. the "fictive eating" reported by Robinson, Vanderwolf & Pappas (1977) from the locus coeruleus), generally speaking it is necessary for food to be available. Furthermore, it is clear that many variables which influence naturally occurring feeding (eg. deprivation, taste, temperature, stomach loads, drugs, and conditioning procedures) have similar effects on elicited feeding. Does this similarity, however, justify the conclusion that ESB is inducing "hunger" as was suggested by Miller (1960) or Blundell and Herberg (1973)?

This is essentially an unrealistic question. In the first place, the lengthy review of some of the ways in which animals can be induced to

eat was designed to highlight the complexity of the situation. It is not profitable to think of hunger as a unitary process. Feeding behavior can be induced by a number of factors which at some level must involve separate neural substrates (Stevenson, 1969), although ultimately they may share the same motor output. Since electrical stimulation is such an artificial technique there is not much chance that it could reproduce the entire neural sequence involved in naturally-induced feeding. The best we can do is to compare in detail the functional properties of centrally and normally-induced feeding to determine where the two are similar and where they are different (Roberts, 1969). Through this process we ought to be able to learn more about both phenomena.

In the first study, it was found that electrical stimulation could produce a relatively pure feeding response which in most cases was not contaminated by elicited drinking even when conditions were employed (following the suggestion of Roberts, 1969) which removed the potentially competing stimuli of the food. The pattern of drinking which was obtained suggested a competition for control of the motor system produced by simultaneous activation of separate though overlapping neural circuits (Wise, 1968). This does not mean, of course, that it might not have been possible to induce the animal to display elicited drinking by employing the extensive training conditions of Valenstein (1971) but rather it underscores the fact that without such training the feeding response predominated. Teitelbaum (1974) has argued that electrical stimulation generally produces only one behavior because there is inhibition of competing responses. One system, it is argued, can have an advantage by either anatomical proximity (Roberts, 1969; Olds et al., 1971), by sensitivity to frequency of stimulation (Mogenson, Gentil &

Stevenson, 1971), by an altered internal environment by prior food or water deprivation (Devor et al., 1970), by the physical stimuli in the environment (Valenstein, 1969; Roberts, 1969, 1970), and by the animals' past experience (Valenstein, 1971; Wise, 1969). It should be pointed out that in this entire thesis there was not one instance in which an animal displayed elicited drinking as defined here.

Furthermore, this elicited feeding was abolished by lesions through the stimulating electrodes but there was no comparable disruption of spontaneous intake of food and water. This suggests that the same degree of neural integrity is not necessary for both phenomena, or more specifically that the neural mechanisms underlying these phenomena are different. That is not to say that the neural tissue activated when elicited feeding is produced is not also involved in some way with feeding induced by more natural circumstances. Spontaneous feeding, after all, is the product of a number of different factors so that damage to a part of this neural system may not be readily detected because of redundancy in the system, or because there are alternate routes to the same behavior. It would seem reasonable, however, to conclude that elicited feeding does not involve activation of the entire system at some critical junction point since lesions which disrupt elicited feeding bilaterally produce little, if any, effect on spontaneous feeding.

The dissociation between elicited feeding and a facet of spontaneous feeding - that is, deprivation-induced feeding - is a major theme of this thesis. Apparently this difference in neural organization manifests itself in different diet preferences when the animal is induced to eat by deprivation as opposed to when ESB is used. Under deprivation

there is a clear hierarchy going from pellets, to wet mash (i.e., ground pellets and water), to the preferred HFD, but with ESB there is no differentiation between the mash and the HFD. Smith (1972) has also reported that ESB does not act like deprivation with respect to diet preference. He found that with deprivation animals were more responsive to taste since they licked less nutritive bitter quinine adulterated sucrose and more non-nutritive saccharin than they did when non-deprived; ESB, however, did not alter the taste reactivity of non-deprived animals. It is not likely in this case, however, that we are dealing with a change in taste sensitivity since with both deprivation-induced and electrically elicited feeding the animals preferred the HFD over the pellets. The lack of differentiation between the HFD and mash may indicate that the consistency of the diet is a more important factor under ESB since animals can engage in the same sequence of ingestive behavior with both diets.

In further pursuit of the neural mechanisms of elicited feeding and their similarity-dissimilarity to that of natural feeding, the involvement of the CA system was examined. A prime target for analysis was the DA nigrostriatal bundle since a number of investigators had suggested that it played a critical role in the aphagia and adipsia of the LH syndrome (Ungerstedt, 1971b; Oltmans & Harvey, 1972). Accordingly, stimulating electrodes were placed in the NSB at the point where lesions produce aphagia but elicited feeding was not obtained. Instead the predominant behaviors elicited were forced movements; these observations are consistent with the involvement of DA neurons in the control of movement (Andén, 1966; Ungerstedt & Arbuthnott, 1970). Since failure to obtain elicited feeding does not necessarily mean that DA neurons are not important for elicited feeding, the question of mechanisms was pursued

further using lesions and pharmacological manipulations.

Intraventricular injections of 6-OHDA successfully suppressed elicited feeding even after the animals had recovered the ability to regulate their daily food and water intake suggesting that CA pathways are necessary for elicited feeding (Phillips & Fibiger, 1973b, 1976). Since this technique is relatively indiscriminant with respect to the particular contribution of the various pathways (Ungerstedt, 1973), individual components were attacked using electrolytic lesions and 6-OHDA. Unilateral lesions ipsilateral to the stimulating electrode were used to control for any nonspecific effects of the lesions which might disrupt the elicited behavior but not reflect damage to tissue being activated by the ESB. Destruction of the locus coeruleus and the dorsal NA pathway produced a disruption of elicited feeding but this was attributed to nonspecific effects in that elicited feeding was also disrupted from sites contralateral to the lesion; moreover, the lesions produced a temporary hypophagia. Furthermore, two-stage lesions to the NSB, the combined dorsal and ventral NA pathways, and the ventral periventricular pathway also failed to selectively suppress elicited feeding. Elicited feeding, however, was suppressed by CA blockers. Haloperidol, administered both intraperitoneally and intraventricularly, suppressed elicited feeding without disruption of deprivation-induced feeding, strongly suggesting that an intact DA system is necessary for elicited feeding. NA blockers did not show any clear suppression although there was some suggestion in one measure of elicited feeding. However, since haloperidol does have some effect on NA (Andén et al., 1970) it would be unwise to exclude NA involvement at this point. One conclusion which can be drawn from these findings is that CA neurons are important in

elicited feeding, and that there is a contribution made by both DA and NA neurons. Such a conclusion is consistent with the involvement of CA in aphagia and adipsia: it has not yet been possible to produce aphagia and adipsia without some damage to the NA system as well as the DA neurons (Fibiger et al., 1973; Marshall et al., 1974; Stricker & Zigmond, 1976).

When the lesioned animals were subjected to a variety of tests designed to determine the range of ingestive responses remaining, the only group which showed any impairment was the intraventricular 6-OHDA animals. They were not able to respond in the short-run to a hypertonic saline injection but did so when given 24 hrs. This observation has recently been made by Stricker and Zigmond (1976) and is used as support for their ideas about the reorganization of the CA system following damage. These animals also showed increased finickiness to quinine adulteration but showed no deficits for hoarding or poison avoidance. This failure to find deficits for poison avoidance is supported by Stricker and Zigmond (1974) but runs counter to the observation that CA neurons are important for the acquisition of an active avoidance response (Cooper, Breese, Howard & Grant, 1972; Mitcham & Thomas, 1972). The failure of the lesions in the individual systems to produce deficits previously reported (eg. disrupted hypertonic saline response from NSB damage - Fibiger et al., 1973) can be attributed in part to the use of two-stage lesions (Finger et al., 1973).

One must not, however, conclude that the CA pathways are exclusively involved in either elicited feeding or in spontaneous feeding. Phillips and Fibiger (1976) have reported that other oral behaviors (i.e., elicited drinking and gnawing) have been disrupted by intraventricular injections of 6-OHDA. Furthermore, electrical self-stimulation of the

brain (through electrodes which support elicited feeding, drinking, or gnawing) is also disrupted - but on a more transitory basis -- by this lesion. Catecholamines have been shown to be important in this phenomenon in a large number of studies (see review by German & Bowden, 1974; Mogenson & Phillips, 1976). Moreover, there has been a recent reassessment of the deficits associated with the LH syndrome (Marshall et al., 1974) and damage to the CA system (Mogenson & Phillips, 1976; Stricker & Zigmond, 1976). These new approaches question whether the deficits (such as temporary aphagia and adipsia as well as the long-term deficits associated with feeding and drinking: see Epstein, 1971 for a summary) are the result of specific "motivational" problems or whether they reflect more general difficulties associated with initiation of behavior and the ability to respond to a wide range of stimuli. This reassessment will hopefully provide a better understanding of the nature of the mechanisms involved in feeding as well as other complex behavioral sequences.

Not only has elicited feeding been shown dissociable from naturally occurring feeding by lesions through the tips of the stimulating electrode and with respect to diet preference, but there is also a dissociation in terms of CA involvement. Animals recover the ability to regulate food and water intake after CA damage but they do not recover elicited feeding. Moreover, haloperidol does not disrupt deprivation-induced feeding at dosages which do suppress elicited feeding. It seems, therefore, that elicited feeding requires a greater degree of neural integrity in the CA system than is necessary to maintain deprivation-induced feeding. There are other studies in the literature which have also pointed out this dissociation between elicited ingestive

behaviors and the naturally occurring responses. Valenstein, of course, has contributed a great deal in this area demonstrating that animals showing elicited feeding were reluctant to switch to eating an altered form of a familiar food (Valenstein et al., 1968b). Animals did not switch from a different, but familiar, container under stimulus-bound drinking. Their taste preferences also differed from those of water deprived animals (Valenstein, Kakolewski & Cox, 1968). Smith (1972), moreover, found that ESB did not create a preference for calories (i.e., sucrose) over non-nutritive saccharin as did food deprivation. Berthoud and Baettig (1972; 1974b) reported that insulin rather than increasing stimulus-bound feeding as one might expect, actually decreased food intake. All of these differences make it clear that elicited behaviors are not identical with their naturally occurring counterparts.

In that respect Valenstein has been right in emphasizing the dissimilarities. It is still not clear, however, precisely what the nature of elicited feeding is, although there is no lack of suggestions. One view is that elicited behaviors occur because pathways or integrating areas specifically involved with these behaviors have been triggered (Roberts, 1969, 1970; Wise, 1974). In order to account for the differences noted above Wise (1974) has suggested that ESB produces an additional emotional arousal component which interferes with the display of elicited behavioral sequences. Caggiula (1969) emphasized the reinforcement component associated with placements which produce stimulus-bound behavior and suggested that it might account for the ability to switch behaviors by removing the initial goal object (Valenstein et al., 1968a). Hoebel (1969) has reviewed the interrelation between self-stimulation from feeding sites and variables which influence feeding

Valenstein (Valenstein et al., 1970) has emphasized the involvement of the neural substrate underlying species-specific behaviors and how discharging this excited substrate can provide the motivation to behave. The ESB induces a general state which is not sufficiently specified to exclude the possibility of response substitution. Teitelbaum (1974) has suggested that ESB may produce its effect on elicited behaviors by de-encephalizing the animal so as to reduce the level of organization of behavior to an ontogenetically more primitive stage, while Antelman (Antelman, Szechtman, Chin & Fisher, 1975) has pointed out the similarities between electrically elicited behavior and behaviors elicited by a tail pinch. Whatever the ultimate resolution of these disparate views of elicited feeding it is clear that we must accept Teitelbaum's (1974) warning that we have been hindered by our acceptance of the technique of electrical stimulation as a scientific paradigm. We can no longer afford to assume that behavior elicited by hypothalamic stimulation is normal motivated behavior, i.e., affected by all the variables that govern normal adult rat behavior.

SUMMARY

Electrical stimulation of the hypothalamus can elicit feeding behavior which is directly bound to the brain stimulation. Although this phenomenon has been studied for a number of years, there is still considerable controversy over both its essential nature and the relationship it bears to "normal" eating. One aspect of this controversy centres on whether the electrical stimulation is activating a neural system specifically involved in eating or whether a nonspecific system is involved. In the first study, electrodes were implanted into the lateral hypothalamic-medial forebrain bundle region of the brain, and the rats tested for elicited ingestive behavior. The majority of electrode sites (62%) maintained elicited eating only and even in those cases in which some drinking did occur, the response was weak, failing in all cases to attain the criteria established for elicited ingestive behavior. These results were obtained in spite of a procedure which favoured the occurrence of drinking by removing food as a competing stimulus during electrical stimulation of the brain. Such findings argue against a nonspecific neural system for feeding and drinking and support the view that there are separate - although probably over-

lapping - systems involved.

Even if there are separate neural systems involved in elicited ingestive behavior, how does elicited eating relate to "normal" eating as indicated by the daily intake of food? Electrolytic lesions were made in the area surrounding the electrode tip in order to determine whether it was possible to dissociate between the neural tissue necessary to maintain elicited feeding as opposed to that necessary for regulating daily food and water intakes. Animals with electrodes which bilaterally supported elicited eating received "small" lesions at both electrode sites, whereas animals with only one effective electrode received a "small" lesion at the effective site and a "large" lesion at the ineffective site in order to bilaterally destroy the same functional tissue. Although electrically elicited feeding was abolished in all cases there was no corresponding deficit in daily food and water intake, or in body weight. Accordingly, electrically elicited feeding and the daily intake of food can be dissociated with respect to the tissue necessary to maintain these behaviors.

This dissociaton of elicited feeding and naturally occurring feeding was pursued by examining the preference displayed for three diets during electrical stimulation or after 48 hrs of food deprivation. Under the deprivation condition the diets could be hierarchically ordered from least to most preferred as pellets, wet mash, and high fat diet. With elicited feeding, however, there was no difference in terms of the current threshold to produce elicited eating with the wet mash and high fat diets, although both diets were preferred over the pellets. Since the pellets and mash were composed of the same essential ingredients except for water, it seems that the consistency

of the diet is a stronger determinant of preference than the ingredients per se when eating is induced by electrical stimulation but not by food deprivation. This may reflect differences in the motor sequences needed to chew pellets as opposed to eating the mash or HFD.

A more complete understanding of the nature of elicited feeding would be available if the underlying neural mechanisms could be better delineated. Recent findings have implicated catecholamine fibres in ingestive behavior and have led to the concern that many of the effects previously attributed to the nuclei of the hypothalamus may in fact have resulted from the involvement of these catecholamine fibres of passage. Accordingly, since the nigrostriatal bundle (dopaminergic pathway) has been linked by lesion work to an involvement with eating, stimulating electrodes were implanted in this fibre system in an attempt to obtain elicited ingestive behavior. Electrical stimulation of the nigrostriatal bundle, however, did not elicit ingestive behavior but rather induced forced turning in a direction contralateral to the electrode placement. Such findings are consistent with other data indicating that asymmetrical stimulation of the dopamine system produces rotational behavior.

The involvement of the catecholamine system in the phenomenon of elicited eating was assessed by damaging various components of this system and noting the effect on elicited feeding. Accordingly, 6-OHDA was administered intraventricularly after a pretreatment with a monoamine oxidase inhibitor and as a result daily food and water intake was severely disrupted but recovered after 10 days. Electrically elicited feeding, however, was strongly suppressed even after daily

intakes of food and water were completely recovered. These results support the view that the catecholamine system is involved in elicited eating but do not delineate the contribution made by the various component pathways. Consequently, individual pathways were lesioned in an attempt to determine which one was primarily responsible for the phenomenon. Disruption of the dorsal noradrenergic system was accomplished by electrolytically lesioning the locus coeruleus ipsilateral to the stimulating electrode as well as by injection of 6-OHDA directly into the pathway. Because of the diffuse nature of the sources of the ventral noradrenergic pathway it was not possible to selectively destroy just this pathway; therefore, both the dorsal and ventral noradrenergic systems were destroyed using an injection into the combined pathways. Injections of 6-OHDA were also made in the substantia nigra to disrupt the nigrostriatal dopamine pathway as well as into the ventral periventricular system. None of these unilateral lesions disrupted elicited eating from the ipsilateral electrode without also interfering with the elicited eating from the contralateral electrode. This transitory disruption of elicited feeding was paralleled by a disruption of daily food and water intake. Even when the bilateral lesion was completed using a second stage, it was not possible to specifically disrupt the elicited feeding. It would seem, therefore, that the presence of any one component of the catecholamine system is not necessary for maintaining elicited feeding although damage to the entire system results in severe disruption. Furthermore, the ventricular injections of 6-OHDA was able to dissociate electrically elicited eating from the daily intake of food which once again argues against a unitary approach to eating behavior.

The lesioned animals were subjected to a variety of challenges designed to highlight more subtle deficits in ingestive behavior. The intraventricular 6-OHDA group was the only lesioned group which differed from the control animals on any of the tests. These animals showed a reduced response to the hyperosmotic challenge while displaying heightened sensitivity to quinine adulteration of the diet. There was no deficit, however, in either poison avoidance or in terms of hoarding. The failure of the substantia nigra-lesioned animals to show deficits similar to the ventricularly lesioned animals was attributed to the two-stage lesioning procedure.

Another line of attack designed to illuminate the mechanism responsible for elicited feeding involved the administration of pharmacological blocking agents. When haloperidol (dopamine blocker) was administered IP it disrupted electrically elicited eating but it did not alter intake induced by 23 hrs food deprivation; drinking in response to 23 hrs deprivation, however, was disrupted by the haloperidol. When haloperidol, phentolamine (α-adrenergic blocker), and MJ-1999 (β-adrenergic blocker) were given intraventricularly, elicited eating was disrupted only with the haloperidol; deprivation-induced eating was not affected. These results suggest that a normally functioning dopamine system is necessary for the occurrence of elicited eating; such a conclusion, however, is not consistent with the lesion data. The apparent conflict can possibly be resolved by the realization that while haloperidol primarily disrupts the dopamine system it also interferes to a lesser degree with other catecholamines. As such its action may be more similar to the nonspecific intraventricular lesion than to the direct injection of 6-OHDA into the substantia nigra.

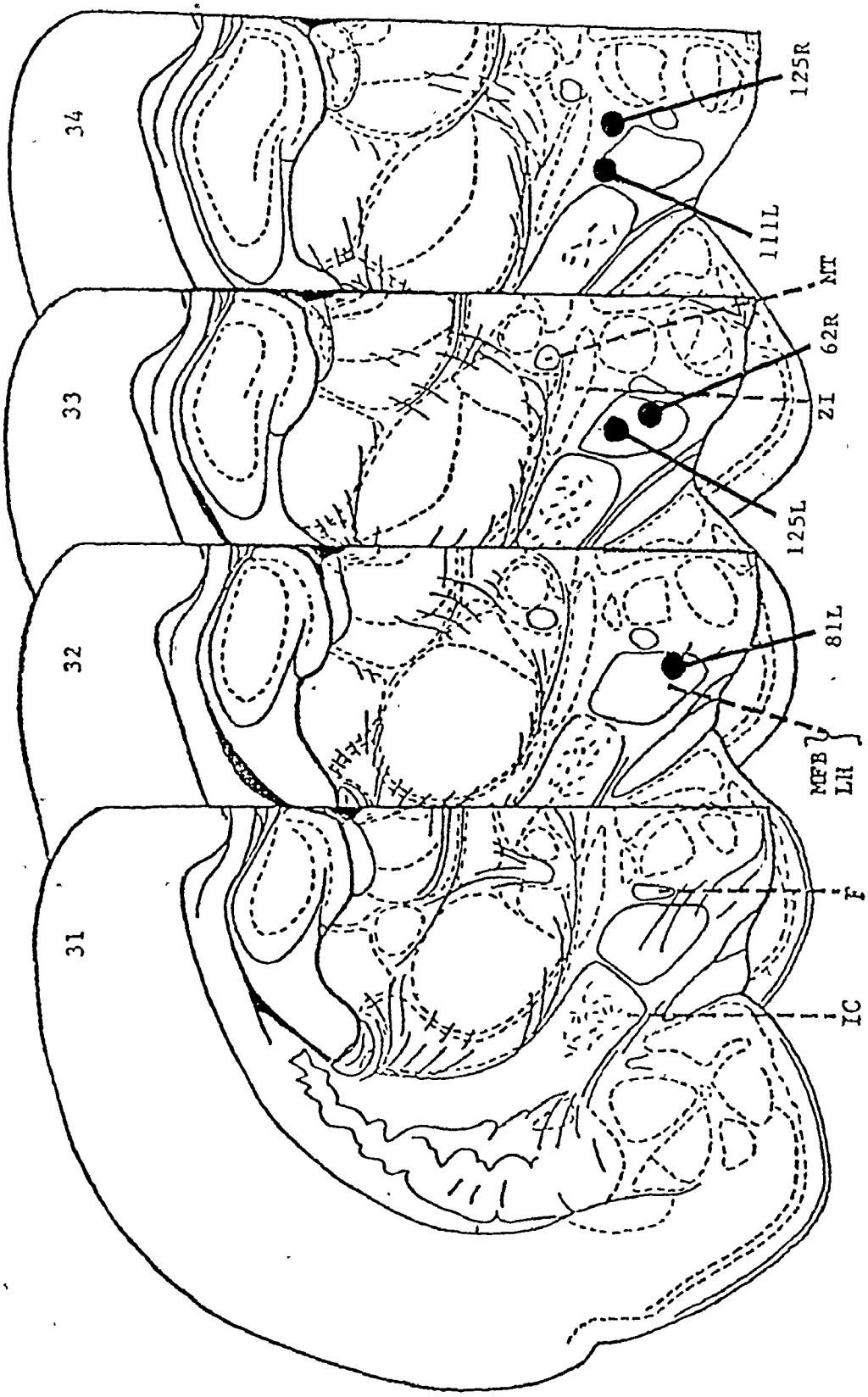
It would seem, therefore, that while there is support for the veiw that there are separate neural systems activated by electrical stimulation of the brain the resulting behavior is not identical to that obtained under non-artificial conditions. It should be pointed out, however, that the points of difference between elicited feeding and natural feeding noted in this study really apply only to deprivation-induced feeding. It would be worthwhile to use other ways of inducing feeding in a comparison with elicited feeding so as to determine whether or not there is greater similarity with these other mechanisms. It is not possible at this point, however, to specify which neural pathways are related to elicited feeding except to say that the catecholamine pathways play a critical role in the mediation of this phenomenon.

APPENDIX 1 - STIMULATING ELECTRODE HISTOLOGY

The sites of the stimulating electrodes were determined by comparing serial sections of the rat brain to the drawings of König and Klippel (1963) stereotaxic atlas. Only the sites which supported elicited feeding are presented. Electrode sites have all been transposed to the left half brain. The letter following the subject number indicates whether the electrode was on the left (L) or right (R) side of the brain.

The abbreviations of structures are as follows: F - fornix; IC - internal capsule; LH - lateral hypothalamus; MFB - medial forebrain bundle; MT - mammilothalamic trait; ZI - zona incerta.

Figure A-1. Electrode sites which supported electrically elicited feeding in Experiment 2. The other placements can be found in Figures A-2, A-5, A-6, and A-9. The electrode sites used to determine diet preference are marked with an *.


34
33
32
31
125R
111L
MT
62R
ZI
125L
81L
MFB
LH
F
IC

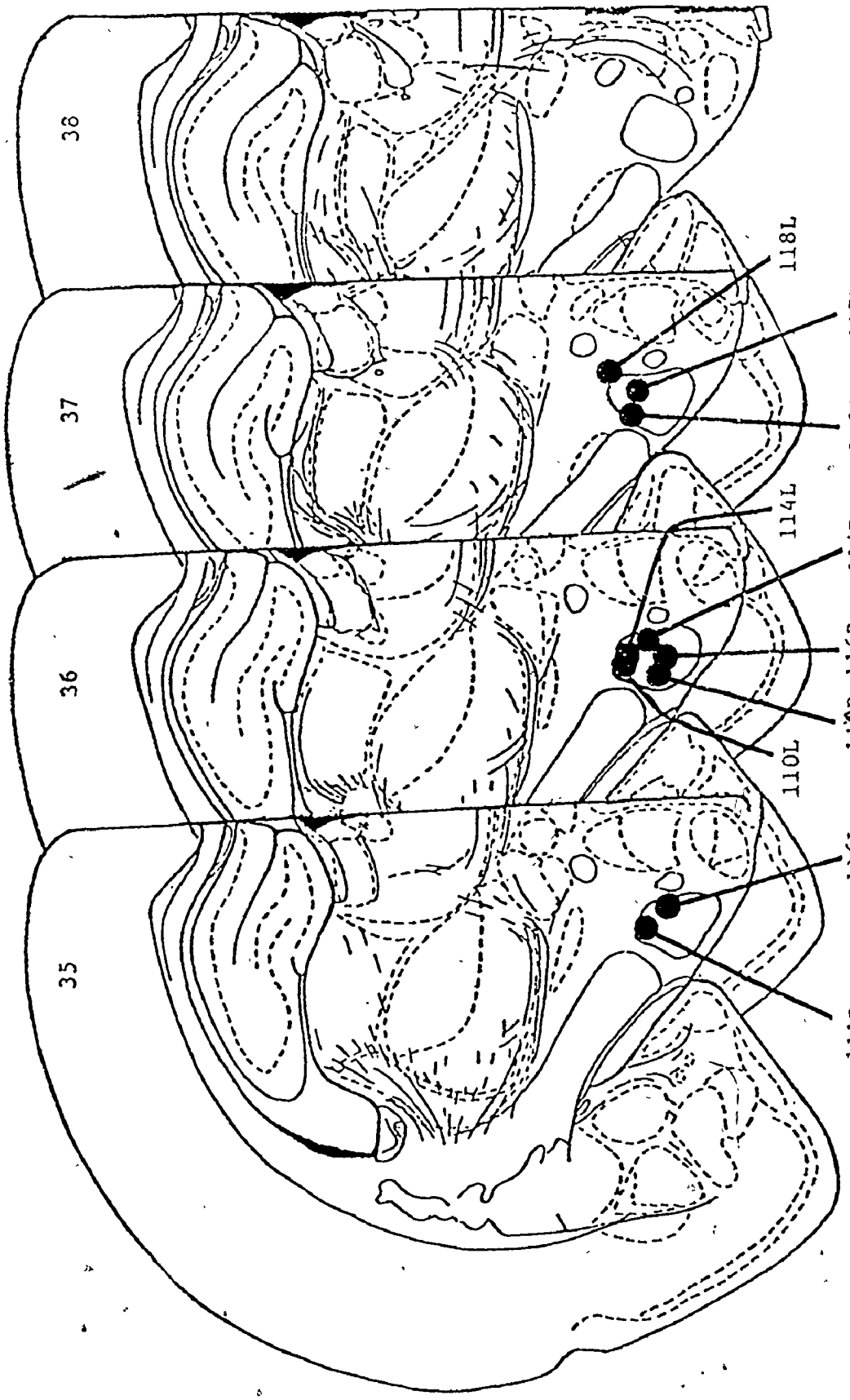
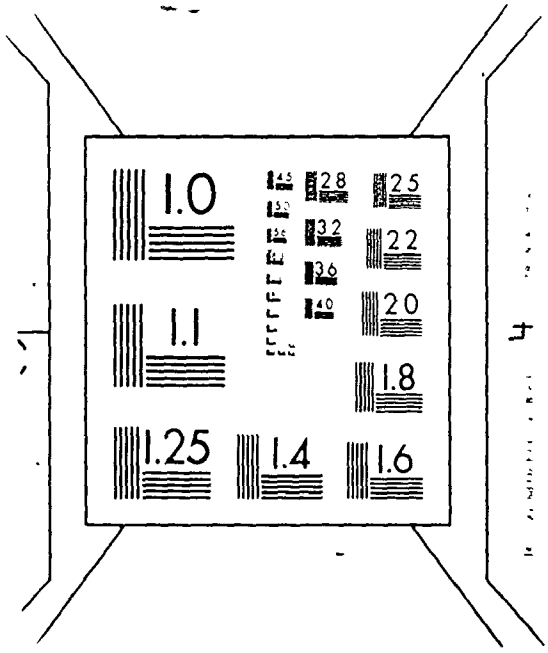
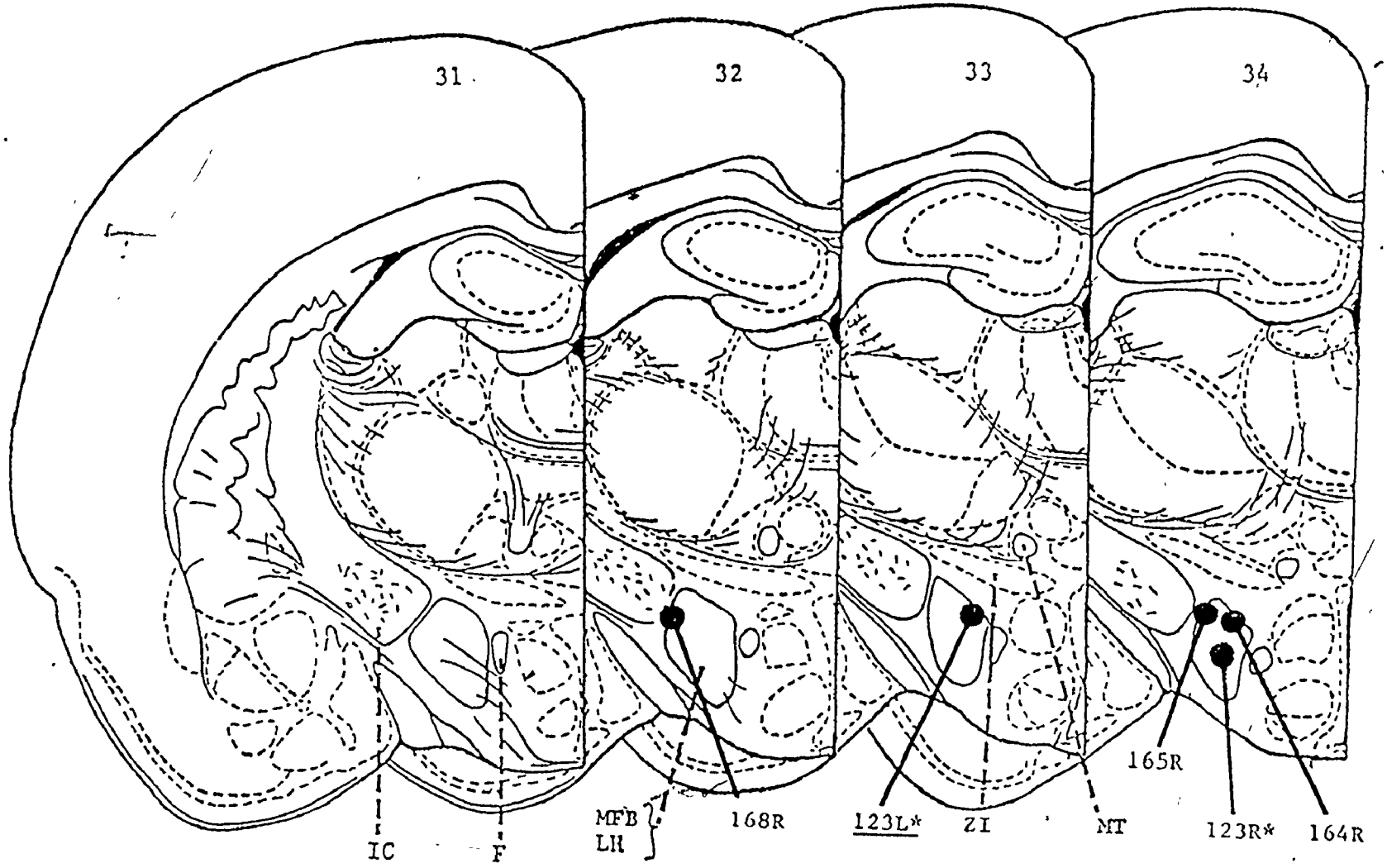

38
37
36
35
118L
117L
110R
114L
114R
116R
118R
110L
116L
111R

Figure A-2. Electrode sites which supported electrically elicited feeding in Experiment 4. These animals also had cannulae in the lateral ventricles. Underlined electrode sites indicate the first tested in a pair of effective sites. Electrode sites marked with an * were also used in Experiment 2 to determine diet preference. (Note only 123L* was used in Experiment 4.)

3 3

OF/DE




31
32
33
34
IC
F
MFB
LH
168R
123L*
ZI
MT
165R
123R*
164R

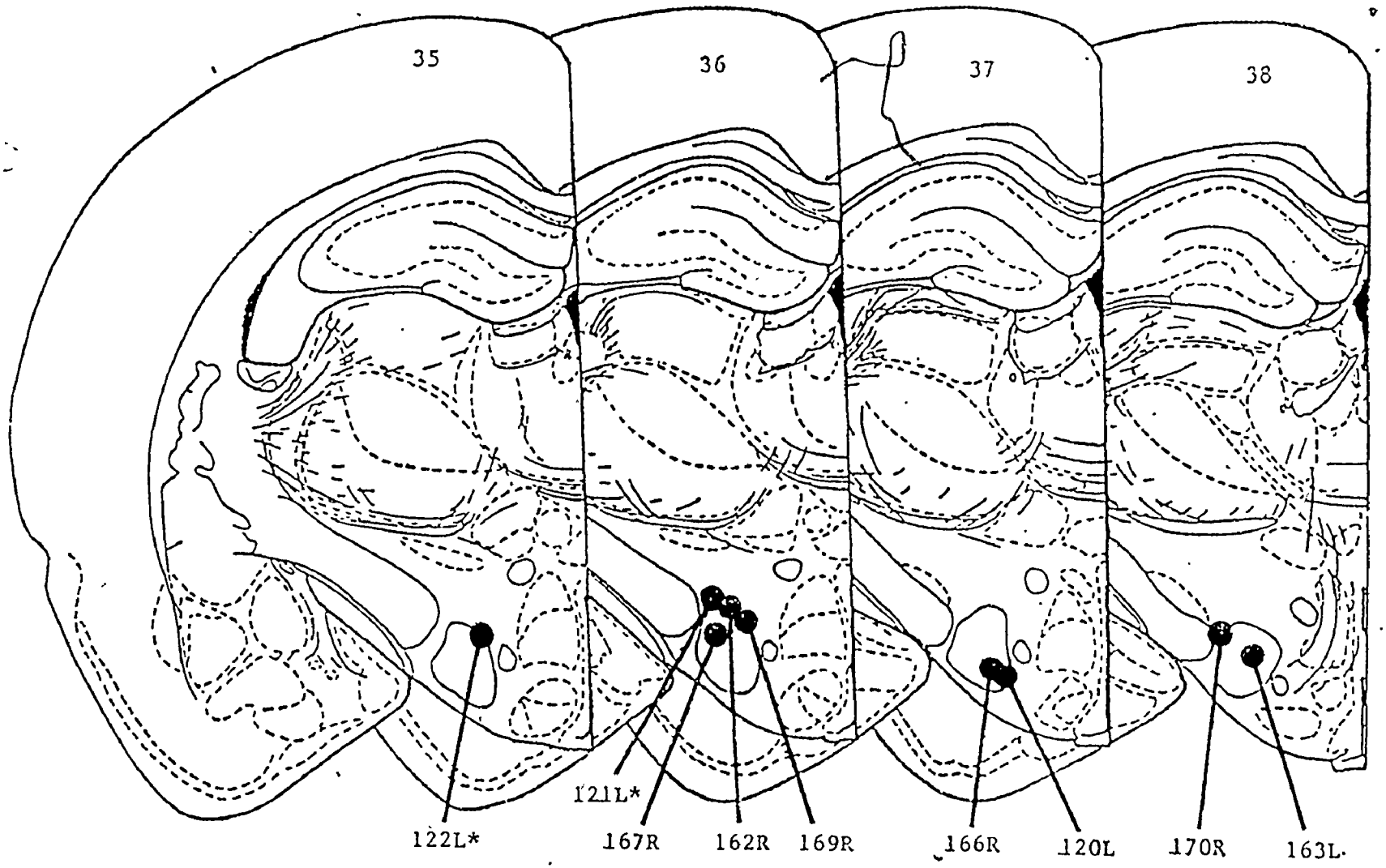
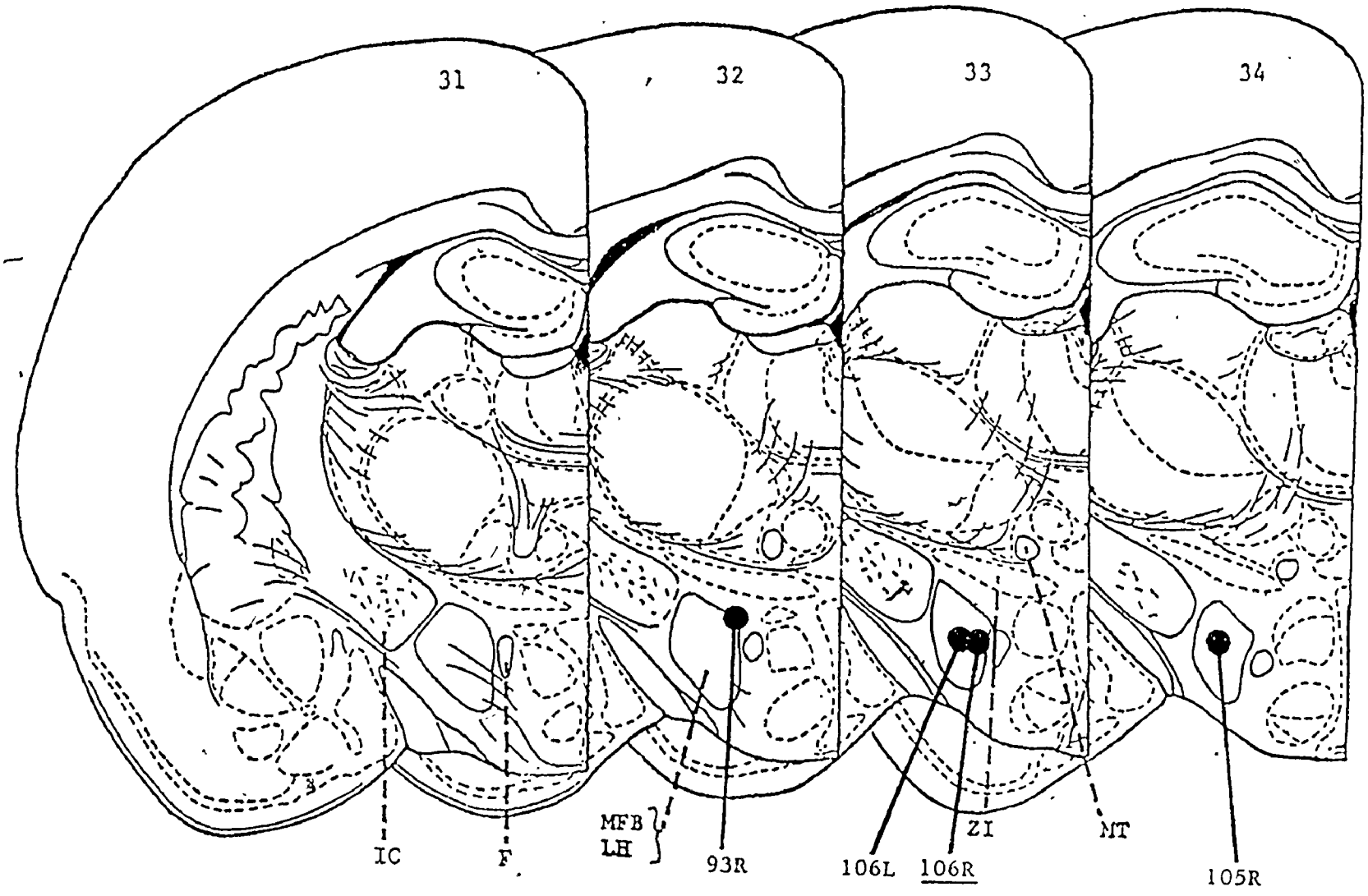

35
36
37
38
122L*
121L*
167R
162R
169R
166R
120L
170R
163L

Figure A-3. Electrode sites which supported electrically elicited feeding in Experiment 5. These animals also had lesion wires in the locus coeruleus. Underlined electrode sites indicate the first tested in a pair of effective sites.


31
32
33
34
IC
F
MFB
LH
93R
106L
106R
ZI
MT
105R

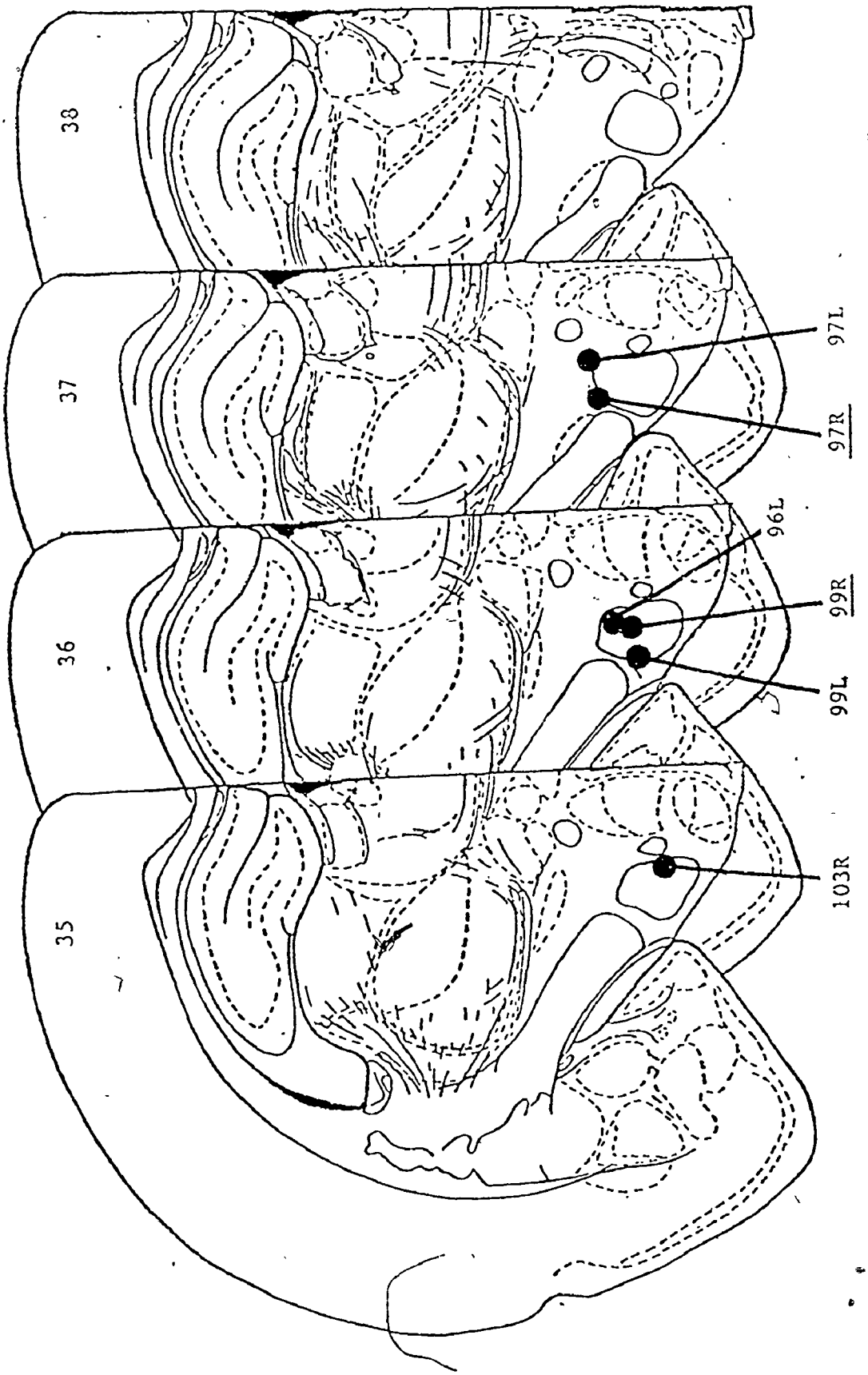
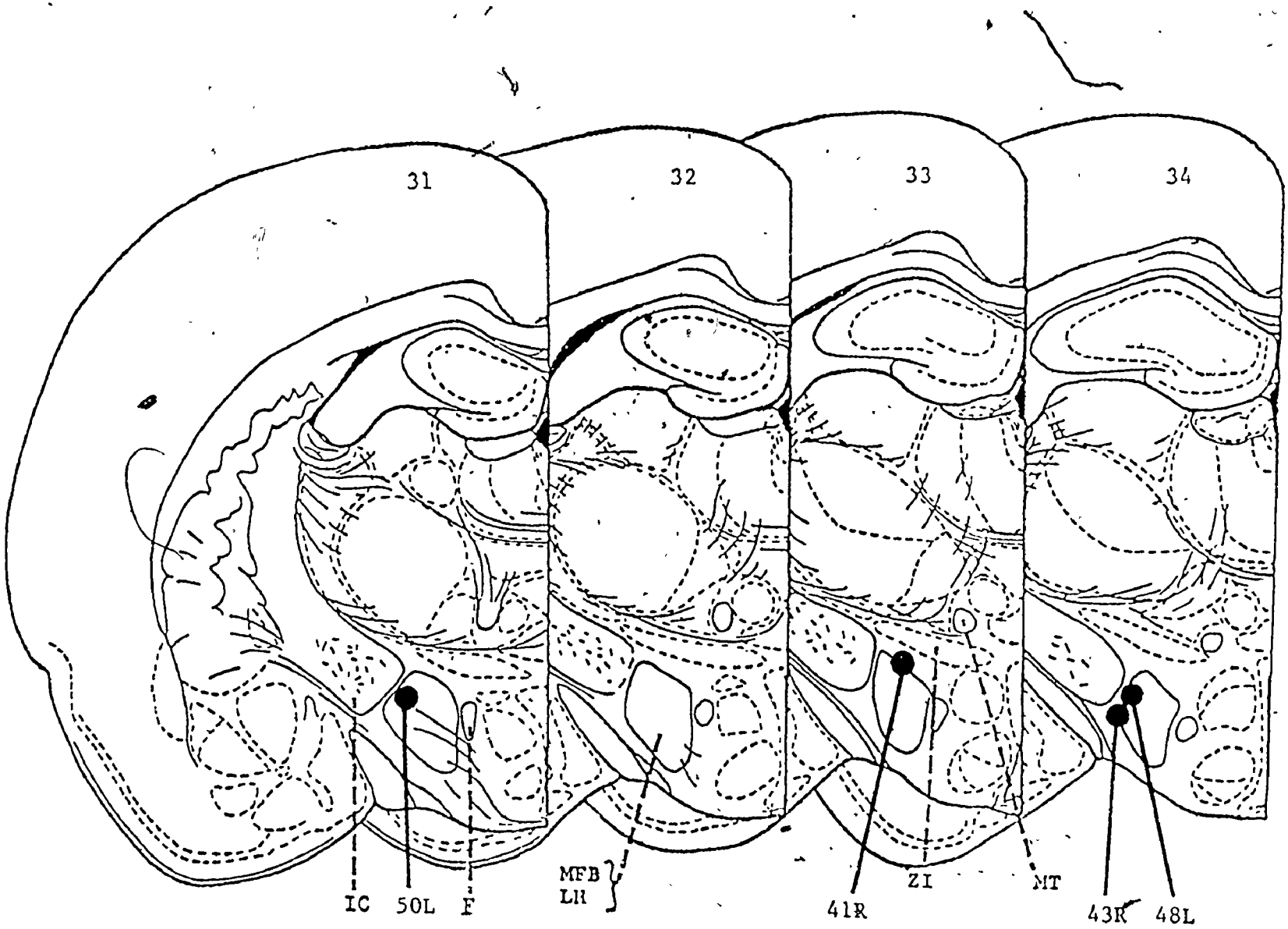

38
37
36
35
97L
97R
96L
99R
99L
103R

Figure A-4. Electrode sites which supported electrically elicited feeding in Experiment 5. These animals also had cannulae in the dorsal noradrenergic bundle. Underlined electrode sites indicate the first tested in a pair of effective sites.


31
32
33
34
IC
50L
F
MFB
LH
41R
ZI
MT
43R
48L

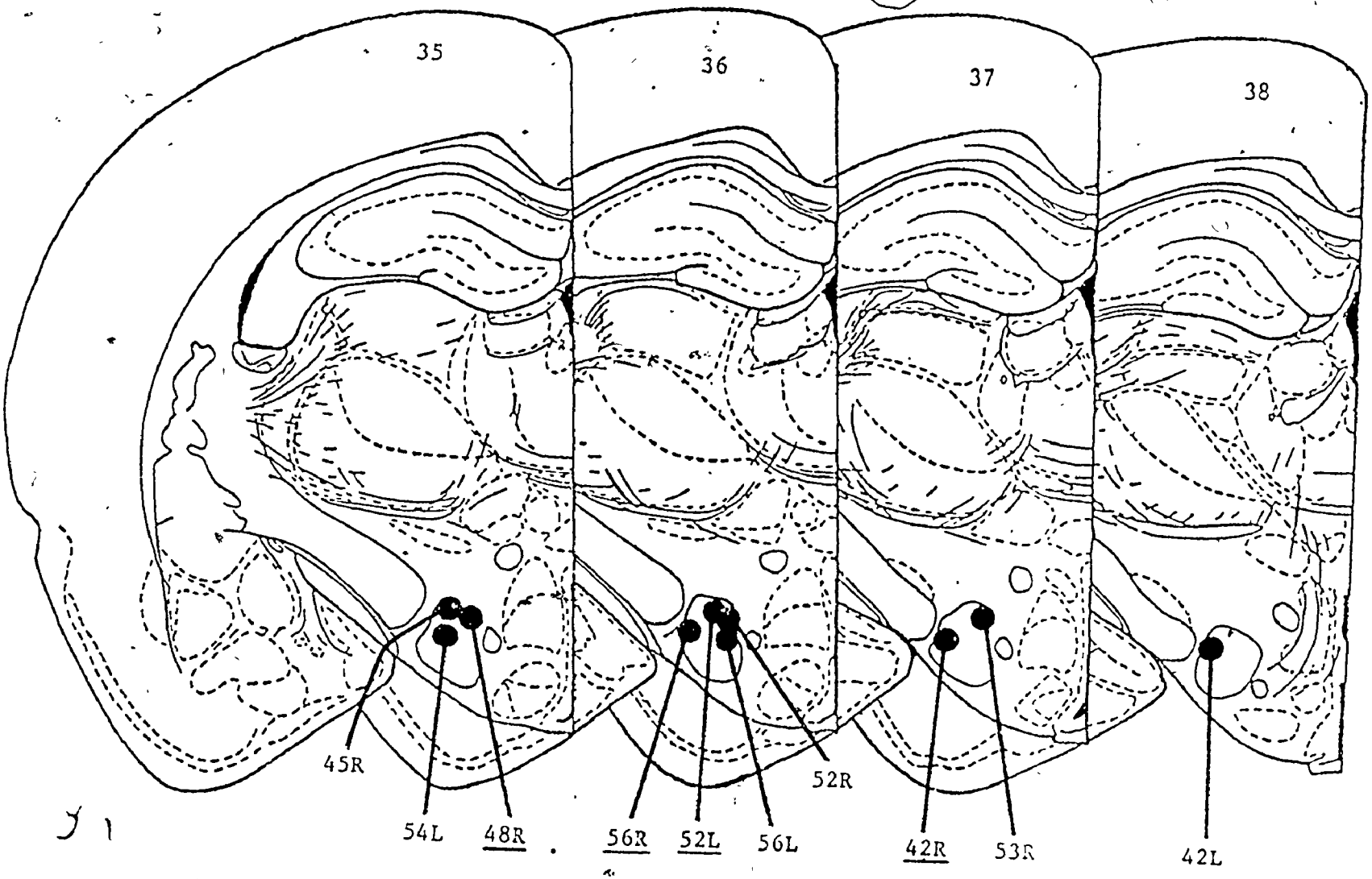
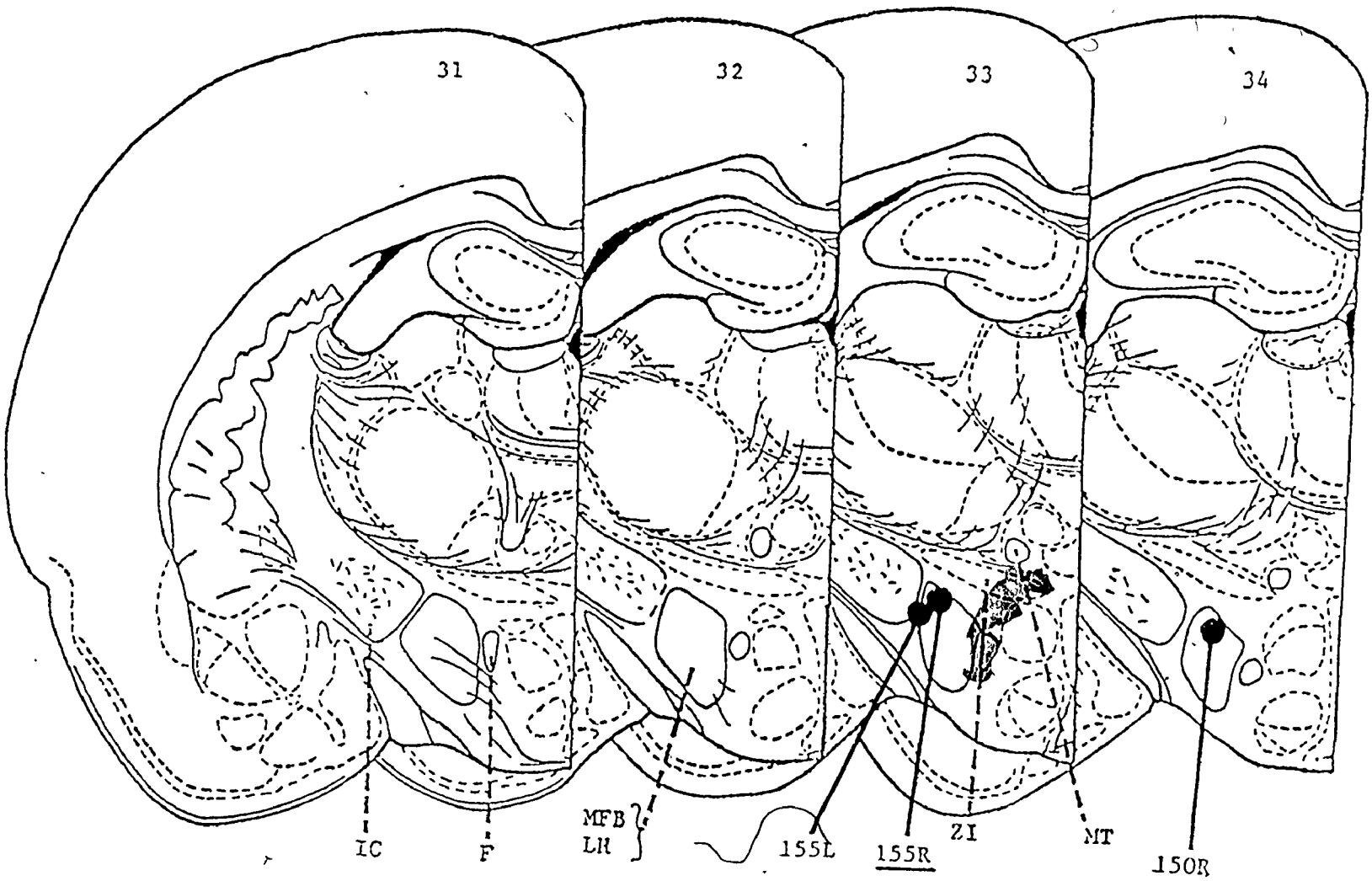

35
36
37
38
45R
54L
48R
56R
52L
56L
52R
42R
53R
42L

Figure A-5. Electrode sites which supported elicited feeding in Experiment 6. These animals also had cannulae in the noradrenergic pathway at the level of the central grey. Underlined electrode sites indicate the first tested in a pair of effective electrode sites. Electrode sites marked with an * were also used in Experiment 2 to determine diet preference.


31
32
33
34
IC
F
MFB
LH
155L
155R
ZI
MT
150R

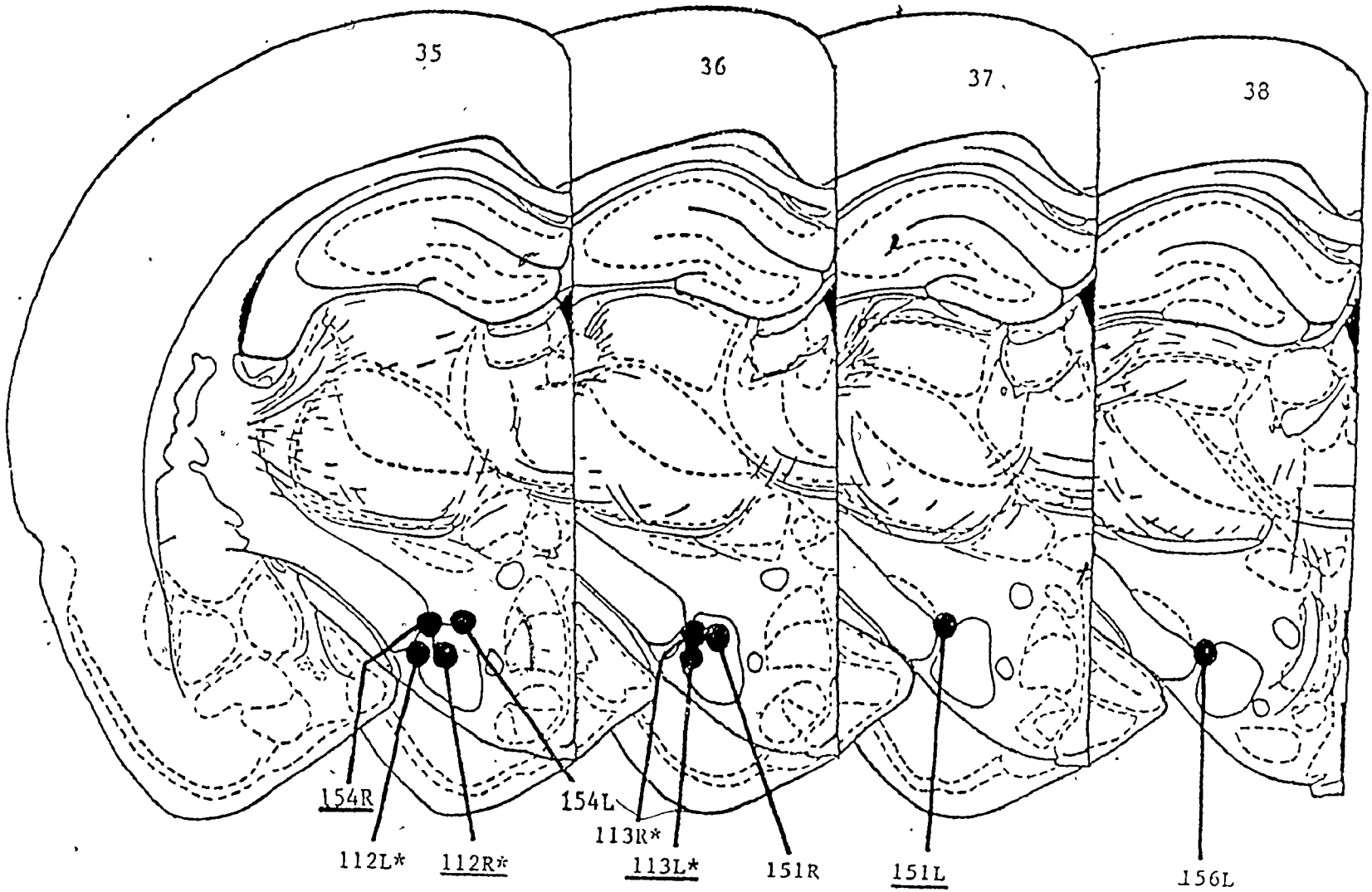
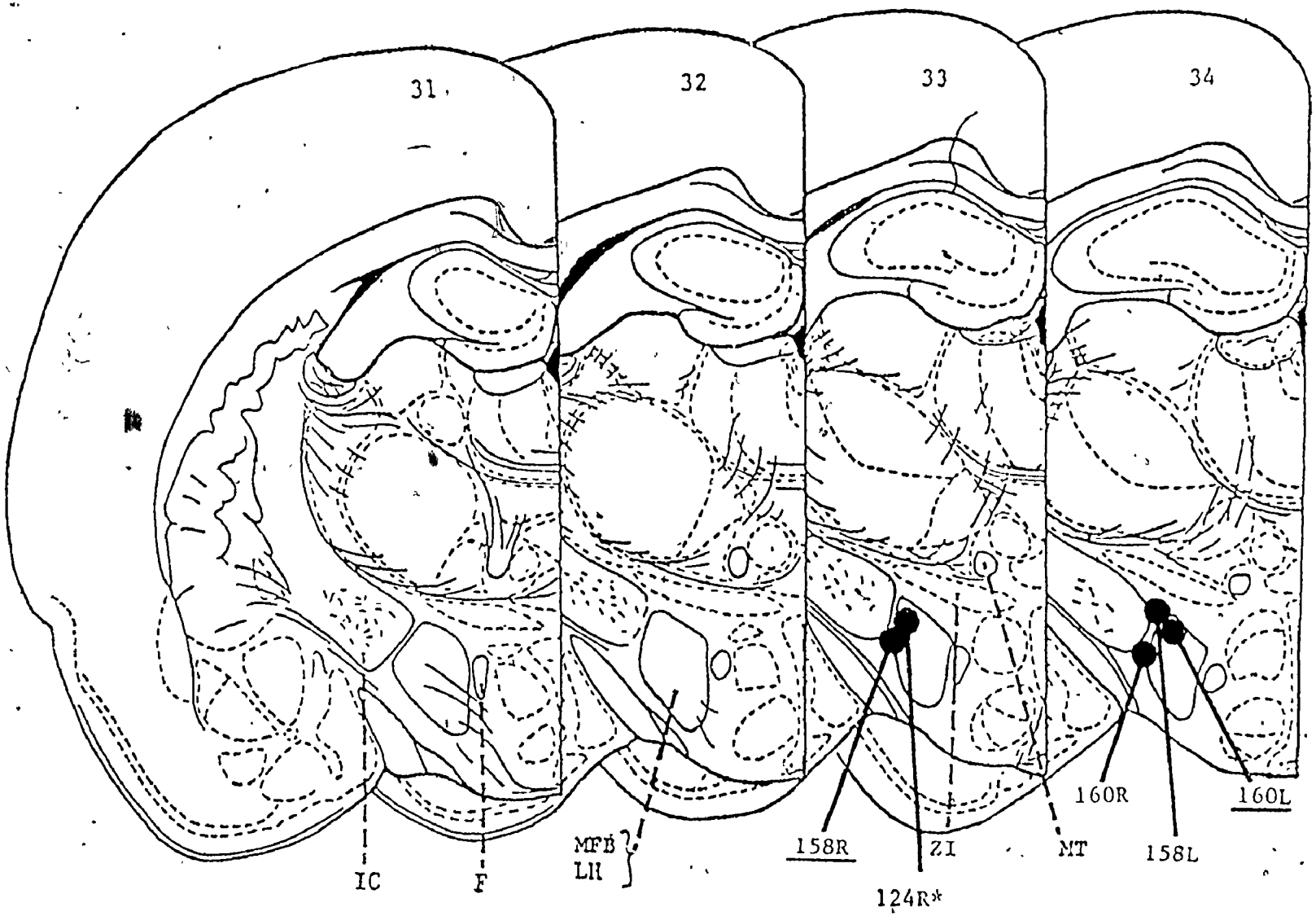

35
36
37
38
154R
112L*
112R*
154L
113R*
113L*
151R
151L
156L

Figure A-6. Electrode sites which supported elicited feeding in Experiment 6. These animals also had cannulae in the substantia nigra. Underlined electrode sites indicate the first tested in a pair of effective sites. Electrode sites marked with an * were also used in Experiment 2 to determine diet preference.


31
32
33
34
IC
F
MFB
LH
158R
124R*
ZI
MT
160R
158L
160L

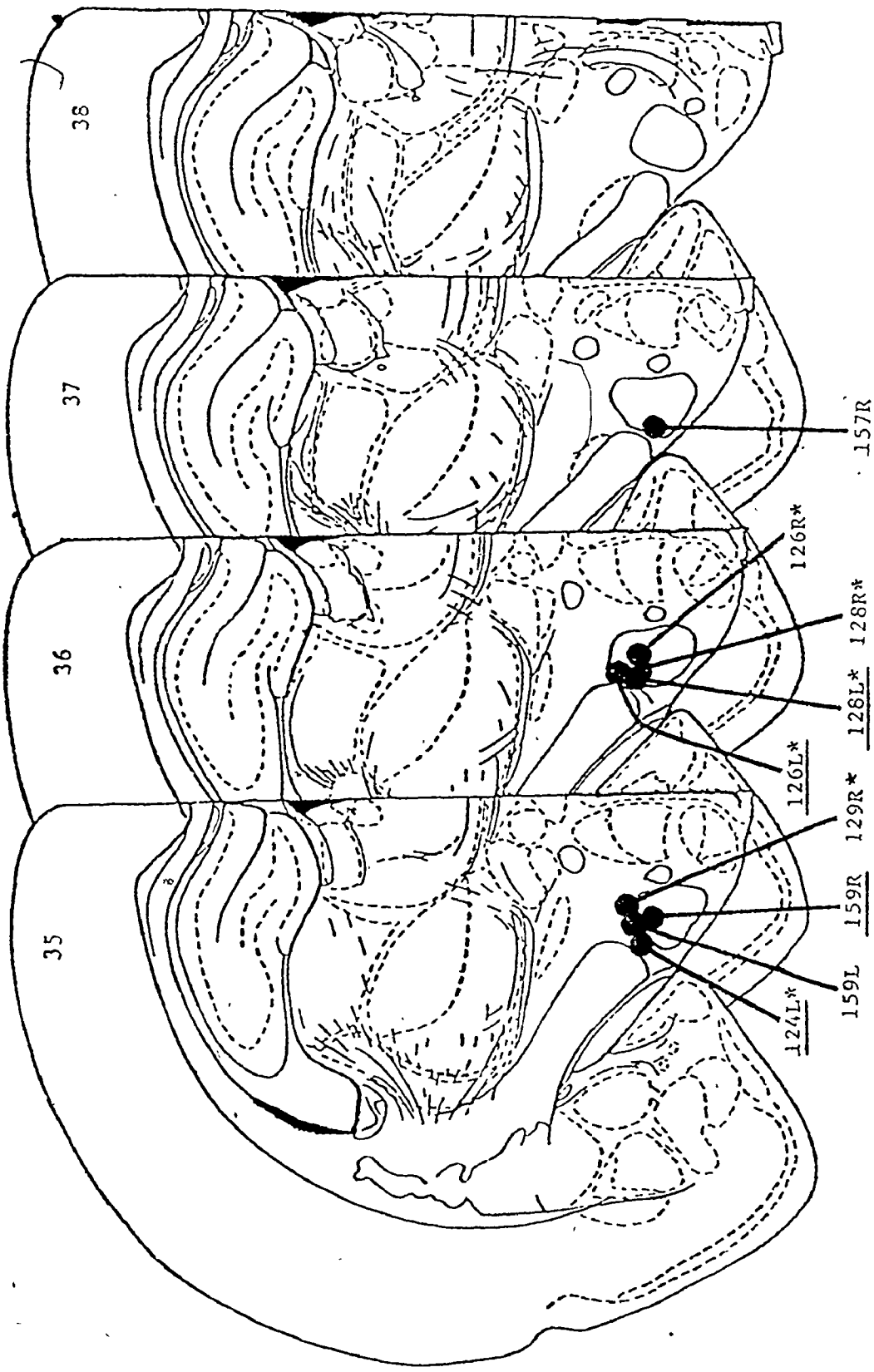
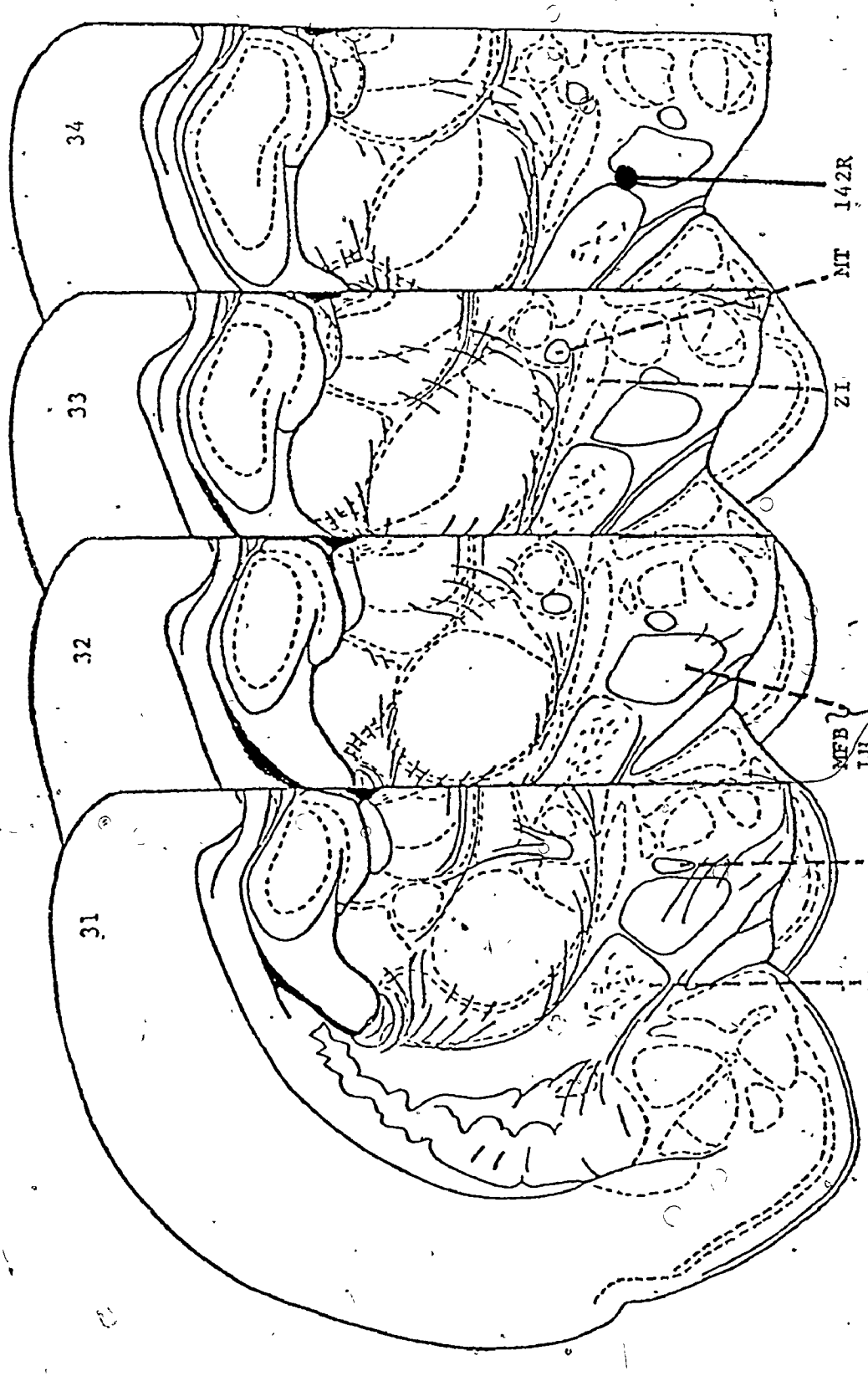

38
37
36
35
157R
126R*
128R*
128L*
126L*
129R*
159R
159L
124L*

Figure A-7. Electrode sites which supported elicited feeding in Experiment 6. These animals also had cannulae in the periventricular region. Underlined electrode sites indicate the first tested in a pair of effective sites.


34
33
32
31
142R
MT
ZI
MFB
LH
F
IC

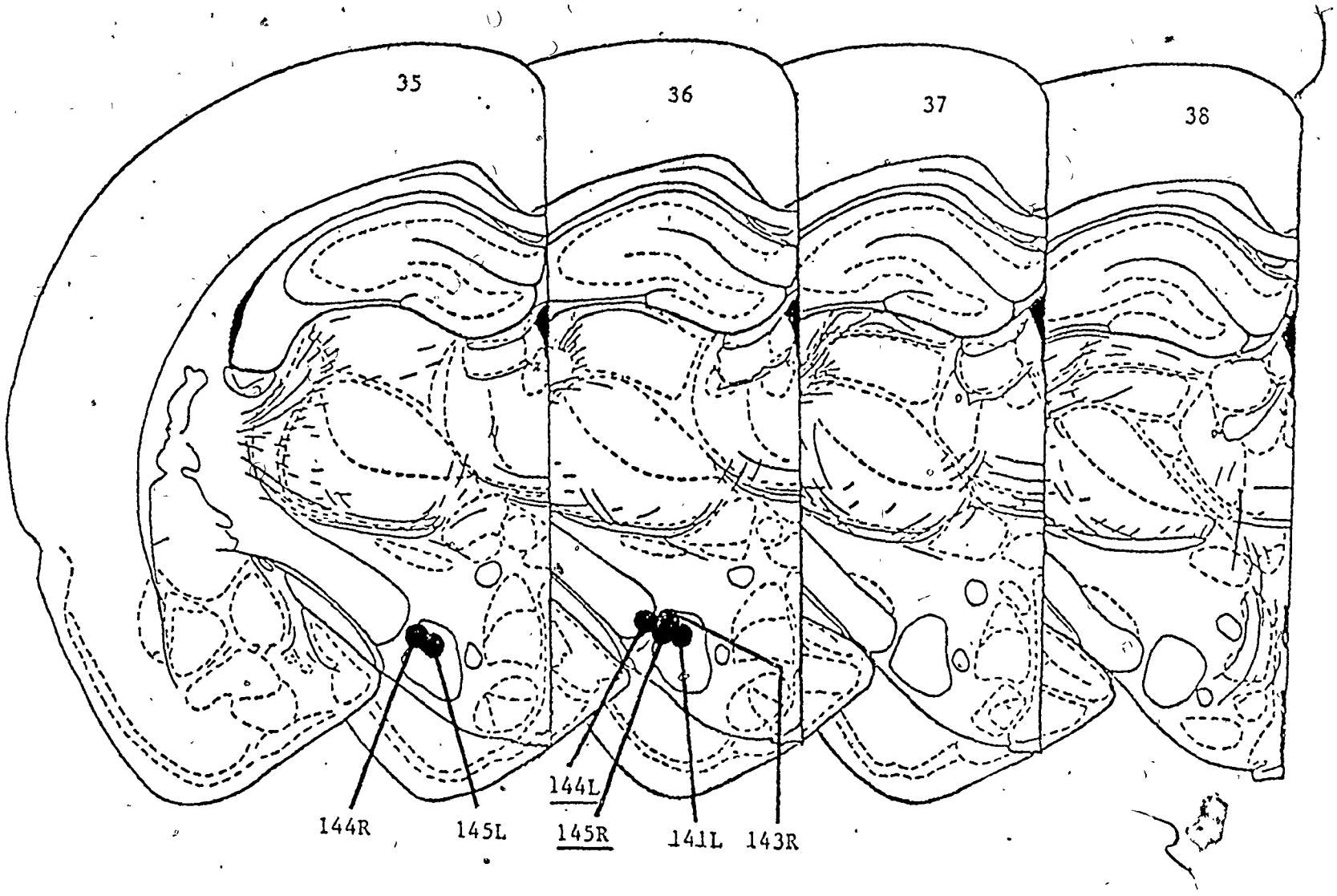
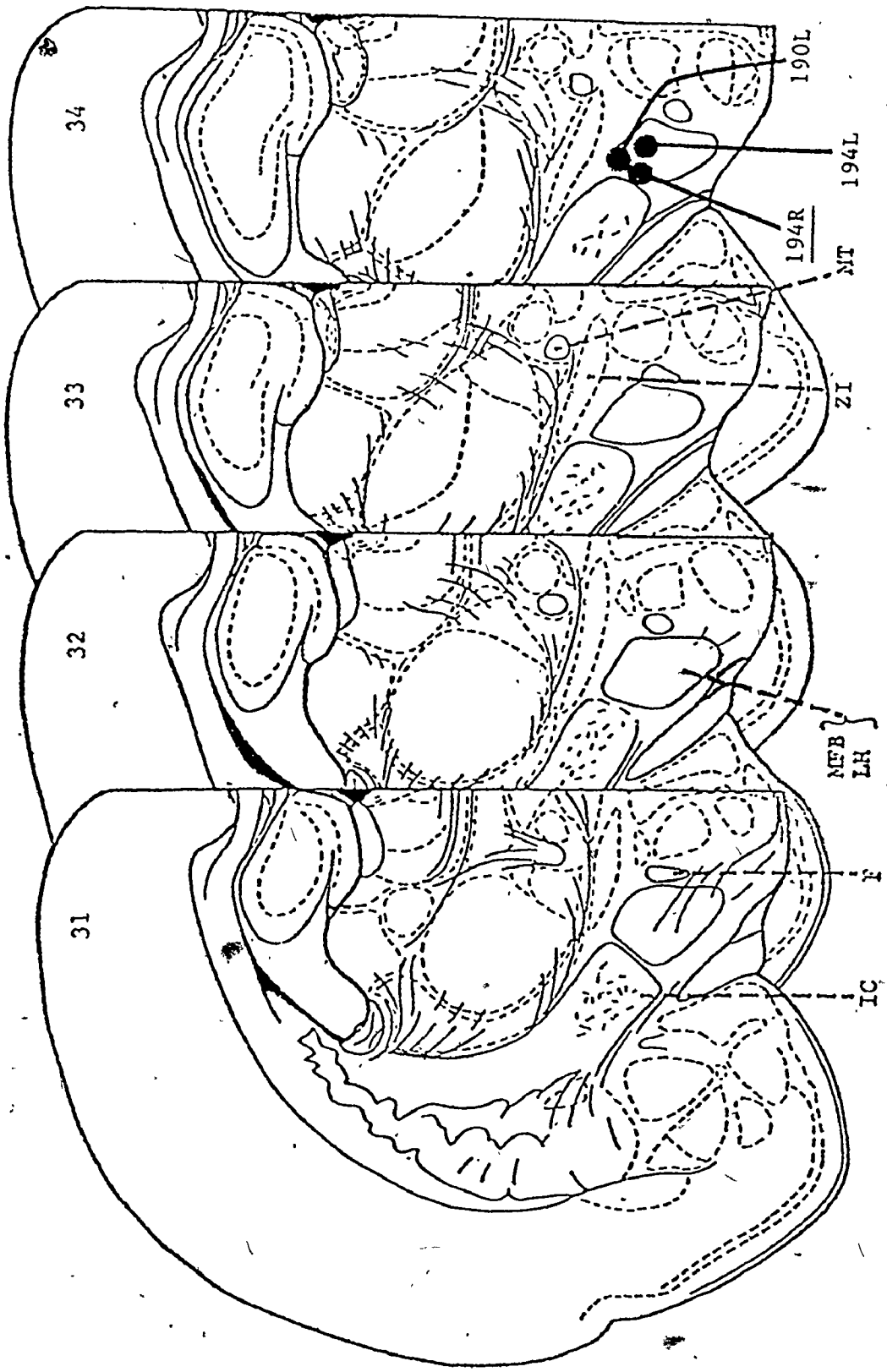

35
36
37
38
144R
145L
144L
145R
141L
143R

Figure A-8. Electrode sites which supported elicited feeding for the Control animals in Experiment 6. Underlined electrode sites indicate the first tested in a pair of effective sites.


34
33
32
31
190L
194L
194R
MT
ZI
MTB
LR
F
IC

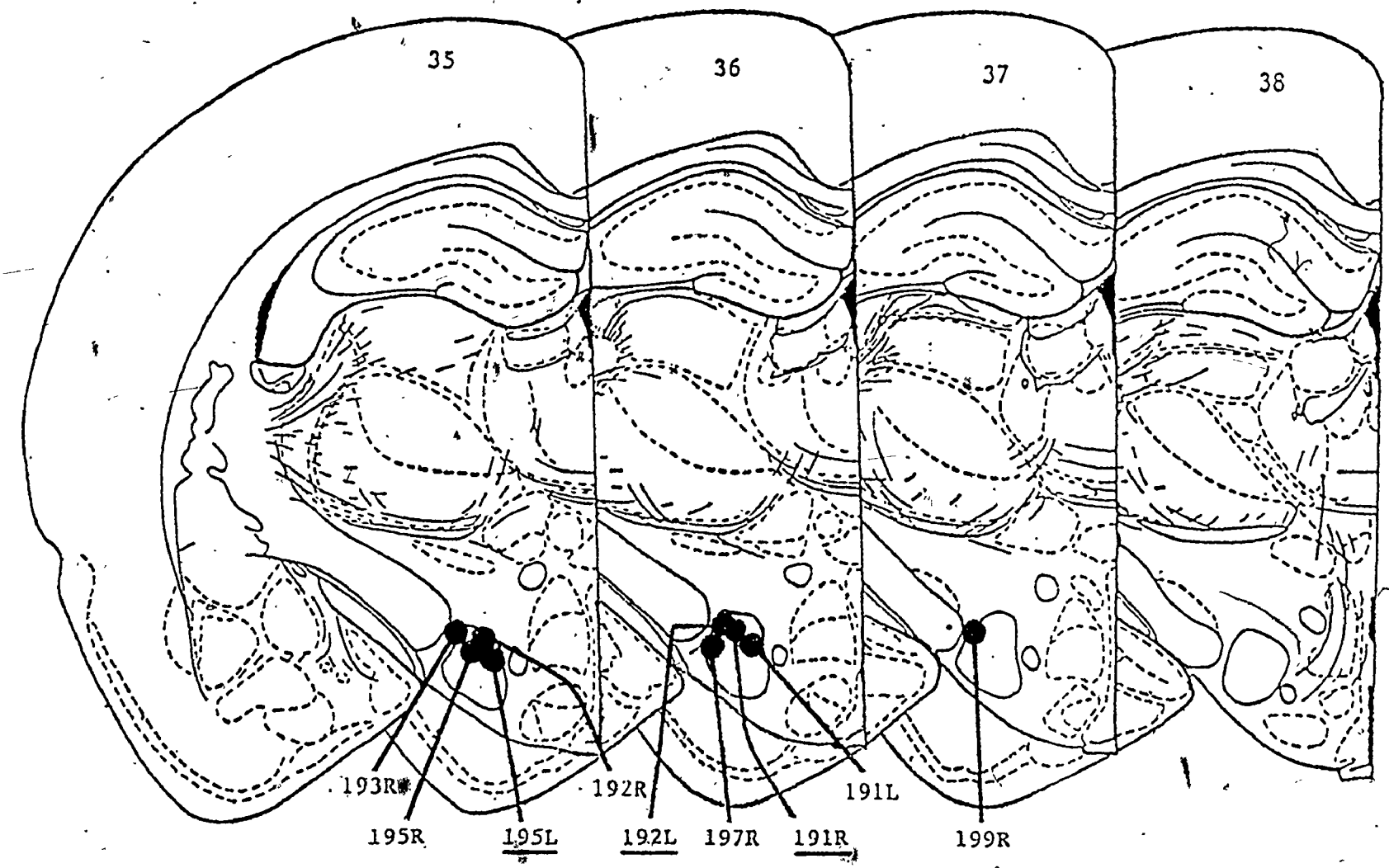
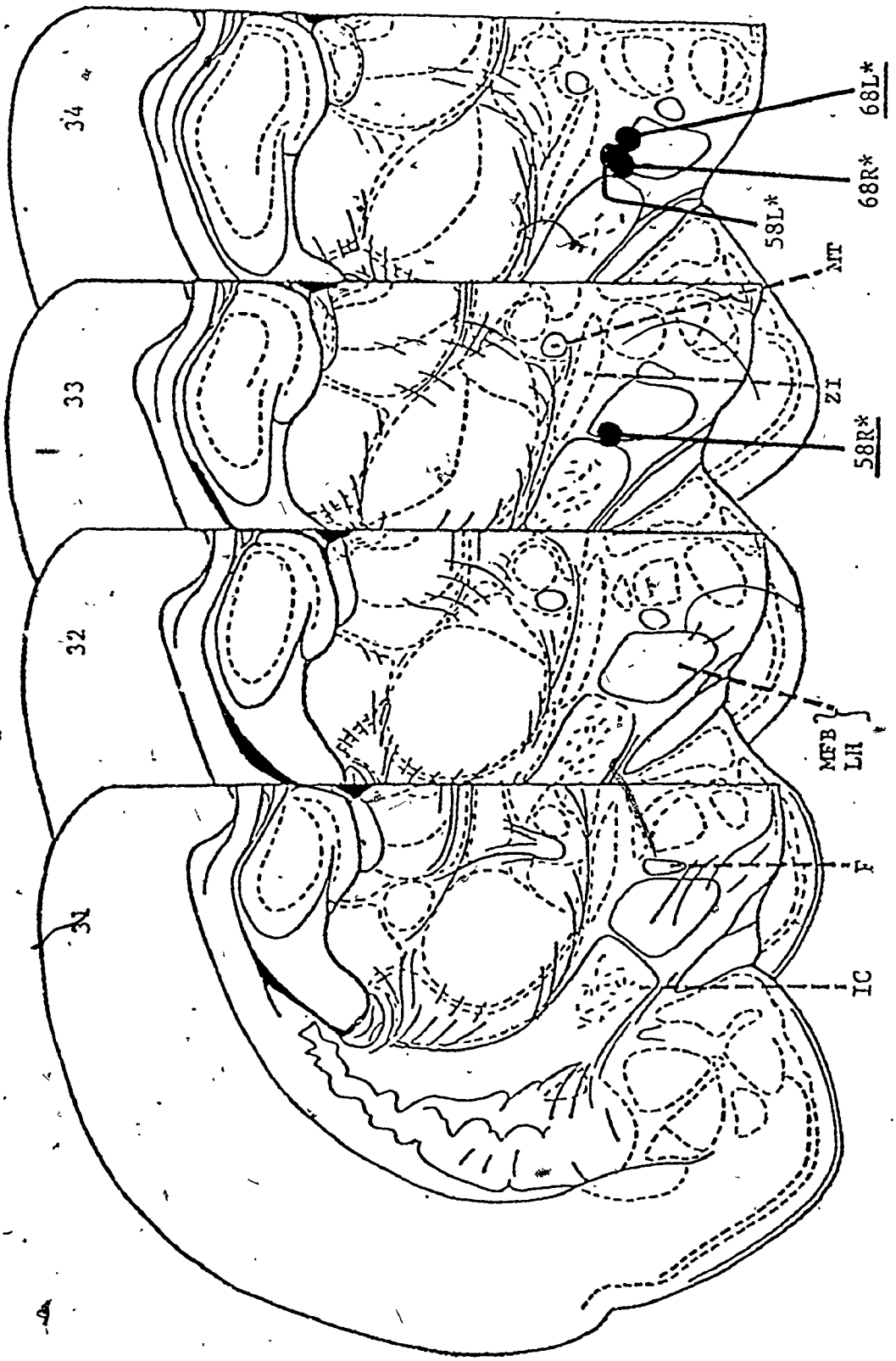

35
36
37
38
193R
195R
195L
192R
192L
197R
191L
191R
199R

Figure A-9. Electrode sites which supported elicited feeding in Experiment 8. Underlined electrode sites were the ones used in this experiment; the other electrode site was used in Experiment 2 to determine diet preference.


34
33
32
31
68L*
68R*
58L*
MT
ZI
58R*
MFB
LH
F
IC

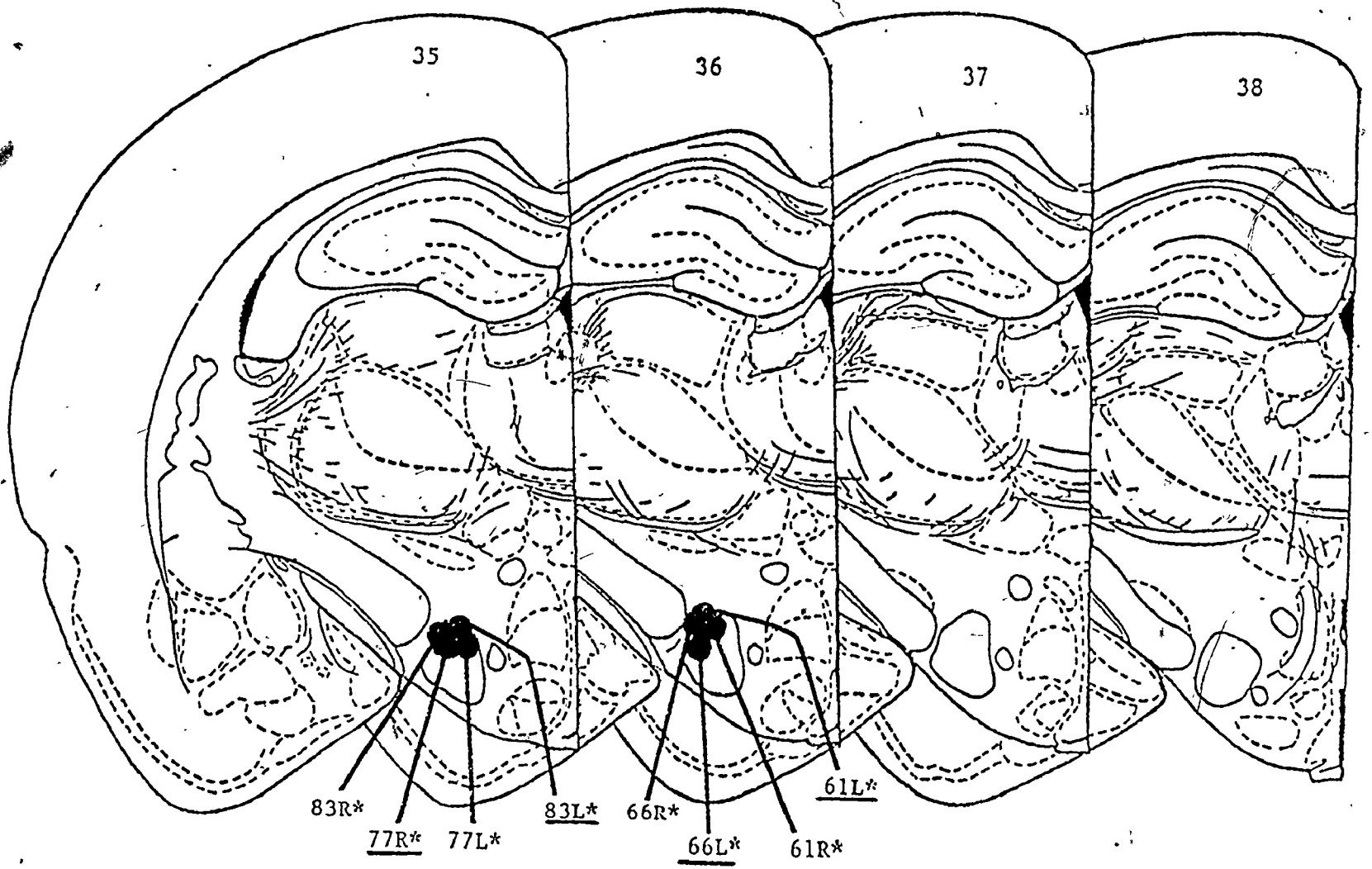
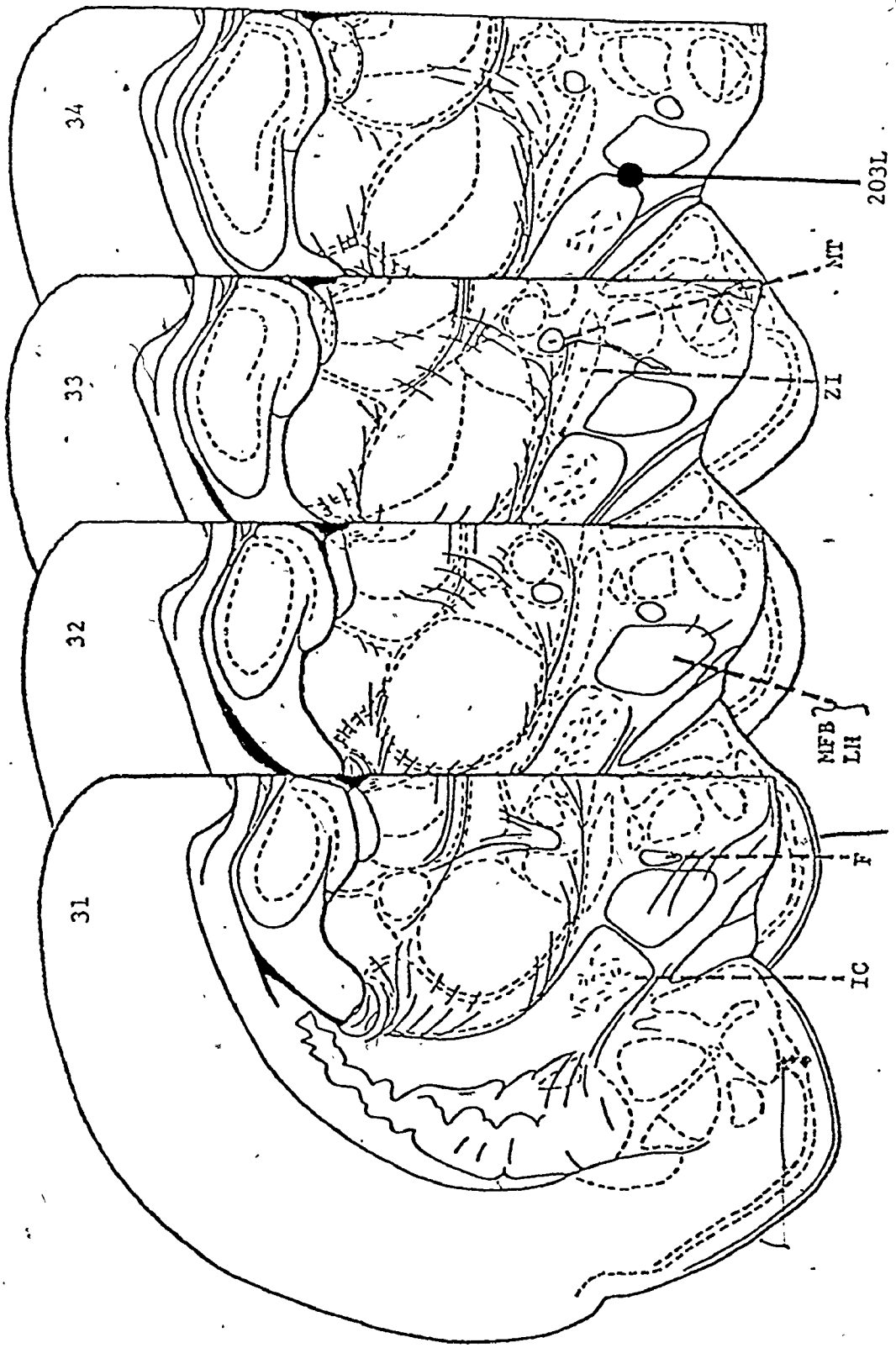
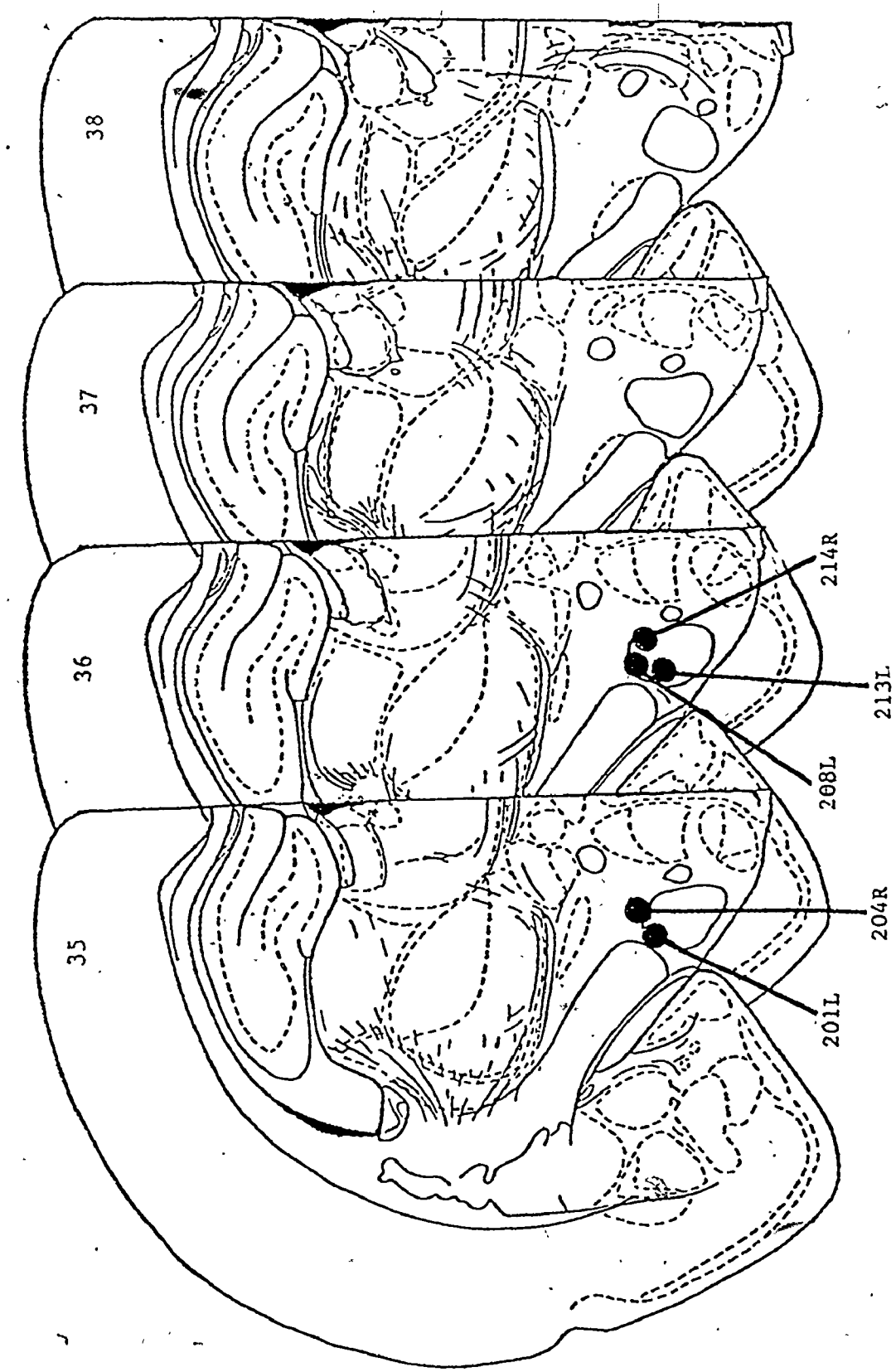

35
36
37
38
83R*
77R*
77L*
83L*
66R*
66L*
61R*
61L*

Figure A-10. Electrode sites which supported elicited feeding in Experiment 9. These animals also had cannulae in the lateral ventricles.


34
33
32
31
203L
MT
ZI
MFB
LH
F
IC


38
37
36
35
214R
213L
208L
204R
201L

APPENDIX 2 – STATISTICAL RESULTS

Part I contains the analysis of variance (ANOVA) tables for all the experiments in the order in which they were discussed. The simple one-way, one-way with repeated measures, and factorial ANOVA with repeated measures were calculated according to Winer (1971). The randomized block factorial design (repeated measures on both factors in a two-way ANOVA) is from Kirk (1968). When the groups with repeated measures contained unequal numbers the method of least squares was used (Winer, 1971).

Part II contains the comparisons for the means in the order in which they are discussed.

The level of significance is indicated by asteriks: $^{*}p < .05$, $^{**}p < .01$.

PART I

Table 1. Summary table of a one-way analysis of variance (ANOVA) for daily food intake: Expt. 1.

SOURCE	SS	DF	MS	F
TREATMENT	0.319	2	0.16	0.078
ERROR	24.725	12	2.06	
TOTAL	25.044	14		

Table 2. Summary table of a one-way ANOVA for daily water intake: Expt. 1.

SOURCE	SS	DF	MS	F
TREATMENT	6.933	2	3.467	0.113
ERROR	368.300	12	30.692	
TOTAL	375.233	14		

Table 3. Summary table of a one-way, repeated measures ANOVA for the diet preference ratio: Expt. 2.

SOURCE	SS	DF	MS	F
BETWN Ss	1,601.880	11		
WTHIN Ss	38,872.580			
FOOD	32,707.445	2	16,353.723	58.358**
RESIDUAL	6,165.135	22	280.233	
TOTAL	40,474.460	35		

Table 4. Summary table of a 3x3, repeated measures ANOVA for elicited feeding thresholds: Expt. 2.

SOURCE	SS	DF	MS	F
BETWN Ss	188,477.013			
ORDER	5,227.410	2	2,613.705	0.028
Ss WTHIN GRPS	183,249.603	34	5,389.694	
WTHIN Ss	327,116.667			
DIET	174,774.324	2	87,387.162	47.378**
DIET x ORDER	8,474.829	4	2,118.707	1.149
DIET x Ss WTHIN	143,867.064	78	1,844.450	

Table 5. Summary table of a 2x2, repeated measures ANOVA for the frequency of elicited feeding: Expt. 4.

SOURCE	SS	DF	MS	F
BETWN Ss	88.234	12		
LESION (A)	83.188	1	83.188	181.237**
Ss WTHIN GRPS	5.046	11	0.459	
WTHIN Ss	205.160	13		
PRE-POST (B)	112.154	1	112.154	278.298**
A x B	88.573	1	88.573	219.784**
B x Ss WTHIN	4.433	11	0.403	

Table 6. Summary table of a 2x2, repeated measures ANOVA for the amount of food consumed during elicited feeding: Expt. 4.

SOURCE	SS	DF	MS	F
BETWN Ss	261.918	12		
LESION (A)	46.322	1	46.322	2.363
Ss WTHIN GRPS	215.596	11	19.600	
WTHIN Ss	437.872	13		
PRE-POST (B)	226.147	1	226.147	44.888**
A x B	156.312	1	156.312	31.027**
B x Ss WTHIN	55.419	11	5.038	

Table 7. Summary table of a one-way, repeated measures ANOVA for the frequency of elicited feeding after electrolytic lesions: Expt. 5.

SOURCE	SS	DF	MS	F
BETWN Ss	76.228	9		
WTHIN Ss	58.200	20		
LESION	8.966	2	4.483	1.639
RESIDUAL	49.234	18	2.735	

Table 8. Summary table of a one-way, repeated measures ANOVA for the amount of food consumed during elicited feeding after electrolytic lesions: Expt. 5.

SOURCE	SS	DF	MS	F
BETWN Ss	304.228	9		
WTHIN Ss	81.662	20		
LESION	20.708	2	10.354	3.058
RESIDUAL	60.954	18	3.386	

Table 9. Summary table of a one-way, repeated measures ANOVA for the total threshold for elicited feeding after electrolytic lesions: Expt. 5.

SOURCE	SS	DF	MS	F
BETWN Ss	75,150.000	9		
WTHIN Ss	21,666.667	20		
LESION	3,601.667	2	1,800.834	1.794
RESIDUAL	18,065.667	18	1,003.611	

Table 10. Summary table of a one-way, repeated measures ANOVA for the frequency of elicited feeding after 6-OHDA lesions: Expt. 5.

SOURCE	SS	DF	MS	F
BETWN Ss	22.698	6		
WTHIN Ss	17.240	14		
LESION	6.952	2	3.476	4.089*
RESIDUAL	10.288	12	0.856	

Table 11. Summary table of a one-way, repeated measures ANOVA for the amount of food consumed during elicited feeding after 6-OHDA lesions: Expt. 5.

SOURCE	SS	DF	MS	F
BETWN Ss	90.580	6		
WTHIN Ss	78.566	14		
LESION	26.654	2	13.328	3.081
RESIDUAL	51.912	12	4.326	

Table 12. Summary table of a one-way, repeated measures ANOVA for the total threshold for elicited feeding after 6-OHDA lesions: Expt. 5.

SOURCE	SS	DF	MS	F
BETWN Ss	85,316.667	6		
WTHIN Ss	4,383.333	14		
LESION	178.571	2	89.286	0.255
RESIDUAL	4,204.762	12	350.397	

Table 13. Summary table of a 4x4, repeated measures ANOVA for the frequency of elicited feeding: Expt. 6.

SOURCE	SS	DF	MS	F
BETWN Ss	174.517	27		
LES SITE (A)	4.137	3	1.379	0.194
Ss WTHIN GRPS	170.380	24	7.099	
WTHIN Ss	80.052	84		
LESION (B)	1.685	3	0.562	0.629
A x B	14.092	9	1.566	1.754
B x Ss WTHIN	64.275	72	0.893	

Table 14. Summary table of a 4x4, repeated measures ANOVA for the amount of food consumed during elicited feeding: Expt. 6.

SOURCE	SS	DF	MS	F
BETWN Ss	1,384.994	27		
LES SITE (A)	55.785	3	18.595	0.336
Ss WTHIN GRPS	1,329.209	24	55.384	
WTHIN Ss	184.957	84		
LESION (B)	6.519	3	2.173	1.014
A x B	24.081	9	2.676	1.248
B x Ss WTHIN	154.357	72	2.144	

Table 15. Summary table of a 4x4, repeated measures ANOVA for the total threshold for elicited feeding: Expt. 6.

SOURCE	SS	DF	MS	F
BETWN Ss	205,074.102	27		
LES SITE (A)	13,535.173	3	4,511.724	0.565
Ss WTHIN GRPS	191,538.929	24	7,980.789	
WTHIN Ss	37,475.000	84		
LESION (B)	1,081.250	3	360.417	0.794
A x B	3,728.393	9	414.266	0.913
B x Ss WTHIN	32,665.357	72	453.686	

Table 16. Summary table of a one-way ANOVA for the difference scores in the amount of water consumed in 3 hrs following hyperosomotic stress: Expt. 7.

SOURCE	SS	DF	MS	F
TREATMENT	1,628.304	5	325.661	3.480*
ERROR	3,836.547	41	93.574	
TOTAL	5,464.851	46		

Table 17. Summary table of a one-way ANOVA on the number of pellets remaining in the alleyway on the morning of the second day: Expt. 7.

SOURCE	SS	DF	MS	F
TREATMENT	250.389	5	50.078	1.855
ERROR	1,349.611	40	26.992	
TOTAL	1,600.000	45		

Table 18. Summary table of a one-way ANOVA on the difference scores in the amount of food consumed after quinine adulteration: Expt. 7.

SOURCE	SS	DF	MS	F
TREATMENT	328.145	5	65.629	5.346**
ERROR	495.034	41	12.074	
TOTAL	823.179	46		

Table 19. Summary table of a randomized block factorial design on the frequency of elicited feeding after IP injections of haloperidol: Expt. 8.

SOURCE	SS	DF	MS	F
BLOCKS	20.806	5	4.161	4.212**
TREATMENTS	148.806	5		
DRUG (A)	96.695	1	96.695	97.869**
DOSAGE (B)	27.723	2	13.862	14.030**
A x B	24.388	2	12.194	12.342**
RESIDUAL	24.694	25	0.988	
TOTAL	194.306	35		

Table 20. Summary table of a randomized block factorial design on the amount of food consumed during elicited feeding after IP injections of haloperidol: Expt. 8.

SOURCE	SS	DF	MS	F
BLOCKS	197.024	5	39.405	17.366**
TREATMENT	103.239	5		
DRUG (A)	53.023	1	53.023	23.368**
DOSAGE (B)	24.547	2	12.273	5.409*
A x B	25.669	2	12.835	5.657**
RESIDUAL	56.726	25	2.269	
TOTAL	356.988	35		

Table 21. Summary table of a randomized block factorial design on the amount of food consumed after 23 hrs of food deprivation: Expt. 8.

SOURCE	SS	DF	MS	F
BLOCKS	85.640	5	17.128	5.664**
TREATMENTS	24.147	5		
DRUG (A)	2.918	1	2.918	0.965
DOSAGE (B)	15.634	2	7.822	2.587
A x B	5.586	2	2.793	0.924
RESIDUAL	75.590	25	3.024	
TOTAL	185.377	35		

Table 22. Summary table of a randomized block factorial design on the amount of water consumed after 23 hrs water deprivation: Expt. 8.

SOURCE	SS	DF	MS	F
BLOCKS	261.618	5	52.324	12.825**
TREATMENTS	25.785	5		
DRUG (A)	19.507	1	19.507	4.781*
DOSAGE (B)	5.264	2	2.632	0.645
A x B	1.014	2	0.507	0.124
RESIDUAL	102.007	25	4.080	
TOTAL	389.410	35		

Table 23. Summary table of a one-way, repeated measures ANOVA on the frequency of elicited feeding after intraventricular injections of blockers: Expt. 9.

SOURCE	SS	DF	MS	F
BETWN Ss	26.424	5		
WTHIN Ss	78.306	35		
DRUG	19.316	5	3.870	1.970
RESIDUAL	58.991	30	1.966	

Table 24. Summary table of a one-way, repeated measures ANOVA on the amount of food consumed during elicited feeding after intraventricular injections of blockers: Expt. 9.

SOURCE	SS	DF	MS	F
METWN Ss	477.141	5		
WTHIN Ss	175.558	35		
DRUG	109.128	5	21.826	9.858**
RESIDUAL	66.430	30	2.214	

Table 25. Summary table of a one-way, repeated measures ANOVA on the amount of food consumed after 23 hrs of food deprivation: Expt. 9.

SOURCE	SS	DF	MS	F
BETWN Ss	284.241	5		
WTHIN Ss	114.308	30		
DRUG	17.890	5	3.578	0.928
RESIDUAL	96.418	25	3.857	

PART II

Table 26. Newman-Keuls test for the difference the diet preference ratio: Expt. 2.

DIET		Mash	HFD
	TOTALS	476.7	930.6
Pellets	44.7	432.0**	885.9**
Mash	476.7		453.9**
CRITICAL VALUES:		233.16	269.12

Table 27. Newman-Keuls test for the difference in the threshold for elicited feeding: Expt. 2.

DIET		Mash	Pellets
	TOTALS	2,195	5,060
HFD	1,745	450	3,315**
Mash	2,195		2,865**
CRITICAL VALUES:		982.25	1,118.09

Table 28. The simple main effects of the mean frequency of elicited after 6-OHDA intraventricularly using the Scheffé method: Expt. 4, Figure 4-1.

	LES-PRE	LES-POST	CON-PRE	CON-POST	
MEANS:	9.61	2.04	9.50	9.33	
COMPARISON					F
1	+1	0	-1	0	0.850
2	0	-1	0	+1	374.060**
3	+1	-1	0	0	497.685**
4	0	0	+1	-1	0.531

$F'(3,24)=14.16^{**}$; $F'(3,28)=13.71^{**}$

Table 29. The simple main effects of the mean amount of food consumed during elicited feeding after 6-OHDA intraventricularly using the method of Scheffé: Expt. 4, Figure 4-2.

	LES-PRE	LES-POST	CON-PRE	CON-POST	
MEANS:	11.71	1.28	9.47	8.87	
COMPARISON					F
1	+1	0	-1	0	3.218
2	0	-1	0	+1	36.942**

$F'(3,24)=14.16^{**}$

Table 30. Direct difference t-test on the frequency of elicited feeding immediately before and after the electrolytic lesion in the locus coeruleus: Expt. 5.

PRE-LESION	POST-LESION	
MEANS: 9.40	6.30	$S_D^2 = 23.780$

$t_9 = 3.41^{**}$ CRITICAL VALUE = 2.82^{**}

Table 31. Direct difference t-test on the amount of food consumed during elicited feeding immediately before and after the electrolytic lesion to the locus coeruleus: Expt. 5.

	PRE-LESION	POST-LESION	
MEANS:	7.02	3.34	$S_D^2 = 4.334$

$t_9 = 5.608^{**}$; CRITICAL VALUE = 2.82^{**}

Table 32. Newman-Keuls test for the frequency of elicited feeding after 6-OHDA lesion in the dorsal noradrenergic pathway: Expt. 5, Table 5-2.

LESION	TOTALS	PRE	POST II
		62	63
POST II	54	8*	9
PRE	62		1
CRITICAL VALUES:	*	7.54	9.23

Table 33. Scheffé analysis on the difference scores in the amount of water consumed in 3 hrs following hypertonic stress by lesion site: Expt. 7, Table 7-1.

	CON	NA	SN	PRE-VEN	VEN	VEN CON	
M	21.6	22.5	22.5	22.0	7.7	28.5	
COMP							F
1	-1	0	0	0	0	+1	1.826
2	0	0	0	0	-1	+1	14.917*

F'(5,40)=12.25*

Table 34. Scheffé analysis on the difference scores in the amount of food consumed after quinine adulteration by lesion site: Expt. 7, Table 7-3.

	CON	NA	SN	PERI-VEN	VEN	VEN CON	
M	7.6	10.0	9.4	9.2	16.1	8.7	
COMP							F
1	-1	0	0	0	0	+1	0.381
2	0	0	0	0	+1	-1	14.589*
3	-1	+1	0	0	0	0	2.403

F'(5,40)=12.25*

Table 35. The simple main effects of mean frequency of elicited feeding after IP haloperidol or saline using the Scheffé method: Expt. 8, Figure 8-1.

	HAL .05	HAL .10	HAL .15	SAL .05	SAL .10	SAL .15	
M	7.83	4.83	3.83	8.83	8.83	8.67	
COMP							F
1	-1	0	0	+1	0	0	3.04
2	0	-1	0	0	+1	0	48.58**
3	0	0	-1	0	0	+1	71.13**
4	+1	-1	0	0	0	0	27.34**
5	0	+1	-1	0	0	0	3.04
6	0	0	0	+1	0	-1	0.78

F'(5,25)=11.25*, 19.50**

Table 36. The simple main effects of mean amount of food consumed during elicited feeding after IP haloperidol or saline using the Scheffé method of analysis: Expt. 8, Figure 8-2.

	HAL	HAL	HAL	SAL	SAL	SAL	
M	8.27	4.48	5.27	8.54	8.83	7.96	
COMP							F
1	-1	0	0	+1	0	0	0.096
2	0	-1	0	0	+1	0	25.030**
3	0	0	-1	0	0	+1	9.567
4	+1	-1	0	0	0	0	18.942*
5	+1	0	-1	0	0	0	11.892*
6	0	+1	-1	0	0	0	0.817
7	0	0	0	0	+1	-1	1.012

$F'(5,25)=11.25^{*}$, 19.50^{**}

Table 37. The simple main effects of the mean amount of food consumed during elicited feeding after blockers using the Scheffé method of analysis: Expt. 9, Figure 9-2.

	HAL	PHEN	MJ-1999	HAL VEH	SAL	BASE	
M	7.41	10.23	11.44	12.13	11.72	11.84	
COMP							F
1	-1	0	0	+1	0	0	35.13**
2	0	+1	0	0	-1	0	3.49
3	0	0	+1	0	-1	0	0.52
4	-1	0	0	0	0	+1	31.02**

$F'(5,30)=12.65^{*}$, 18.50^{**}

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