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CORTICAL LESIONS AND HYPOTHALAMICALLY-ELICITED FEEDING

Ph.D. PSYCHOLOGY

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EFFECTS OF CORTICAL LESIONS ON EATING PRODUCED BY HYPOTHALAMIC STIMULATION

Unilateral and two-stage bilateral neocortical ablations were observed to have marked effects on feeding elicited by electrical stimulation of the hypothalamus in 56 rats. The effects included elevation of current thresholds for eliciting feeding, impairment of feeding performance, and transient or permanent disruptions of stimulation-elicited feeding. Failure to feed appeared to reflect disorganization of food-seeking rather than of consummatory responses. Spontaneous feeding was largely unaffected.

Analysis of the data by a multiple regression technique indicated that impairment and total disruption of feeding performance were related to the amount of unilateral and bilateral damage to the frontal cortex but not to other cortical regions. Changes in threshold were not related to frontal damage as such; rather, these changes appeared to be a function of an interaction between the site of stimulation and cortical damage. These and other findings are shown to contribute to the elucidation of the nature and mechanisms of cortical-hypothalamic interactions in the production of normal feeding.

EFFECTS OF CORTICAL LESIONS ON EATING PRODUCED BY HYPOTHALAMIC STIMULATION

by

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PREFACE

The notion that the hypothalamus plays a dominant role in the control of feeding behavior is widely supported. Until recently, the role of extrahypothalamic structures has been largely ignored. A number of studies has provided indirect evidence that one of these areas, the neocortex, controls feeding by influencing activity in the lateral hypothalamus. The present investigation provided more direct evidence by examining the effects of subtotal cortical ablations on feeding behavior elicited by electrical stimulation of the lateral hypothalamus. In addition, the effects of a number of variables which might potentially influence the cortical-hypothalamic interactions were considered.

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I

INTRODUCTION

Search for the neural basis of feeding behavior has been dominated by investigations of the role of the hypothalamus. No doubt this focus was prompted by the dramatic nature of the changes in food intake that occur following comparatively small lesions within this structure. Bilateral destruction of the ventromedial region produces overeating (hyperphagia) and results in a subsequent two-to-threefold increase in body weight (Hetherington, 1941; Hetherington & Ranson, 1940, 1942). Comparable damage in the lateral hypothalamus abolishes or reduces eating (aphagia or hypophagia) and may result in death by starvation (Anand & Brobeck, 1951). Findings of this type have led to the view that the ventromedial region of the hypothalamus normally has an inhibitory influence on food intake and functions as a "satiety mechanism", and the lateral region normally has a facilitatory influence and functions as a "hunger mechanism".

More recently, theoretical considerations have pointed to "extrahypothalamic" brain areas that may also be involved in the control of feeding (Hoebel, 1971; Morgane, 1969; Stevenson, 1969). The investigation reported here is a step toward understanding the interaction between one of the extrahypothalamic areas, the neocortex, and the lateral hypothalamus in the control of feeding in the rat.

The Nature of Hypothalamic Control

The hyperphagia produced by lesions of the ventromedial hypothalamus is apparently not due to increased "hunger". In fact, lesioned animals are generally less willing than normals to exert effort or to

overcome noxious stimuli to gain access to food (Miller, Bailey, & Stevenson, 1950; Teitelbaum, 1957). These observations have led to the suggestion that hyperphagia reflects impairment of a mechanism that normally inhibits feeding.

However, the loss of inhibitory control over eating is not complete. For example, animals with ventromedial hypothalamic lesions are generally over-responsive to certain conditions that impair food intake. Increased environmental temperature (Kennedy, 1950), bitter tasting foods (Miller et al., 1950; Teitelbaum, 1955), stomach preloads of water, hypertonic fluids or nonnutritive bulk (Smith, Salisbury, & Weinberg, 1961), and systemic injections of centrally-acting anorexigenic drugs (Epstein, 1959; Stevenson, Montemurro, & Bernardis, 1958; Stowe & Miller, 1957) lead to greater reductions in intake by hyperphagic than normal animals. Hyperphagics also appear to be sensitive to interoceptive stimuli related to obesity, since daily food intake diminishes as body weight is increased (Brobeck, Tepperman, & Long, 1943; Hoebel & Teitelbaum, 1966).

In contrast to animals with ventromedial lesions, animals with lateral hypothalamic lesions behave as if they had been overfed. Teitelbaum and Stellar (1954) observed that such aphagic rats actively avoided contact with food and water and did not swallow food placed in their mouths. This behavior appeared not to be a sensory-motor deficit, but a motivational one. Rogers, Epstein, and Teitelbaum (1965) showed that rats preoperatively trained to lever-press for food delivered intragastrically did not press following lateral hypothalamic lesions. Moreover, Powley and Keesey (1970) reported that aphagia recovered quickly or did not even occur if the animals were food-deprived several

days before the lesion operation. If aphagia were due to a direct motor impairment, such findings would not be expected.

When starvation due to aphagia is prevented by intragastric feeding, most animals show self-initiated feeding after periods ranging from a few days to several weeks (Teitelbaum & Stellar, 1954). At first only sweet-tasting foods are eaten. Then, over a period of several weeks this recovery proceeds through several characteristic stages until the rats are able to maintain themselves on standard laboratory fare (Epstein & Teitelbaum, 1960; Teitelbaum & Epstein, 1962; Williams & Teitelbaum, 1959). Other investigators have reported that aphagia occasionally showed no remittance after several months of careful postoperative handling (Gold, 1967; Morgane, 1961a, 1961b), but in these cases lesion damage generally extended laterally to include fiber systems bordering the hypothalamus.

"Recovered" animals adjust their food intake normally in response to food deprivation, caloric dilution of the diet, and changes in environmental temperature (Epstein & Teitelbaum, 1967). The only persistent changes are chronically low body weight (Powley & Keesey, 1970), inability to regulate water intake independently of food intake (Teitelbaum & Epstein, 1962), and failure to increase food intake sufficiently in response to insulin-induced hypoglycemia (Epstein & Teitelbaum, 1967).

The neural tissue responsible for the recovered feeding has not been determined. Re-lesioning through chronic hypothalamic electrodes, which also enlarged the damaged area, reinstated aphagia (Teitelbaum & Epstein, 1962). This result, however, suggests at least two interpretations. Relesioning could have reinstated aphagia by destroying

hypothalamic tissue spared by the first lesion. Alternately, renewed aphagia could have resulted from additional interruption of adjacent fiber pathways to extrahypothalamic areas which may have mediated "recovered" feeding.

Electrical stimulation of the hypothalamus produces effects that are generally opposite in direction to those produced by lesions. Thus, stimulation of the ventromedial area interrupts ongoing feeding in food-deprived rats (Krasne, 1962) and cats (Morgane, 1969) and stimulation of the lateral area elicits feeding in satiated animals, including the rat (Miller, 1957; Smith, 1956), cat (Brügger, 1943, cited by Stevenson, 1969), goat, sheep (Larsson, 1954), and monkey (Robinson & Mishkin, 1962, 1968).

These electrically-elicited behaviors are generally analogous to those which occur naturally. Cats which stop eating when stimulated in the ventromedial region, often go to sleep much as they would following a large meal (Morgane, 1969). Stimulation of the lateral hypothalamus in the rat appears to produce a motivational state of hunger. Like food-deprived animals they are responsive to factors that normally facilitate or inhibit food intake. These include taste (Tenen & Miller, 1964), stomach preloads of food or water (Devor, Wise, Milgram, & Hoebel, 1970), and anorexigenic drugs (Miller, 1957; Stark & Totty, 1967). Furthermore, animals motivated by electrical stimulation learn instrumental responses rewarded by food (Coons, Levak, & Miller, 1965; Mendelson, 1966) and endure punishment in order to eat (Morgane, 1961c). Such instrumental responses are emitted under stimulation or food

deprivation conditions regardless of the condition of training (Coons et al., 1965; Grastyan, Lissak, & Kekesi, 1956; Miller, 1960; Wyrwicka & Dobrzecka, 1960; Wyrwicka, Dobrzecka, & Tarnecki, 1960).

Some limits to the analogy between naturally-occurring and electrically-elicited feeding have been noted (Valenstein, Cox, & Kakolewski, 1970). For example, food-deprived rats readily ate a familiar food in various forms (e.g., pellet, powder, or liquid). The same animals, when not deprived but motivated by hypothalamic stimulation, would not switch from one food form to another. In addition, stimulated rats often ate food of only one taste quality, whereas under conditions of deprivation they would ingest a range of foodstuffs.

In summary, the notion that the hypothalamus plays a dominant role in the control of feeding behavior is widely supported. However, the degree of control that remains after lateral or ventromedial lesions and the failure of hypothalamically-elicited feeding to mimic the naturally-occurring behavior in all situations suggest that other brain areas are also important. In the following sections more direct evidence for these "extrahypothalamic" influences will be examined.

Extrahypothalamic Involvement in Feeding

Midbrain. Hyperphagia and obesity have been observed following lesions of the midbrain central gray matter in cats (Adametz & O'Leary, 1959; Skultety, 1966, 1969; Skultety & Gary, 1962; Sprague, Chambers, & Stellar, 1961). Augmented intake persisted longest when the lesions interrupted the entire cross sectional extent of this region (Skultety, 1969). Although no comparison has been made of the hyperphagia resulting

from central gray damage with that produced by ventromedial hypothalamic lesions, both have in common the fact that obesity was dependent on the availability of high caloric diets (Miller et al., 1950; Skultety, 1969).

In the rat only one case of obesity has been reported following lesions of the central gray (Parker & Feldman, 1967) although this area has been damaged in other studies without reports of altered food intake. However, the unavailability of highly-palatable foods may account for this discrepancy.

Aphagia and adipsia following midbrain reticular lesions have been cursorily noted in the cat (Skultety & Chamberlain, 1965) and dog (Skultety, 1962) and have been studied extensively in the rat. In this latter animal, bilateral damage to the midbrain reticular formation in the rostrocaudal plane of the red nucleus results in feeding deficits comparable to those reported following lateral hypothalamic lesions (Blatt & Lyon, 1968; Gold, 1967; Lyon, 1966; Lyon, Halpern, & Mintz, 1968; Parker & Feldman, 1967).

This midbrain "feeding area" appears to be a caudal extension of a feeding area reported by Gold (1967) and Morgane (1961a, 1961b) which involves both the far lateral hypothalamus and the adjacent internal capsule. Using a technique of asymmetrical bilateral lesions, Gold (1967) demonstrated that a unilateral lesion centered rostral and dorsal to the red nucleus and a contralateral diencephalic lesion that included the internal capsule and lateral margin of the hypothalamus resulted in a feeding deficit equal to that resulting from bilateral lesions in either area.

Lyon (1966) has cited anatomical evidence that the midbrain feeding area defined by Gold (1967) and Parker and Feldman (1967) might be composed of two overlapping systems which differ in their rostral projections. By his analysis one is located adjacent to the ventrolateral edge of the periaqueductal gray and is comprised mainly of ascending reticular fibers that continue rostrally either to the thalamic midline and intralaminar nuclei or to the subthalamus. The other is ventral, is more diffuse, and contains both ascending and descending fibers connecting the midbrain with the cortex and basal ganglia, as well as to the hypothalamus.

By pairing large unilateral midbrain lesions with more circumscribed contralateral damage in rostral projection areas, Blatt and Lyon (1968) found some support for Lyon's (1966) analysis. They demonstrated that the subthalamic projection of the dorsal midbrain area, but not the thalamic projections were part of a feeding system.

The nature of the deficit underlying aphagia produced by midbrain lesions has not been elaborated in detail. It is uncertain, for example, whether failure to eat represents primarily a motivational dysfunction, as has been suggested for the hypothalamic syndrome, or whether aphagia is secondary to a general impairment of sensory-motor function. Several investigators favor the latter hypothesis (Blatt et al., 1968; Parker & Feldman, 1967). In their view, midbrain aphagia results from an impairment of the ability to associate sensory cues with motor responses appropriate to finding food. However, motivational changes have also been reported, though not directly in association with feeding deficits. Lesions of the ventral midbrain tegmentum result in lowered lever-press

response rates for a variety of reinforcers including food and water (Erlich, 1963), septal stimulation (Schiff, 1964), and mild photic stimulation (Schiff, 1967).

Electrical stimulation of the midbrain has received comparatively little attention, though feeding has been produced by stimulation of midbrain sites in the rat (Corcoran & Clavier, 1971), cat (Wyrwicka & Doty, 1966), and monkey (Robinson & Mishkin, 1968). Effective stimulation sites were in the general region where lesions produce aphagia.

Piriform-amygdala region. Hyperphagia has been observed following complete temporal lobe resection in dogs (Fuller, Rosvold, & Pribram, 1957) and monkeys (Klüver & Bucy, 1939), and after smaller, circumscribed lesions confined to the basal or lateral amygdaloid nuclei in cats (Green, Clemente, & De Groot, 1957) and rats (Grossman & Grossman, 1963) and to central and medial nuclei in cats (Wood, 1958). Subtotal temporal resections in monkeys have also been shown to lead to augmented food intake (Anand, Dua, & Chhina, 1958; Pribram & Bagshaw, 1953; Schwartzbaum, 1960a, 1960b, 1961).

In some respects amygdalar hyperphagia resembles that resulting from ventromedial hypothalamic lesions. In both syndromes there is a degree of dissociation between the amount of food consumed and the effort required to obtain it (Miller et al., 1950; Schwartzbaum, 1961). Schwartzbaum (1960b, 1961) reported that in food-reinforced bar-pressing situations, amygdalectomized, hyperphagic monkeys did not adjust their response rate as did normal monkeys to changes in food deprivation, or in the size of the reward. In other respects amygdalar hyperphagia differs from the hypothalamic syndrome. The rate of weight gain following

amygdalar damage is more gradual than that seen following hypothalamic damage (Morgane & Kosman, 1959). Furthermore, in contrast to the finicky eating habits noted in hypothalamic hyperphagic animals (Kennedy, 1950; Miller et al., 1950) amygdalectomized hyperphagic monkeys attempted to eat inedible objects or foods that were normally not preferred (Pribram & Bagshaw, 1953).

In the same regions where restricted amygdala lesions produce hyperphagia, electrical stimulation interrupts ongoing feeding in the rat (Grossman & Grossman, 1963; White, 1969), and inhibits instrumental responses trained to food reward in the cat (Fonberg & Delgado, 1961). Evidence from the rat implied that these inhibitory effects on feeding are mediated via the stria terminalis and ventromedial hypothalamus since severing the fiber tract or lesioning the hypothalamus nullified stimulation-elicited inhibition evoked from the amygdala (White, 1969).

Other lesion and stimulation evidence suggests that parts of the amygdala may also play a facilitatory role in food intake. Thus, a transient aphagia and hypophagia has resulted from amygdalar damage in cats (Anand et al., 1958) and dogs (Fonberg, 1969; Koikegami, Fuse, Yokoyama, Watanabe, & Watanabe, 1955). In the latter, hypophagia followed damage to the dorsomedial amygdala, but not the ventromedial portion where damage produced the opposite effect (Fonberg, 1969).

Electrical stimulation of the amygdala and piriform cortex in the cat and monkey evokes a variety of motor "automatisms" including such alimentary responses as chewing, biting, swallowing, and salivation. No food ingestion has been reported (Fonberg & Delgado, 1961; Kaada, 1954; MacLean & Delgado, 1953; Shealy & Peele, 1957). Adrenergic

chemical stimulation, however, has been reported to potentiate feeding in food-deprived rats (Grossman, 1969), and cholinergic stimulation to potentiate drinking in water-deprived rats (Grossman, 1969). Neither chemical affected intake in satiated animals.

Hippocampus. Considering the large number of hippocampal lesion studies it is significant that only a few have reported changes in food or water intake. Small, transient increases in the consumption of both food and water have been noted (Erlich, 1963; Fisher & Coury, 1962). Observations by Grossman (1967) suggest that hippocampal lesions may produce slight metabolic disturbances. Following lesions of the entorhinal cortex, which has strong anatomical connections to the ventral hippocampus, food intake occasionally increased without comparable changes in body weight, or food intake remained constant and body weight varied.

Electrical and chemical stimulation studies provide more convincing evidence for hippocampal involvement. Milgram (1969) reported that the offset of stimulation in a restricted area of the dorsolateral hippocampus in the rat evoked a brief period of feeding ("rebound feeding"). These animals would also perform a food-reinforced instrumental response during the post-stimulation period. In a subsequent study it was found that rebound feeding was prevented by lateral hypothalamic lesions which also abolished spontaneous feeding (Server, Milgram, & Hoebel, cited in Hoebel, 1971). Adrenergic and cholinergic chemical stimulation of this general hippocampal area results in feeding and drinking respectively (Coury, 1967).

Septal area. Lesions in the septal region have resulted in a transient increase in food intake (Lorens & Kondo, 1969) but more commonly result in a seemingly-permanent increase in the consumption of water (Carey, 1969; Harvey & Hunt, 1965; Harvey, Lintz, Jacobson, & Hunt, 1965; Lubar, Boyce, & Schaefer, 1968; Lubar, Schaefer, & Wells, 1969; Wolfe, Lubar, & Ison, 1967). The changes in water intake are interesting both for the normally-close correspondance between eating and drinking and for the fact that certain behavioral properties associated with the septal hyperdipsia are similar to those accompanying ventromedial hypothalamic hyperphagia.

For example, septally-damaged rats appear to be less motivated by thirst than control animals. Lesioned rats, when compared to controls, ran more slowly for a water reward (Carey, 1969; Wolfe et al., 1967), had a lower tolerance for quinine in their water (Beatty & Schwartzbaum, 1968; Carey, 1969), drank a greater amount of a 3% saline solution (Lubar et al., 1968), and often lever-pressed at a slower rate for water (Carey, 1969). Also, like hyperphagic rats, septally-damaged animals were abnormally reactive to sweet-tasting substances. Fluid intake could be increased further by the addition of saccharine or sucrose (Beatty & Schwartzbaum, 1968)

Electrical stimulation of the septum has not been reported to affect food intake. In contrast, chemical stimulation elicited prolonged food and water intake (Coury, 1967; Fisher & Coury, 1962). These effects are similar to those observed following chemical stimulation of the hippocampus (Fisher & Coury, 1962).[1]

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[1] It is interesting to note that these changes are similar in direction to those produced by lesions, since stimulation and lesioning techniques generally produce opposite effects. However, the area implicated in the chemical stimulation studies was somewhat dorsal to the region most often damaged in the lesion experiments (Lubar et al., 1969) and may have involved different neural substrates.

Basal ganglia. Large bilateral lesions of the caudate nucleus in the rat result in a three-to-four-day period of aphagia and adipsia (Whittier & Orr, 1962). Complete removal of the cortex and striatum permanently abolishes spontaneous feeding in both the rat (Sorenson & Ellison, 1970) and the cat (Emmers, Chun, & Wang, 1965). Unlike rats made aphagic by hypothalamic lesions, these animals exhibit no aversion to food and readily ingest food brought to their mouths. The deficit therefore appears to be limited to food-seeking mechanisms.

Morgane (1961b) has reported that lesion damage involving the internal portion of the globus pallidus in the rat results in permanent aphagia accompanied by a rate of weight loss which exceeds that observed in intact rats during starvation. Since the efferent outflow of the globus pallidus presumably invades the extreme lateral part of the hypothalamus, Morgane has suggested that hypothalamic aphagia may be partially due to destruction of the hypothalamic projections of these fibers. More recent reports by Gold (1966, 1967) support Morgane's view. In his studies, apparently-permanent aphagia was produced by bilateral lesions centered in the internal capsule that involved both the lateral margin of the hypothalamus and medial border of the globus pallidus.

Due to the complex geography of the internal capsule-globus pallidus region (Knook, 1965) it is not possible to relate the effects of damage to this region to destruction of a particular fiber system. However, the rostrocaudal plane of the capsular damage appears to be of critical importance. Karli and Vergnes (1964) lesioned rats in the internal capsule and ansa lenticularis just caudal to where Gold made

his lesions and found only transient aphagia. Anand and Brobeck (1951) noted no change in food intake in a single rat that had a bilateral lesion damaging the internal capsule at the level of the posterior hypothalamus. Presumably, the lesions in these studies spared pallidofugal fibers that enter the hypothalamus more rostrally.

Electrical stimulation of the basal ganglia elicited food intake in the monkey (Robinson & Mishkin, 1962, 1968) although not consistently in all areas. Three electrodes that were clearly in the globus pallidus never evoked eating. In the rat, however, chemical stimulation of the globus pallidus region effectively increased food intake (Wagner & de Groot, 1963).

Neocortex. Aphagia and adipsia lasting approximately five days have been noted as an incidental finding in a number of studies involving total neodecortication in the rat (Braun, 1966; DiCara, Braun, & Pappas, 1970; Horel, Bettinger, Royce, & Meyer, 1966). The same result was also observed when only the anterior half of the cortex was removed (Braun, 1966). Feeding and drinking, as well as food-reinforced, instrumentally-conditioned responses are abolished during spreading cortical depression ("functional decortication") produced by application of 25% KCl to the dural surface of the brain (Bureš & Burešová, 1960; Levitt & Krikstone, 1968).

Cortical aphagia differs from the lateral hypothalamic syndrome in that decorticate rats do not reject food placed in their mouth and can be easily fed by hand. In this respect the syndrome is similar to that following caudate lesions (Whittier & Orr, 1962).

Soulairac (1952) has reported that removal of less than 40% of the neocortex in the rat resulted in subtle and long lasting changes in food preference. Ablations which spared the frontal cortex (areas 6 and 10 of Krieg) resulted in a slight but significant increase in consumption of lab chow but did not affect glucose consumption (Soulairac & Soulairac, 1958). In all cases the area considered to be the primary cortical projections for taste remained intact (Benjamin & Akert, 1959), implying that there was no primary sensory deficit. Perhaps these changes were related to the incentive value of the food.

In the cat and monkey, removal of small amounts of temporal, occipital, parietal, or frontal (non-polar) cortex did not affect food intake (Anand, Dua, & Chhina, 1961), but large ablations of sensory-motor cortex interfered with food intake. Whether this interference was secondary to a more general deficit in motor performance is uncertain. However, Wang and Akert (1962) have reported that voluntary or spontaneous feeding behavior was absent in decorticate cats for a considerable period even after the motor elements of the behavior had fully recovered.

Destruction of the tip of the anterior cortex (frontal pole) which has the strongest connections with the lateral hypothalamus (Leonard, 1969; Nauta, 1964), has been shown to result in an increase in food intake in the rat (Richter & Hawkes, 1939) and monkey (Fulton, Jacobson, & Kennard, 1932; Richter & Hines, 1934). Hyperphagia in these cases appeared to be a secondary effect of increased energy expenditure due to hyperactivity.

Electrical stimulation of the lateral part of the anterior (motor) cortex evokes rhythmic chewing and swallowing in anesthetized animals

(Babkin & Van Buren, 1951; Bremer, 1923; Sumi, 1969). These responses appeared to be organized at lower neural levels since removal of the gray matter and subsequent stimulation of the exposed white matter did not change the pattern of the evoked responses (Bremer, 1923). Delgado (1952) confirmed and extended these findings in free-moving, unanesthetized cats. Reflexive licking and chewing were observed following stimulation at a number of cortical points. At a few sites stimulation led to responses directed to different objects in the environment. Certain of these points which were in the pre-sylvian gyrus consistently elicited feeding.

Huston and Bureš (1970) have observed voracious eating and drinking in rats recovering from single waves of cortical spreading depression. The onset of these behaviors corresponded in time to the passage of the DC wave over the frontal cortex. As a possible explanation these investigators suggested that the onset of feeding was related to changes in lateral hypothalamic activity since previous work had shown that cortical depression reduced single unit and EEG activity (Bureš, Burešová, & Fifková, 1961), as well as evoked potentials in the hypothalamus (Weiss & Fifková, 1961). Presumably, recovery of cortical function resulted in a sharp increase, or rebound excitation, in the lateral hypothalamus and thus led to the facilitation of feeding.

A notion of a cortical-hypothalamic interaction is also consistent with the results of a study by Teitelbaum and Cytawa (1965). In this experiment spreading cortical depression reinstated aphagia for up to three days in rats that had recovered from the lateral-hypothalamic lesion syndrome while in normal animals spreading depression sup-

pressed feeding for no more than eight hours (Bureš & Burešová, 1960). A subsequent replication of the experiment by Balinska, Burešová, and Fifková (1967) with additional tests of cortical functioning showed that the reinstatement of aphagia was correlated with prolonged depression of the cortex. Why previous hypothalamic damage should alter the speed of recovery from cortical spreading depression remains unexplained. Nevertheless, a cortical-hypothalamic interaction is strongly suggested.

In summary, the evidence reviewed suggests that a number of extra-hypothalamic areas participate in the control of feeding behavior. Much of this evidence further suggests that these areas mediate their controlling influence through the hypothalamus. This is particularly true for rostral limbic regions, such as the amygdala (White, 1969) and hippocampus (Milgram et al., cited in Hoebel, 1971) where stimulation-linked changes in feeding were abolished by hypothalamic lesions. It is also worth noting that anatomical considerations are consistent with a view that all rostral areas implicated in feeding behavior, including the amygdala, hippocampus, septum, basal ganglia, and cortex, could mediate their effects via the hypothalamic and midbrain regions involved in the same function.[2]

The Present Investigation

The purpose of the present work was to extend the evidence for a cortical-hypothalamic interaction in the control of feeding behavior. The general approach of the experiment was to determine thresholds for elicitation of feeding from the lateral hypothalamus before and after cortical ablations. In line with the suggestion of Huston and Bureš

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[2] Excellent reviews of the fiber connections between these areas are provided by Knook (1965) and Nauta and Haymaker (1969).

(1970) that reduction of neural input from the cortex would result in a lowering of activity in the lateral hypothalamic "feeding area", it was expected that cortical ablations would produce an elevation in feeding thresholds.

The experimental design was sufficiently broad to permit study of a number of potentially influential variables. These included (1) the size and locus of cortical ablation, (2) variation in stimulating electrode locations and (3) the laterality (ipsilateral, contralateral) of cortical damage in relation to the stimulation electrodes. It was thought that by pinpointing the effects of these variables it would be possible to gain a better understanding of the role of the cortex in feeding.

II

METHOD

Subjects and Apparatus

Subjects

A total of 160 male hooded rats (Canadian Breeding Farms, St. Constant, Quebec) were used. They were housed individually in cages with food (Purina Rat Chow) and water available ad libitum, except as noted below.

Threshold Testing Chamber

All testing was carried out in a sound-attenuating chamber constructed from an old refrigerator. The interior was ventilated by fans and was illuminated by a 14-watt fluorescent bulb. Inside the chamber, and fully visible through a 39 x 26 cm. plastic window, was a smaller testing box measuring 38 cm. long, 23 cm. wide and 30 cm. deep. The side and back of the box were made of wood, while the top and front were constructed of clear plexiglass allowing an unobstructed view of the interior. The floor was made of roughened plexiglass and was easily removable for cleaning.

Electrical Stimulation

Electrical stimulation consisted of 18-sec. trains of biphasic, rectangular cathodal pulses, 0.2 msec. in width, generated at 100 pps. by a standard square wave generator (Grass, Model SD-5) and amplified by a transistorized constant current circuit (Appendix A). The current ranged from 20 to 800 microamp. and was measured on an oscilloscope as the voltage drop across a 1-Kohm resistor in series with the output

leads of the stimulator. These leads were connected to the electrode by means of a two-channel mercury commutator that was attached to the ceiling of the testing chamber. The swivel action of the commutator prevented twisting of the electrode leads without restricting the free movement of the rat.

Electrode Assembly

The electrode assembly (Figure 1) was constructed so that it could be solidly fixed to the skull while leaving an area of the calvarium either anterior or posterior to bregma free of dental cement for later surgery. Monopolar electrodes were made of straightened stainless steel wire, 0.24 mm. in diameter. The wires were soldered to miniature Winchester pins, and insulated (Compound 714, National Engineering Products) except for the cross-section of the cut tips. A pair of electrodes and a 12 mm. length of a threaded (6-32) nylon machine screw were cemented together while the electrode shafts were held parallel and exactly 3.0 mm. apart in a drilled plastic block. The nylon shaft protruded a few millimeters above the Winchester pins and, during testing, the stimulation leads were anchored to it with a miniature alligator clip, thus removing mechanical strain from the electrical connections. The nylon shaft also prevented the rat from damaging the pins by scraping them against the wire mesh top of the home cage.

Surgery

All surgery was performed under sodium pentobarbital anesthesia (Nembutal, Abbott, 60 mg/kg., i.p.). Following surgery, penicillin (Derapen-C, Ayerst, 30,000, i.m.) was injected to control infection.

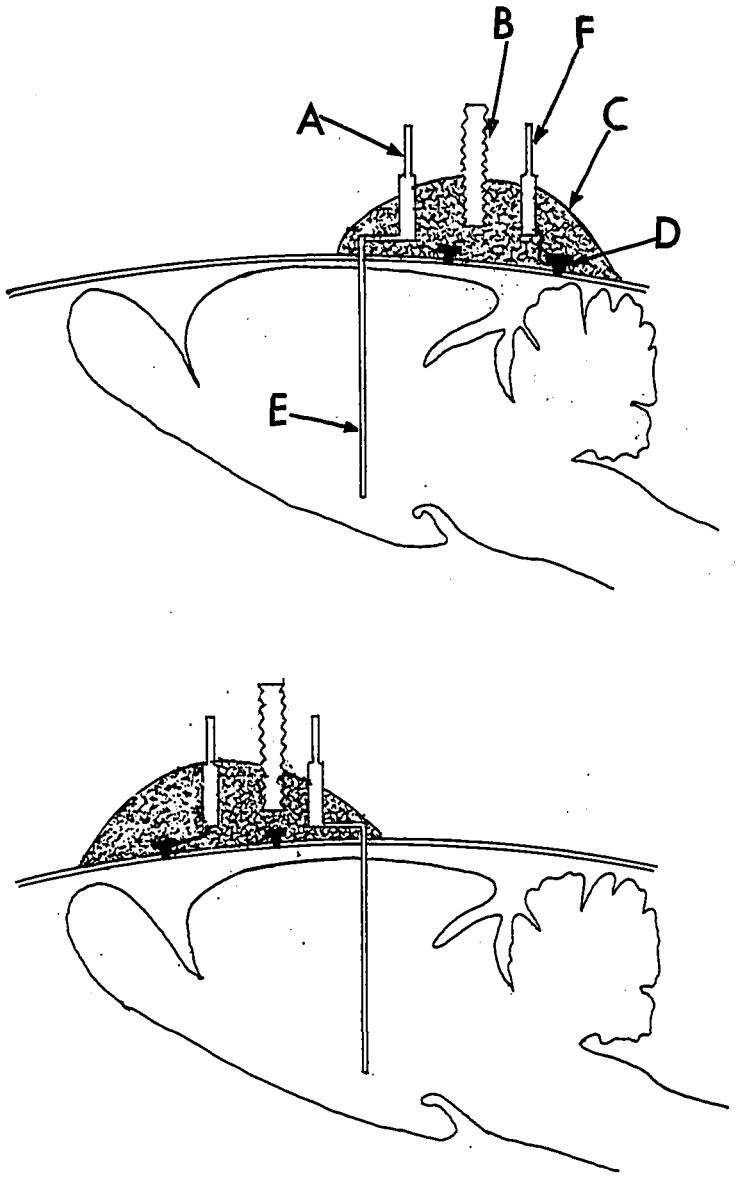

Figure 1. Schematic diagram of mounted electrode assembly

A Winchester pin
B Threaded nylon shaft
C Crown of dental cement
D Skull screw
E Stainless steel electrode
F Reference electrode

Electrode Implantation

The subject's scalp was shaved and scrubbed with merthiolate. The head was fixed in a stereotaxic instrument (Kopff, Model 1404) with the incisor bar set 2.4 mm. below the horizontal plane of the ear bars. The scalp was opened by a midline incision, and the skin flaps and underlying periosteum were reflected laterally. A bilateral partial craniectomy of the skull dorsal to the lateral hypothalamus was performed using a dental burr. Four additional holes were made with a No. 76 drill bit either anterior or posterior to the craniectomy and four small screws (American Optical, SB-2) were then firmly anchored to the skull. Around the screws was wound a length of 4/0 surgical stainless steel wire with a Winchester pin soldered to one end. This latter served as the indifferent electrode for monopolar stimulation. Finally, the tips of the paired electrodes were lowered to the perifornical region of the lateral hypothalamus by directing them to a point 1.5 mm. lateral to the midline, 8.0-8.5 mm. ventral to the surface of the skull, and 5.0-5.5 mm. anterior to the interaural line. Once in position, the electrode assembly was fixed to the four screws and skull surface with dental cement (Cranioplastic, L. D. Caulk). Care was taken to leave the skull surface either anterior or posterior to bregma free of cement.

Cortical Ablations and Sham Controls

Ablations were made by suction, were limited to the neocortex, and were varied in size and location. Ablations and sham operations were performed in two stages, one hemisphere at a time. A six-day period of recuperation was allowed between successive operations.

The anesthetized animal was fixed in the stereotaxic instrument and an incision was made either anterior or posterior to the electrode pedestal. The skin and periosteum were reflected, and for lateral ablations, the temporalis muscle was also reflected to expose the cranium. Using a small dental burr, a partial craniectomy was made to expose the dura. Bone fragments were removed by flooding the area with warm Ringer's solution. The dura was cut and then removed with fine forceps. The cortex, thus exposed, was viewed with the aid of a dissecting microscope. Using a drawn glass pipette with a tip diameter of 0.5-1.0 mm. the exposed portion of the cortex was removed by aspiration. The damaged area was then packed with gelatin sponge (Gelfoam, Upjohn) that was first soaked in thrombin (Thrombin, Upjohn, 75 units/cc.), and the cranium was replaced with a thin layer of dental cement. The incision was closed with silk suture.

The procedure for sham operations paralleled the initial steps of the above procedures except that the cranium was not completely pierced. Instead, a 4 x 4 mm. area of skull was carefully shaved away using a dental burr until only a thin layer remained. Dental cement was applied to the damaged portion of the skull and the incision was sutured.

Procedure

Subjects were tested over several months in groups of 5 to 15 following the sequences summarized in Table 1.

Adaptation to Testing Chamber

Two days after electrode implantation all food was removed from the subjects' home cages. On that day and on four subsequent days subjects were placed in the testing box for one hour during which time

TABLE 1

Summary of Testing Schedules

Day	Procedure	Schedule A	Schedule B
0	Electrode Implantation	x	x
3-7	Adaptation	x	x
10	Screening	x	x
12-20+	Threshold Tests	x	x
0	Ablation Operation Stage I	x	x
1-6	Threshold Tests	x	
0	Ablation Operation Stage II	x	x
1-3	Threshold Tests	x	
8-10	Threshold Tests	x	x
15-17	Threshold Tests		x

they could eat chow (pellets) or a liquid food mixture made according to the recipe given by Teitelbaum & Epstein (1962) from a 35 cc. food cup located in the center of the testing box. Subjects were allowed an additional hour to eat on a feeding stand before being returned to their home cages. By the fifth day, subjects ingested most of their daily intake in the testing box. Food was again made available in the home cages following the final day of adaptation. Subjects were allowed at least two days to readjust to the ad libitum feeding schedule before the screening procedures were initiated.

Screening

One hour before the beginning of the testing session the subject was placed in an alternate testing box in which pellets and liquid food were available. Subjects generally consumed 5-10 cc. of the liquid mixture during this period, although food was now continuously present in their home cages. At the end of the hour the rat was removed to the testing box and stimulation leads were attached to the right or left electrode. After approximately 10 min. had elapsed, the first stimulation trial was initiated.

A trial consisted of an 18-sec. pre-stimulation period followed by an 18-sec. period of electrical stimulation. Trials were timed automatically, but had to be initiated manually. A trial was not begun if a subject was spontaneously eating; and if a subject began eating during the pre-stimulation period the trial was terminated.

On the first trial the current was set at 20 microamp. If no eating occurred the current for the next trial was increased by 10 microamp. As long as no food-directed responses or other stimulation-

linked behaviors such as escape or circling occurred, the current was raised sequentially in 10 microamp. steps to 200 microamp., then by 20 microamp. steps to 520 microamp., and finally by 40 microamp. steps to a maximum of 800 microamp. If circling or escape responses were observed the trial was terminated. When eating or other food-related responses such as pellet-carrying were elicited, repeated trials were given until the behavior occurred at least 10 times within 20 trials.

Threshold Tests

To assure satiety, subjects were offered liquid food and pellets in an alternate testing box for a half-hour period prior to the threshold test.

A "threshold session" consisted of two blocks of stimulation trials, each block containing one ascending and one descending series of trials. Beginning at a current intensity several steps below the level at which eating was elicited in the screening test, the current was increased on every succeeding trial by the current steps used in the screening test. The ascending series continued until eating was elicited in three separate, but not necessarily consecutive, trials. Following the last ascending trial, the current was decreased trial-by-trial until eating failed to occur on three consecutive trials. The ascending-descending sequence was then repeated. The feeding threshold for a given session was calculated as the arithmetic mean of the lowest current intensity at which eating occurred in each of the four (two ascending and two descending) series of trials.

When the subject ate during a stimulation trial, the type of food eaten was recorded (liquid food or pellets), the amount of time spent

eating within the 18-sec. stimulation period was recorded on a manually-operated electronic clock (Hunter, Model 128), and the current intensity was noted.

A second measure, "performance", was based on the persistence of eating. The performance score for a threshold session was calculated as the average number of seconds spent feeding during trials where the current intensity was at or above threshold.

Eating thresholds were determined daily for nine days. If each of the last three daily thresholds varied less than 15% from the mean of the three, the threshold was said to have stabilized, and the subject was assigned randomly to ablation or sham control group. Subjects not meeting this criterion were tested on additional days until the criterion for stabilization was met; this usually meant two or three additional days.

Postoperative Threshold Tests

Two schedules, A and B, were used in conducting tests of the postoperative eating thresholds (Table 1). In schedule A, subjects were tested on each of the six days following the first operation and for three days following the second stage, and, after a four-day period of no testing, were tested again for three days. This sequence of testing was used to evaluate the effect of unilateral ablations on feeding thresholds, as well as to test for short term effects of bilateral ablations. In schedule B, eating thresholds were not measured until the eighth day after the second operation. Subjects were then tested for three days, given a four-day rest and were retested for an additional three days. The second schedule was adopted to evaluate

the effects of bilateral ablations after a longer period of post-operative recovery. Note that every subject was tested at least six times following the second ablation, and that on three of those days (Days 8-10) all subjects were tested in common.

Histology

At the completion of the experiment subjects were deeply anesthetized with Nembutal and were perfused intracardially with normal saline followed by a 10% formalin solution. The perfused brains were immediately removed and stored in formalin for at least one week, following which they were transferred to a 30% solution of sucrose and formalin and soaked an additional two to four days before sectioning on a freezing microtome.[3] Sections were cut at 40 micra in the same frontal orientation as described in the König and Klippel (1963) atlas. Every fifth section through the ablated area and every second one through the region of the electrode tips were mounted and stained alternately for cell bodies and fiber tracts with thionin and hematoxylin respectively.

Stained sections at 0.5-1.0 mm. intervals through the ablation were matched to a set of standard frontal diagrams redrawn from König and Klippel (1963). With the aid of a light projector, the ablation boundaries were traced onto the appropriate diagrams. Included within the boundaries were all cortical areas that were removed directly, all areas where secondary vascular damage caused degeneration or changes in coloration of the stained tissue, and all cortex that was clearly undercut and thereby functionally isolated by the ablation.

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[3] Sucrose reduces the formation of ice crystals during freezing so that the tissue may be successfully cut over a wider temperature range.

An estimate of the volume of damaged tissue in each hemisphere was made in the following manner. With a planimeter, the cross-sectional area within the boundaries of the ablation was measured in each frontal diagram. To obtain a volume estimate, the average cross-sectional area was multiplied by the maximum anterior-posterior dimension of the ablation.

To determine the topographic localization of the ablation, standard diagrams of the dorsal and lateral aspects of the cortex were reconstructed from the frontal plane diagrams of König and Klippel (Appendix B). The Brodman areas of the cortex were redrawn from Krieg (1947). Coordinates for the ablation boundaries were measured from the frontal diagrams and replotted onto the cortical diagrams.

Statistical Treatment of the Data

Since potentially-independent variation could be measured in a number of dimensions, such as electrode locations within the hypothalamus, ablation volume, location, etc., a multiple regression method appeared to be most appropriate for assessing the interrelations of the various dependent and independent measures.

Quantification of the Data

Dependent measures. The threshold and performance data for each postoperative session were expressed in terms of the percentage of the mean preoperative values as determined in the last three threshold sessions. Postoperative body weight was expressed as the percentage of the weight on the day of the first stage operation. Where statistical procedures called for a single measure of postoperative change in each

dependent variable, the percentage scores for appropriate sessions were averaged. Thus, to test unilateral ablation effects, the percentage scores for postoperative days 1-6 (Stage I) were averaged, and for bilateral effects, the percentage scores were averaged for postoperative days 8-10 (Stage II) only, since on these days (8, 9, and 10) the two testing schedules overlapped.

Independent measures. Cortical ablations were scaled in two ways. First, each ablation was described by the percentage of total cortical volume destroyed. This measure "total cortex", was included to assess the importance of ablation size regardless of location. The second scaling method expressed the ablation in terms of the percentage of destruction that occurred in each of four cortical regions, and was included to assess cortical specificity with respect to the ablation effects. The four areas were frontal, parietal, temporal, and occipital cortex. These regions have been associated with motor, somatosensory, auditory, and visual functions, respectively, on the basis of stimulation and evoked potential studies (Woolsey, 1958). The boundaries of these four regions are shown in Figure 2.

In order to quantify electrode location, the distances between an electrode tip and three reference planes were measured. The distances anterior to stereotaxic zero (antereo-posterior plane), dorsal to the ventral margin of the medial forebrain bundle (dorso-ventral plane), and lateral to the midline (medio-lateral plane) were measured from the projections of the electrode tips onto the frontal plane drawings of König and Klippel (1963). A fourth measure "net deviation", was the distance between an electrode tip and the center of the sample distribution of all positive sites (determined by the medians of the other

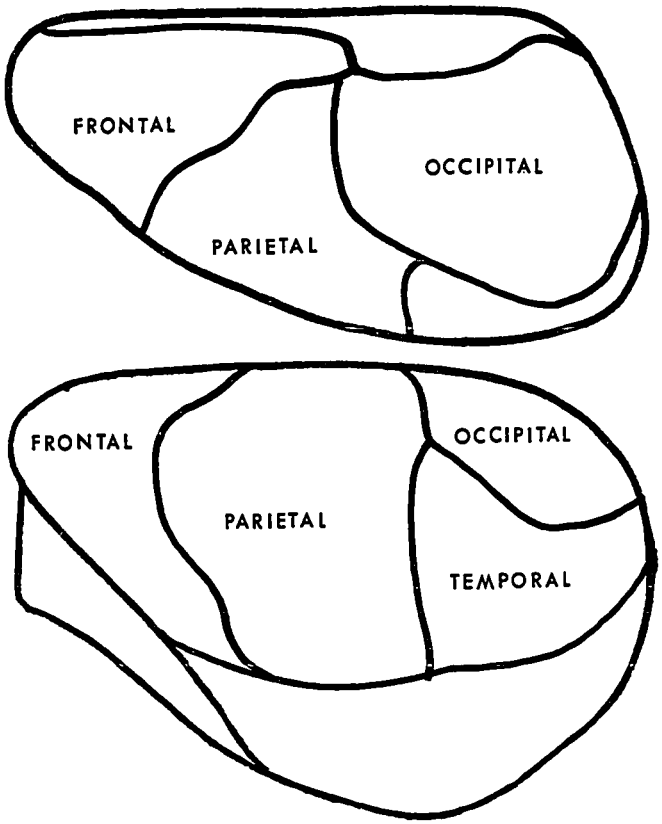

Figure 2. Boundaries of the four cortical regions.

three dimensions) and was calculated trigonometrically. A fifth measure was used only for analysis of unilateral ablation effects. This measure, "laterality", specified the stimulated hemisphere relative to the side of the ablation. Electrodes contralateral to the ablation were scored "0" and those ipsilateral were scored "1". All five electrode measures were treated statistically as separate variables.

Three additional variables, "testing schedule", "preoperative threshold", and "preoperative performance" were also included to assess the effect of the two postoperative schedules and to control for differences in preoperative levels of the dependent measures. All electrodes tested according to schedule A were assigned a score of "0" and those tested by B, a score of "1". Preoperative threshold and performance consisted of these respective scores averaged over the last three preoperative sessions.

Statistical Analyses

The variables used in each analysis are shown in Table 2. A multiple regression technique was used to determine the degree of relationship between certain classes of independent variables and a dependent variable, with the influences of other "uncontrolled" variables held constant. For example, the relationship between the five ablation measures (total, frontal, parietal, temporal, and occipital) and postoperative feeding threshold might have been complicated by the uncontrolled differences in the location of the stimulation electrodes. Since these potentially interactive influences could be evaluated by calculating their degree of correlation with postoperative threshold, their effect could therefore be controlled statistically by using a partial correlation technique.

TABLE 2

Variables Used in the Multiple Regression Analyses

Independent Measures	Dependent Measures				
	Thresh. Change		Perf. Change		Body Wt.
	Unilat.	Bilat.	Unilat.	Bilat.	Bilat.
Ablation Variables					
Total	x	x	x	x	x
Frontal	x	x	x	x	x
Parietal	x	x	x	x	x
Temporal	x	x	x	x	x
Occipital	x	x	x	x	x
Elec. Location Variables					
Antereo-Posterior	x	x	x	x	
Dorso-Lateral	x	x	x	x	
Medio-Lateral	x	x	x	x	
Net Deviation	x	x	x	x	
Laterality	x		x		
Additional Variables					
Test Schedule (A, B)		x		x	
Preoperative Thresh.		x		x	
Preoperative Perf.		x		x	

The strategy of the analysis was to first remove that portion of the total variance in the dependent variable which could be attributed to "uncontrolled" variables. The degree of relationship between the residual or "unexplained" variance and a class of independent measures (e.g., the ablation variables) was then examined.

A stepwise multiple regression method (Draper & Smith, 1966) was used to detect the relevant sources of uncontrolled variation for a given analysis. Briefly, stepwise multiple regression is a computerized variation of standard multiple regression. "Stepwise" refers to the manner in which the regression equation is constructed. At each "step" one variable is added to the regression equation. The variable added is the one that makes the greatest reduction in the error sum of squares; that is, the one with the highest F value. Following each step the computer printed out the variable that was added and its associated F value as well as the partial correlation for those variables not included in the regression equation and their associated F values.

The variables entering the equation were limited to those which produced a reduction in the error sum of squares meeting a criterion for a minimum F value. In general, it is desirable that the regression equation not be overburdened by superfluous variables, since each additional variable in the equation reduces the number of degrees of freedom in the residual by one. In the present application of this technique, the F criterion for inclusion into the regression equation was 1.00. The uncontrolled variables not reaching criterion were deleted from the analysis.

Following the last step of the analysis all of the uncontrolled variables were either in the regression equation or had been deleted.

In the example cited above, these variables would be the five electrode location measures. The variables not in the equation would be the five ablation measures. The partial correlation coefficient for each of these variables represented the degree to which it was correlated with the residual variance in threshold.

In some analyses it was advantageous to continue the program for one or two additional steps in order to partial out intercorrelations between variables not in the equation. These steps will be noted in the Results section.

When the results of the regression analyses indicated that only certain variables were important (e.g., ablation size), subjects were divided into groups on the basis of this variation and the dependent variable was assessed for each postoperative session by a two-way analysis of variance for repeated measures on one factor (Winer, 1962). This secondary analysis served as a check on the reliability of the regression findings since in the first analysis the dependent measures of threshold, performance, and body weight were each expressed as single measures averaged over a limited postoperative period.

Finally, differences between pre- and postoperative thresholds and performance were assessed for each group separately by t-tests for correlated means.

III

RESULTS

Positive electrode placements were obtained in 84 rats. Of these, 9 died as a result of subsequent surgical procedures, and 7 were sacrificed when their electrode assemblies were accidentally loosened. For the 68 remaining animals, gross examination and histological analyses were made to determine that (1) the electrode assembly was firmly in place at the time of sacrifice, (2) any damage to subcortical structures (caudate, hippocampus, amygdala) was minimal, and (3) no obvious signs of neural infection were present. By these criteria 12 subjects were rejected from further analysis.

The results are therefore based on 56 subjects, 36 of which received cortical ablations and 20 which served as sham operated controls. Since about one-third of the subjects had two positive electrodes, data were obtained from 48 electrodes in animals receiving ablations and from 32 in animals undergoing sham operations.

Location of Electrode Tips

The anatomical locations of positive stimulation sites and a number of neutral sites are reconstructed in Figure 3. Electrode locations for individual subjects can be found in Appendix C. Although feeding was elicited from wide ranging points, there was a marked concentration of positive sites along the medial border of the medial forebrain bundle adjacent to the fornix. There were no significant correlations between the four electrode-location measures and threshold or performance (Table 3). Thus, the level of the preoperative threshold

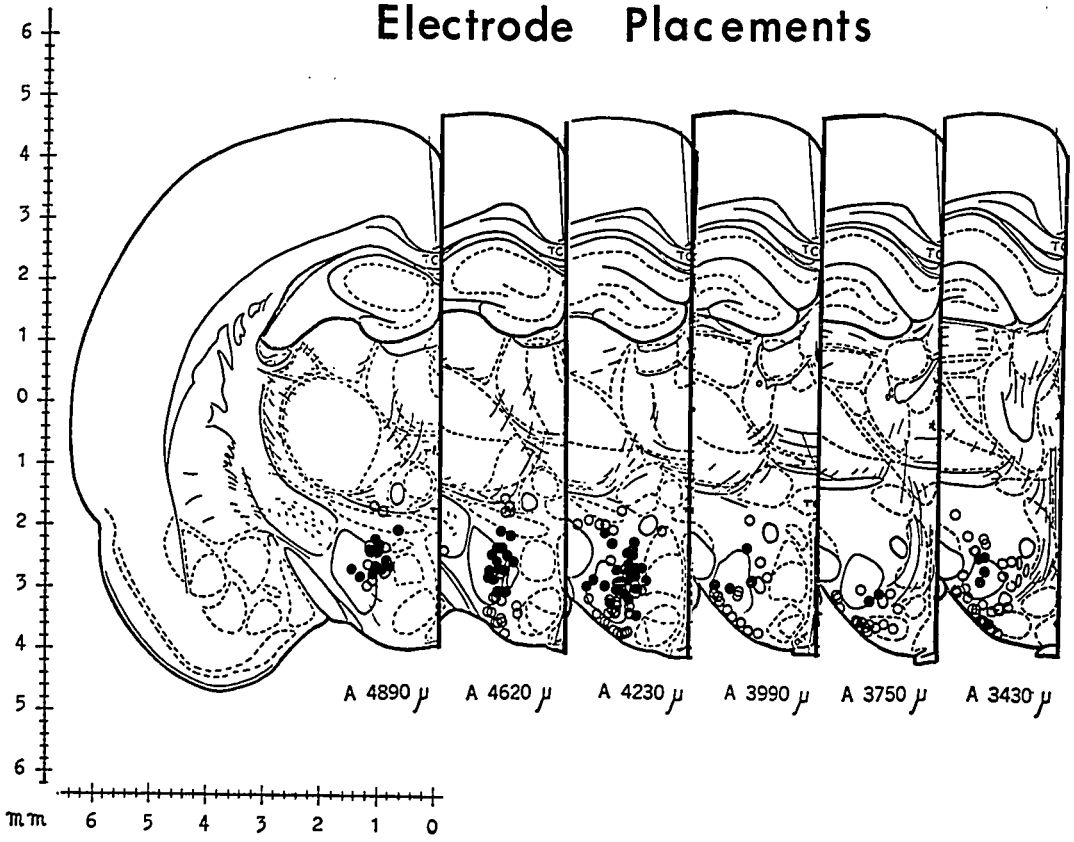

Figure 3. Anatomical locations of positive (filled circles) and neutral (open circles) electrode placements. (Figures redrawn from Konig and Klippel (1963).

Table 3

Correlations between Threshold, Performance,

and Four Electrode Location Measures.

Variable		T	P	D-V	M-L	A-P	ND
Threshold	(T)	1.000	-.331	.173	-.073	-.106	-.003
Performance	(P)		1.000	.017	.008	.116	-.196
Dorsal-Ventral	(D-V)			1.000	-.369	.201	.000
Medio-Lateral	(M-L)				1.000	-.169	.146
Anterior-Posterior	(A-P)					1.000	-.103
Net Deviation	(ND)						1.000

or performance appeared to be unrelated to variation in the location of the stimulating electrodes within the hypothalamic region sampled.

Preoperative Responses to Electrical Stimulation

Initially, stimulation evoked a wide range of food-related responses. For example, during screening and the first few threshold tests, 12 rats ate only food pellets and not the liquid food. Two rats ate only small pellet crumbs; and 4 ingested no food but each of the 4 picked up a pellet with its mouth during stimulation. As testing continued all but 4 subjects (A2R, A4L, A5LR, B26L)[4] switched their preferences so that by the end of the preoperative testing sessions liquid food was preferred.

On the first day of testing the median threshold for all electrodes was 117 microamp. and ranged between 30 and 550 microamp. By the final day of preoperative testing the median had dropped to 75 microamp., but the range remained about the same, 35 to 485 microamp. Marked decreases in feeding threshold were observed in eight animals. No sustained threshold increases were observed during testing.

This reduction in threshold was specific to feeding behavior since the minimal current levels for the induction of alerting and/or exploratory behavior were largely unchanged. Threshold decreases were often, but not always, associated with a shift in preference to the liquid diet from pellets, and to an increase in performance.

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[4] The following nomenclature was used to describe individual subjects and their electrodes. "A" or "B" refers to testing schedule, the numeral refers to the subject; and "L" and "R" designates whether the positive electrode was on the left, on the right, or on both.

A few subjects with two positive electrodes responded differently to stimulation depending on which electrode was tested. For example, subject A12LR initially ate food in pellet form when stimulated on the left, and liquid food when stimulated on the right. Another subject, A15LR, ate only liquid food when stimulated on the left and licked the cage floor and walls when stimulated on the right. After two to four sessions, however, both animals consistently ingested liquid food when either electrode was tested. For the last three preoperative sessions the correlation between electrode pairs in terms of threshold and performance values were .72 and .70 respectively ($p < .01$).

Distribution of Cortical Ablations

Figure 4 illustrates the degree of overlap in the ablation sample. Reconstructions of the individual ablations can be found in Appendix D. The total percentage of cortical damage and percentages of frontal, parietal, temporal, and occipital cortex damage are listed for each subject separately in Appendix E.

The sample included both large and small ablations and almost all neocortical regions were represented. Due to the restrictions imposed by the electrode assembly those areas most accessible to surgical manipulation tended to be the areas most often damaged. Fronto-lateral areas were most frequently damaged followed by mid-lateral and posterior areas. Ablation size (volume) measured bilaterally ranged from a minimum of 0.4% (subject A7R) to a maximum of 43.0% (subject B31R).

The damage was confined to the neocortex with the exception of two animals (A13L, A14LR) where the ablation overlapped into part of the cingulate cortex and cingulum bundle on one side. Most ablations, and

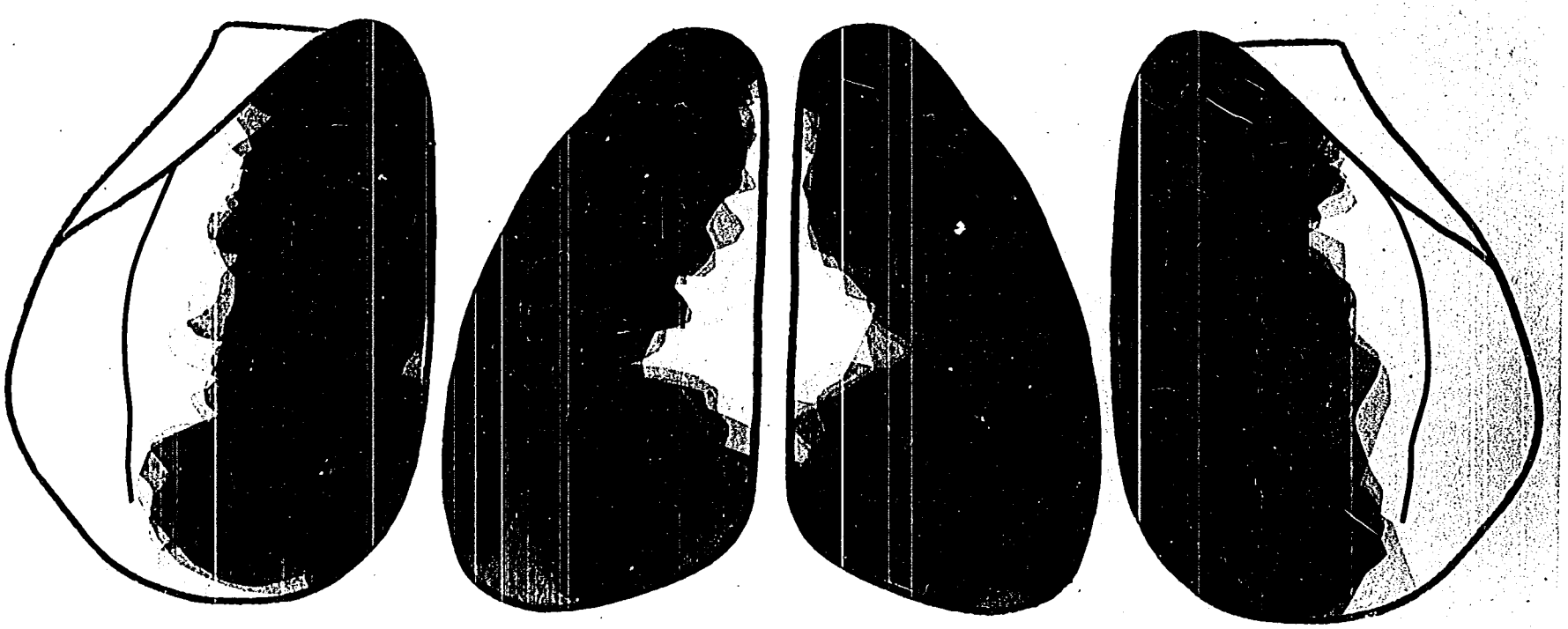

Figure 4. Degree of overlap of cortical ablations.

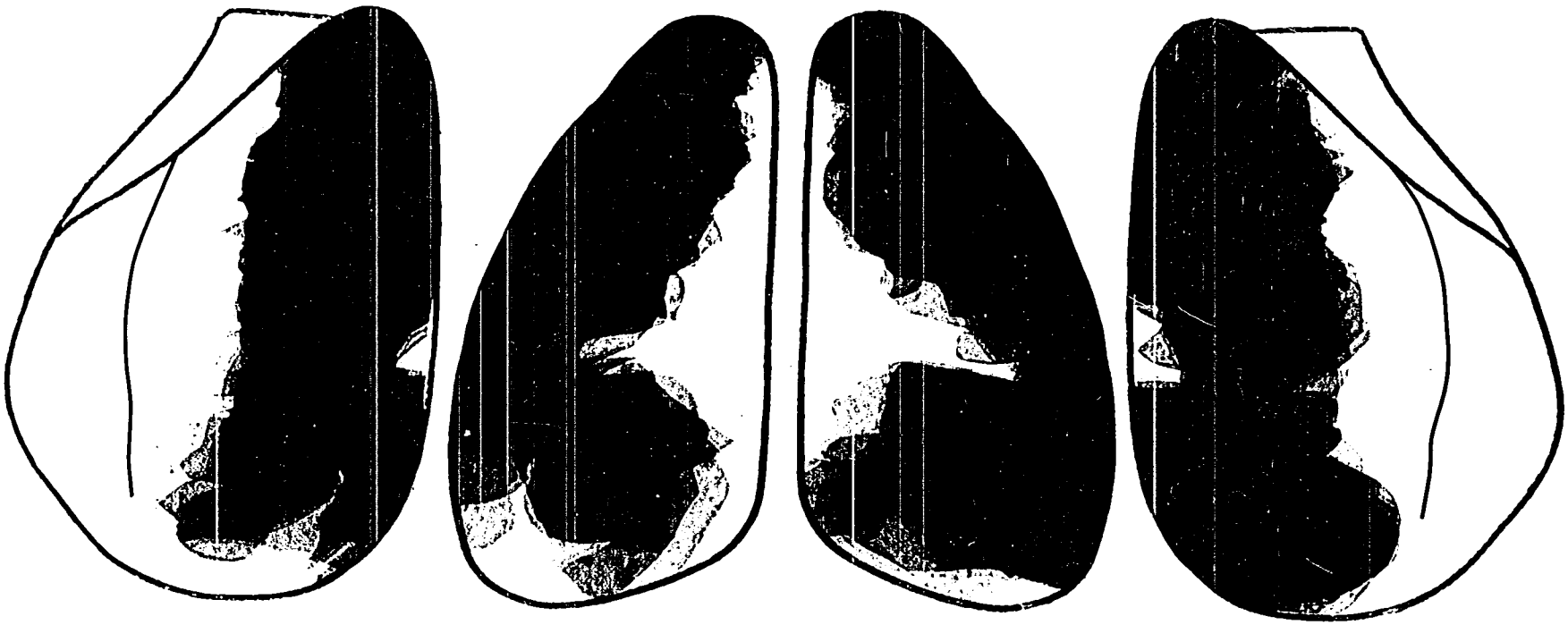

Figure 4. Degree of overlap of cortical ablations.

especially the larger ones, extended into the deepest cortical layer and corpus callosum. In this case fibers of passage were damaged, and the area of functional disruption was therefore larger than is indicated by the values in Appendix E. Figure 5 illustrates the depth of a typical ablation in serial cross sections.

Unilateral Ablations: Threshold and Performance Changes

On each of the six days between the first and second stage of the operations, 15 ablated subjects and 9 sham-ablated subjects were tested. In the ablation group, data were obtained from 24 electrodes in the sham group from 15 electrodes.

Postoperative feeding thresholds for ablated subjects were generally higher than their preoperative levels (Mean = 169.65% of preoperative threshold) while performance was slightly reduced (Mean = 95.05% of preoperative performance). Two subjects, A4L and A1LR, did not eat in response to stimulation through one of their electrodes, for one and five days respectively. These subjects will be treated later in a separate section along with bilaterally ablated subjects with the same deficit.

Means and standard deviations for each of the dependent and independent variables in the multiple regression analyses appear in Appendix F. The intercorrelation matrix for these variables is presented in Appendix G.

Multiple regression analysis of unilateral ablation threshold data. The purpose of the first analysis was to determine whether the postoperative thresholds were best related to the total amount of destroyed cortical tissue or to the extent of destruction within one of

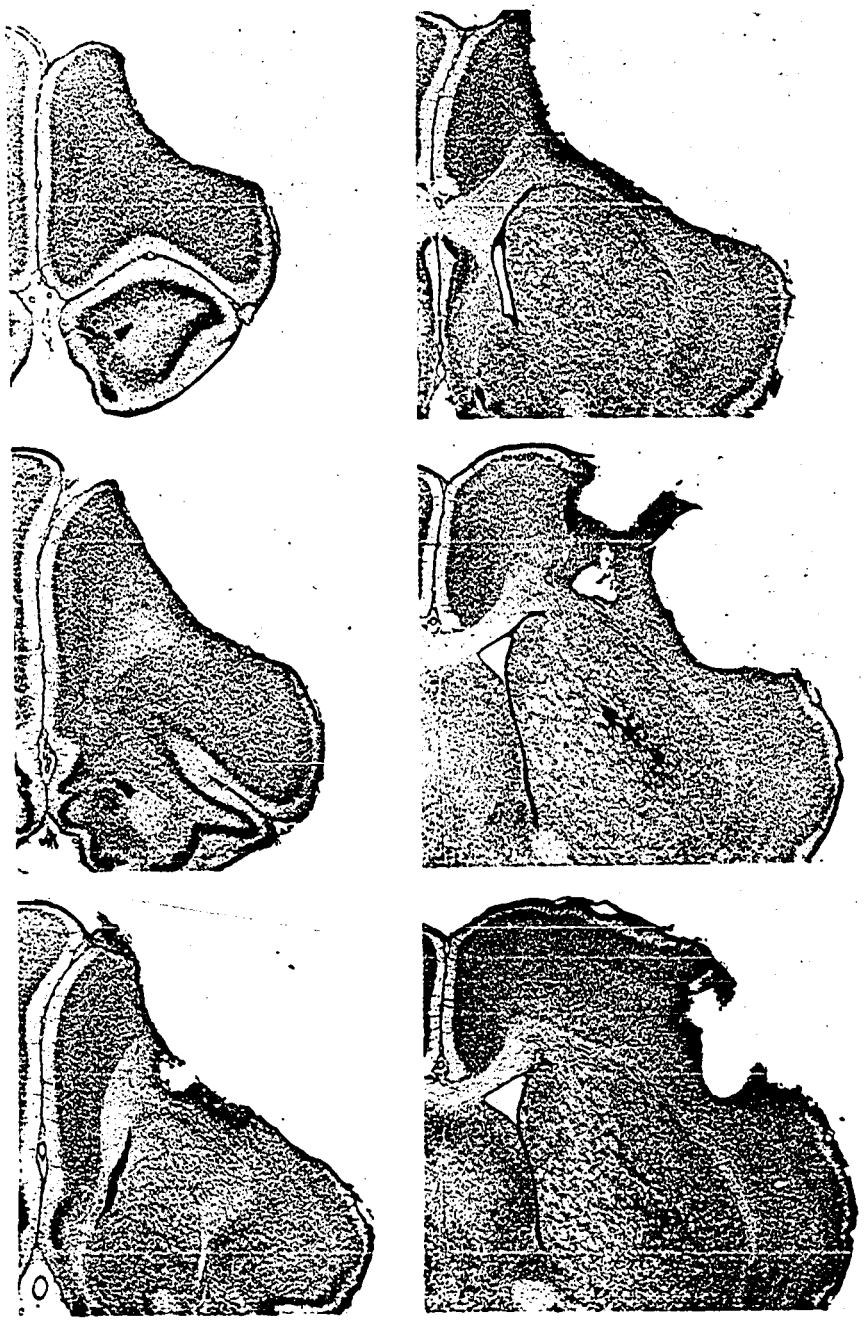

Figure 5. Cortical ablation in serial cross section.

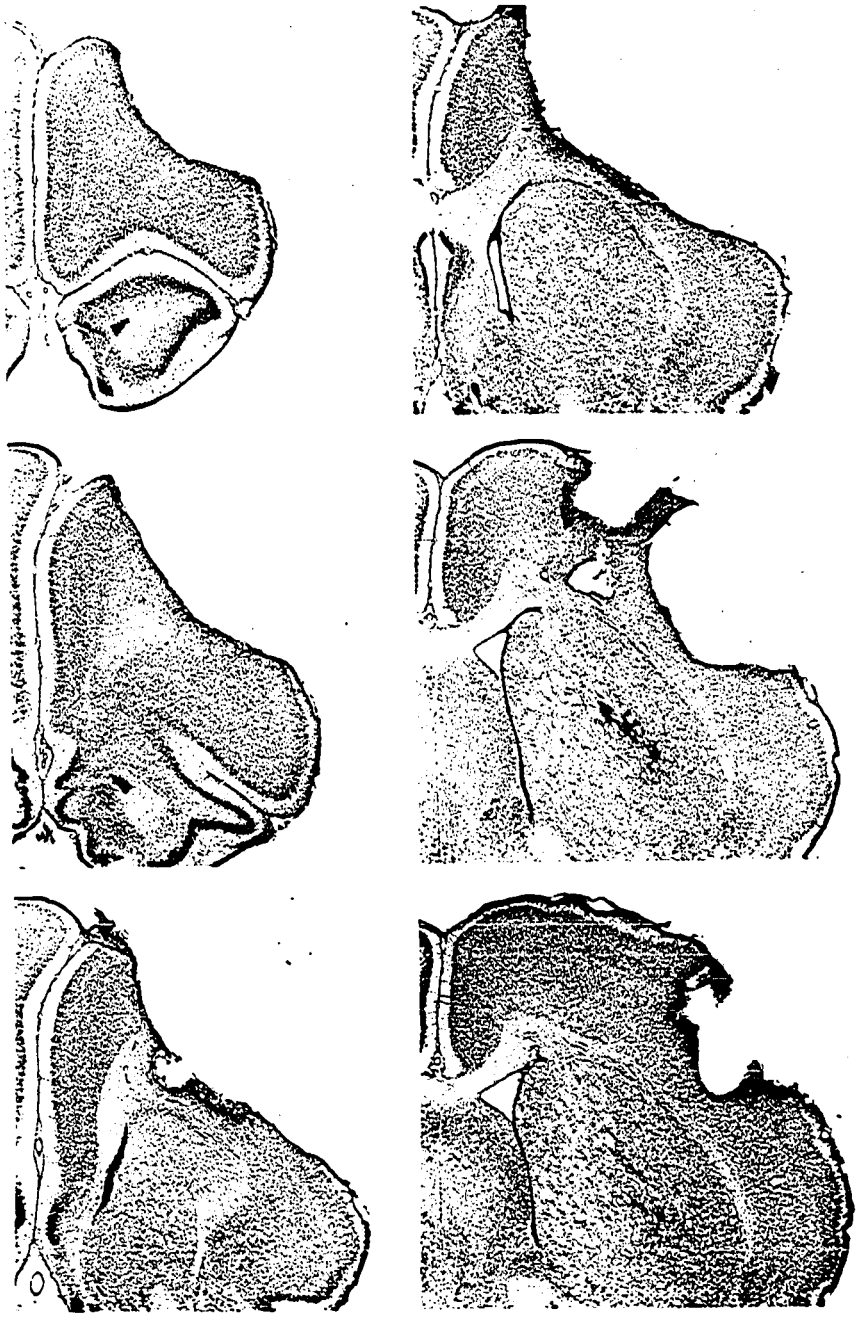

Figure 5. Cortical ablation in serial cross section.

four cortical regions (frontal, parietal, occipital, and temporal). To make this analysis it was necessary to partial out that portion of the variance in the threshold measure that could be attributed to variations in uncontrolled, nonablation measures. Potentially, these included the five electrode location measures (anterior-posterior, medial-lateral, dorsal-ventral, net deviation, and laterality).

Of the five nonablation variables sampled, only the dorsal-ventral variance ($F = 3.39$) met the criterion for inclusion in the multiple regression equation of "uncontrolled" variables. Thus, it was the only variable that was subsequently partialed out. It will be recalled that only those variables were included in the multiple regression equation that resulted in a reduction in the error sum of squares associated with an F ratio greater than 1.00.

The resulting correlation between the residual of the multiple regression and the five ablation measures is shown in Table 4a. Only the partial correlations for total damage ($r_{part} = 0.49$) and parietal damage ($r_{part} = 0.53$) were statistically significant ($p < .05$). The four regional measures of the cortical ablation were highly correlated with the measure of total cortical damage (Appendix G). In an additional step of the analysis the effect of these intercorrelations was controlled for by adding the total cortical damage variable to the regression equation.

Table 4b summarizes the results of this second step. As can be seen, when the influence of the total damage variable ($F = 5.29$) and dorso-ventral electrode location variable ($F = 2.73$) were accounted for, none of the four measures of damage in specific cortical areas were

TABLE 4

Variations in Threshold due to Variations in

Ablation Size and Location: Unilateral Ablation Data

a. Before adding Total to equation

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Dorso-ventral	3.39	Total	0.49	17	5.29*
		Frontal	0.32	17	1.91
		Parietal	0.52	17	6.55*
		Occipital	-0.16	17	0.50
		Temporal	-0.01	17	0.00

b. After adding Total to equation

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Dorso-ventral	2.73	Frontal	-0.11	16	0.15
Total	5.29	Parietal	0.25	16	0.81
		Occipital	-0.00	16	0.00
		Temporal	-0.14	16	0.22

Variables Deleted: Anterior-Posterior, Medio-Lateral, Laterality, Net Deviation.

*$p > .05$

significantly correlated with threshold change. This analysis indicated that (1) thresholds increased in proportion to the total amount of cortex damaged and (2) there was no relationship between damage in one of the specific cortical regions sampled that could not be attributed equally well to the size of the total ablation.

A second multiple regression analysis was performed to determine the degree of interaction between differences in electrode location and the observed relationship between the size of the ablation and threshold increase. For this analysis the correlation between the total damage variable ($F = 9.90$) and threshold was partialed out. The results (Table 5) show that none of the resulting partial correlations between the electrode location measures and residual variation in threshold were significant. These results indicated that the feeding thresholds at stimulation sites in either hemisphere were similarly affected by ablations as were those of divergent sites within the hypothalamus.

In order to further study the relationship observed between ablation size and threshold change, as well as to assess the threshold changes over time, the ablated subjects were divided into two groups; those with ablation greater than the median size were assigned to a large-ablation group and the remaining subjects were assigned to a small-ablation group. The mean thresholds for these two groups on each of the six postoperative sessions were then compared to the mean threshold of the sham-ablated subjects.

These data are presented graphically in Figure 6. Although the mean thresholds in the large-ablation group appeared to be much higher than those in the other two groups, the differences did not attain the .05 level of significance (Table 6). No doubt this was due to the

TABLE 5

Variation in Threshold due to Variations in

Electrode Location: Unilateral Ablation Data

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Total	9.90	Net Deviation	0.01	17	0.00
		Laterality	0.03	17	0.02
		Dorso-ventral	0.17	17	0.49
		Medio-lateral	-0.01	17	0.00
		Anterior-posterior	-0.05	17	0.04

Variables Deleted: Frontal, Parietal, Occipital, Temporal

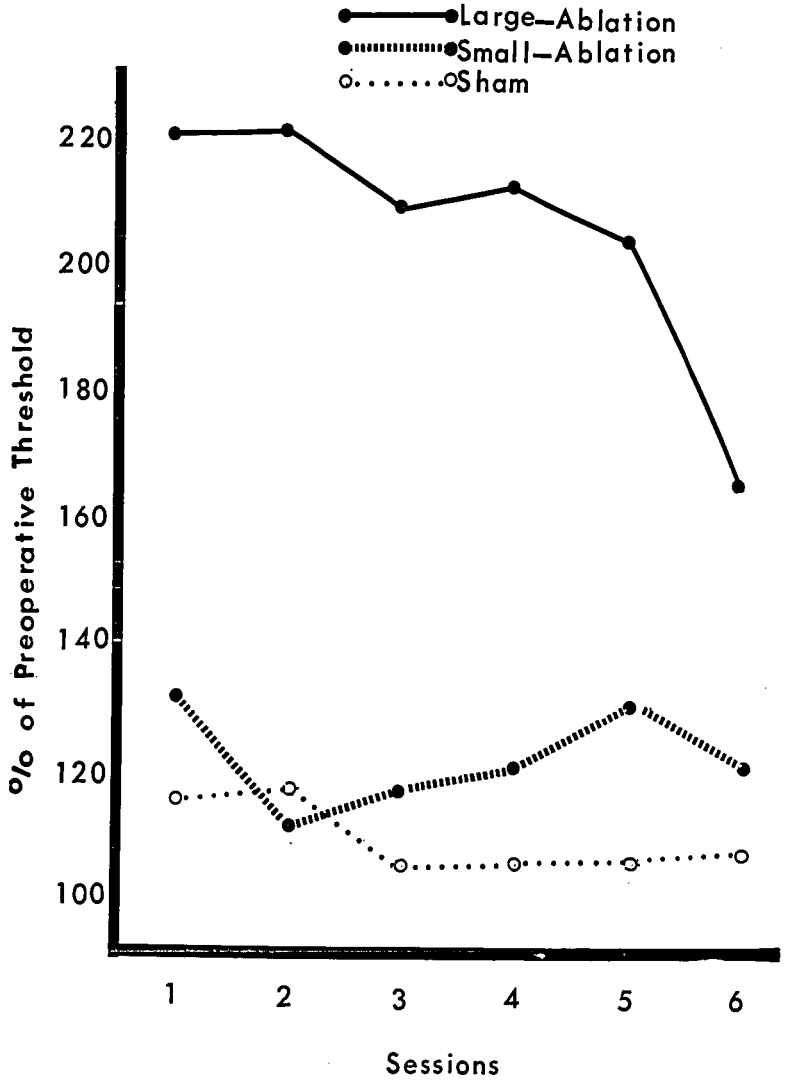

Figure 6. Mean thresholds across six postoperative sessions for subjects with large cortical ablations, small cortical ablations, and sham-ablated subjects: Unilateral ablation data.

TABLE 6

Two-Way Analysis of Variance of Postoperative Thresholds in Sessions 1-6 with Subjects Grouped According to Ablation Size: Unilateral Ablation Data.

Source	df	MS	F
Between subjects	36		
Groups (A)	2	196657.63	2.91
Subj. w. groups	34	67595.50	
Within subjects	185		
Sessions (B)	5	2514.39	2.60*
AB	10	2044.21	2.11*
B X subj. w. groups	170	967.06	

* $p < .05$

TABLE 7

Within Group Changes in Thresholds: Unilateral Ablation Data

Group	df	t Sessions 1-3	4-6
Large-abl.	10	2.27**	2.06*
Small-abl.	10	2.81***	1.76
Sham	14	0.63	0.34

* $p < .05$ ** $p < .025$ *** $p < .01$

extreme within-groups variance. However, the analysis did reveal both a significant sessions main effect ($p < .05$) and a significant sessions by groups interaction ($p < .05$). As can be seen in Figure 6, the elevated thresholds in the large-ablation group attenuated across sessions while those in the small-ablation and sham groups remained relatively unchanged.

Since these between-group comparisons were based only on postoperative scores no measure was provided of pre- to postoperative change within groups. In order to assess these changes, the mean thresholds for each group were evaluated separately by t-tests for correlated means (Table 7). Comparisons were made between the mean of the thresholds measured in the last three preoperative sessions and postoperative thresholds average over three-day blocks (sessions 1-3 and 4-6) separately. Both the large- and small-ablation groups showed a significant threshold increase between preoperative sessions and postoperative sessions 1-3 ($p < .02$ and $p < .01$, respectively). In the second block of sessions (sessions 4-6) only the thresholds for the large-ablation group remained elevated ($p < .05$). The mean threshold of the sham group remained unchanged.

Multiple regression analysis of unilateral ablation performance data. The relationship between postoperative performance and both total cortical damage and damage in the four cortical regions was assessed by the same statistical steps as were used in the preceding analysis of threshold change. The results are summarized in Tables 8a and 8b. After a preliminary step of partialing out the effect of variation in one electrode location (net deviation, $F = 1.21$), the highest correlate of performance was damage to the frontal cortex

TABLE 8

Variation in Performance due to Variations in Ablation Size and Location: Unilateral Ablation Data

a. Before adding Total to equation

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Net Deviation	1.21	Total	-0.29	17	1.53
		Frontal	-0.49	17	5.44*
		Parietal	-0.21	17	0.78
		Occipital	0.36	17	2.66
		Temporal	0.23	17	0.96

b. After adding Total to equation

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Net Deviation	1.01	Frontal	-0.53	16	5.78*
Total	1.33	Parietal	0.07	16	0.26
		Occipital	0.22	16	0.92
		Temporal	0.39	16	3.57

Variables Deleted: Anterior-Posterior, Laterality, Medio-Lateral, Dorso-Ventral

*$p < .05$

(r_{part} = -0.49, $p < .05$). When the effect of the total cortical damage variable was removed by adding that variable to the regression equation (Table 8b), the measure of frontal damage was still significantly correlated with performance (r_{part} = -0.53, $p < .05$). These results indicated that performance decreased in proportion to the amount of destruction to the frontal cortex while equal damage to other regions was less effective.

In a similar manner the importance of variation in electrode location was assessed by first partialing out the correlation between percent damage to the frontal cortex and performance. None of the resulting partial correlations between the electrode location measures and residual variation in performance were statistically significant (Table 9). Thus, the effect of frontal damage on performance appeared to be independent of variation in electrode location.

In order to further compare the relationship between frontal ablation size and performance change, and to study changes in performance over time, the ablated subjects were divided into three groups in accordance with the percentage of frontal involvement. Those subjects with ablations not involving the frontal cortex were assigned to a non-frontal group; those with greater than median frontal damage were assigned to a large-frontal group; and the rest were formed into a small-frontal group. The mean performance scores for these groups and for sham-ablated subjects were then compared over the six postoperative sessions. These data are presented in Figure 7. The analysis is summarized in Table 10. The only significant finding was in the groups main effect ($p < .05$): the large-frontal group had lower mean performance scores than the other groups.

TABLE 9

Variation in Performance due to Variations in Electrode Location: Unilateral Ablation Data

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Frontal	5.72	Net Deviation	0.20	17	0.72
		Laterality	-0.04	17	0.03
		Dorso-ventral	0.19	17	0.65
		Medio-lateral	0.02	17	0.01
		Anterior-posterior	-0.01	17	0.00

Variables Deleted: Total, Parietal, Occipital, Temporal

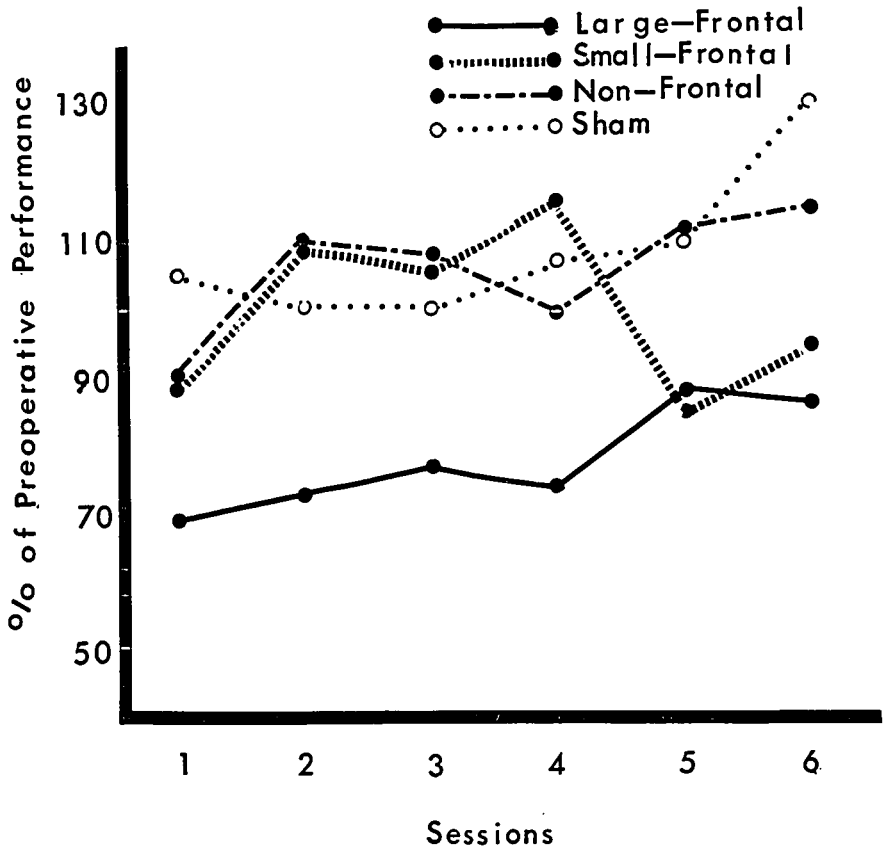

Figure 7. Mean performance across six postoperative sessions for subjects with large-frontal, small-frontal, non-frontal, and sham ablations: Unilateral ablation data.

Comparison of pre- to postoperative performance within groups (Table 11) revealed a significant decrease ($p < .05$) in the large-frontal group from preoperative performance in the first three-day block of postoperative sessions but not the second. The other three groups were not impaired, and in fact, the non-frontal group showed a substantial elevation in performance in the second block of post-operative sessions ($p < .05$).

Bilateral Ablations: Threshold and Performance Change

In six out of the 36 subjects tested following second stage ablation, electrically-elicited feeding was selectively abolished in one or both electrodes for periods ranging from one day to the time the animals were sacrificed 30 days later. These subjects will be described in a separate section. The remaining ablated subjects as a group showed an increase in threshold (mean = 130.20% of preoperative threshold) and a reduction in performance (mean = 94.26% of preoperative performance). The means, standard deviations and intercorrelations of the independent and dependent variables for these subjects can be found in Appendix H. The intercorrelation matrix for these variables is presented in Appendix I.

In general, the bilateral ablation data were treated statistically in the same manner as the unilateral ablation data. Three new variables were added to the analysis: testing schedule (schedule A and schedule B), preoperative threshold, and performance. The preoperative threshold variable was used only in the analysis of threshold change and the preoperative performance variable was used only in the analysis of performance change.

TABLE 10

Two-Way Analysis of Variance of Postoperative Performance in Sessions 1-6 with Subjects Grouped According to Extent of Frontal Cortex Damage: Unilateral Ablation Data.

Source	df	MS	F
Between subjects	34		
Groups (A)	3	8347.50	3.33*
Subj. w. groups	31	2507.84	
Within subjects	175		
Sessions (B)	5	1102.60	1.51
AB	15	805.83	1.10
B X subj. w. groups	155	729.92	

* $p < .05$

TABLE 11

Within Group Changes in Performance: Unilateral Ablation Data.

Group	df	t values	
		Sessions 1-3	4-6
Large-FC	6	3.2907**	1.3723
Small-FC	5	0.7142	0.2921
Non-FC	6	0.0220	2.7657*
Sham	14	0.6054	1.5299

* $p < .05$ ** $p < .01$

Multiple regression analysis of bilateral ablation threshold data. Table 12 summarizes the results of the analysis of the relationship between postoperative threshold and both total damage and damage to the four cortical areas. After a preliminary step of partialing out the effect of variation due to the dorsal-ventral electrode location variable ($F = 9.21$) and testing schedule variable ($F = 5.65$), the resulting partial correlations between the dependent variable (threshold) and the five ablation variables were negligible. Thus, the results indicated that variation in total ablation size had no bearing on the extent of threshold change nor did the degree of damage to any of the four cortical regions.

The results of a second analysis evaluating the relationship between postoperative threshold and electrode location are summarized in Tables 13a and 13b. The effects due to variation in testing schedule ($F = 6.48$) were partialed out resulting in significant partial correlations between threshold and variation in both the dorsal-ventral ($r_{part} = 0.45$, $p < .01$) and medial-lateral ($r_{part} = -0.42$, $p < .02$) electrode location dimensions.

The possibility exists that these latter two measures were not independent. Therefore, a single new variable based on deviations along a combined dorsal-medial and ventral-lateral axis (DM/VL) was constructed. To test whether this new single variable would account for the results attributed to both the medial-lateral and dorsal-ventral measures the analysis was rerun with this new variable added to the regression equation (Table 13b). The resulting partial correlations for dorsal-ventral and medial-lateral measures were low and

TABLE 12

Variation in Threshold due to Variations in Ablation Size and Location: Bilateral Ablation Data

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Dorsal-ventral	9.21	Total Cortex	0.11	31	0.35
Schedule	5.65	Frontal Cortex	0.04	31	0.05
		Parietal Cortex	-0.02	31	0.01
		Occipital Cortex	0.15	31	0.75
		Temporal Cortex	0.03	31	0.03

Variables Deleted: Preop. Threshold, Medio-Lateral, Anterior-Posterior

TABLE 13

Variations in Threshold due to Variations in Electrode Location: Bilateral Ablation Data

a. With four electrode location variables

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Schedule	6.48	Net Deviation	-0.21	32	1.53
		Dorso-ventral	0.45	32	8.12
		Medio-lateral	-0.41	32	6.70
		Anterior-posterior	-0.24	32	1.90

b. With DM/VL replacing Dorso-Ventral and Medio Lateral

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Schedule	6.48	Net Deviation	-0.21	32	1.53
		Anterior-posterior	-0.24	32	1.90
		DM/VL	0.47	32	9.21

Variables Deleted: Total, Frontal, Parietal, Occipital, Temporal, Preop. Threshold.

nonsignificant indicating that the DM/VL measure best accounted for the relevant variation in these two measures. These findings indicated that threshold increases were larger when the stimulation sites were in the dorsal and medial part of the sample distribution.

A third regression analysis tested whether threshold change was influenced equally when subjects were tested by schedule A as when they were tested by schedule B. The results shown in Table 14 indicate that after the differences in electrode location as measured by DM/VL ($F = 10.83$) and differences in preoperative threshold ($F = 1.22$) were partialed out, the remaining variation in postoperative threshold was significantly correlated with the testing schedule variable ($r_{part} = -0.36$, $p < .05$). This finding indicated that subjects tested according to schedule A showed a greater increase in threshold than those tested by schedule B regardless of their preoperative thresholds or electrode locations.

In order to compare the thresholds of ablated and sham-ablated subjects in the six postoperative sessions, the data were divided into four ablation groups and four sham groups on the basis of electrode location and testing schedule--the two variables best associated with threshold change. The electrodes of sham and ablated subjects combined were first divided into a dorsal-medial and ventral-lateral electrode group according to their anatomical location relative to the sample median for this dimension. Each of these two groups was further sub-divided into ablation and sham-ablation groups, and these in turn were dichotomized according to testing schedule (schedules A and B). The mean threshold change scores for each group in each postoperative session

TABLE 14

Variations in Threshold due to Variations in Testing Schedule: Bilateral Ablation Data

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
DM/VL	10.83	Schedule	-0.36	31	4.76*
Initial Thresh.	1.22				

Variables Deleted: Total, Frontal, Parietal, Occipital, Temporal, Anterior-Posterior, Net Deviation

*$p < .05$

are shown in Figure 8 and the analysis of variance for these data is summarized in Table 15. The only significant finding was a groups main effect ($p < .01$). The ablated subjects tested by schedule A in which stimulation occurred at dorsal-medial sites had greater threshold increases than the other seven groups.

As in the case of the unilateral analyses, differences between pre- and postoperative thresholds within each group were evaluated by t-tests (Table 16). These comparisons revealed significant threshold increases in the schedule B, dorsal-medial electrode ablation group (Abl/D-M/B) in the first and second three-session block ($p < .02$ and $p < .01$, respectively) and a significant increase in the schedule A, dorsal-medial electrode ablation group (Abl/D-M/A) in the second three-session block ($p < .05$).

In summary, bilateral ablations resulted in significant threshold increases only in subjects where stimulation sites were located in the dorsal-medial part of the sample. These effects were generally more marked in subjects tested by schedule A, that is, those subjects tested between the two stages of the ablation and immediately following the second stage. The mean thresholds of sham groups with comparable electrode locations were unchanged.

Multiple regression analysis of bilateral ablation performance data. Table 17 summarizes the results of the analysis of the relationship between change in performance and both total damage and damage to the four cortical areas. After a preliminary step of partialing out the effect of variation due to the anterior-posterior location variable ($F = 1.47$) the only significant correlate of postoperative performance

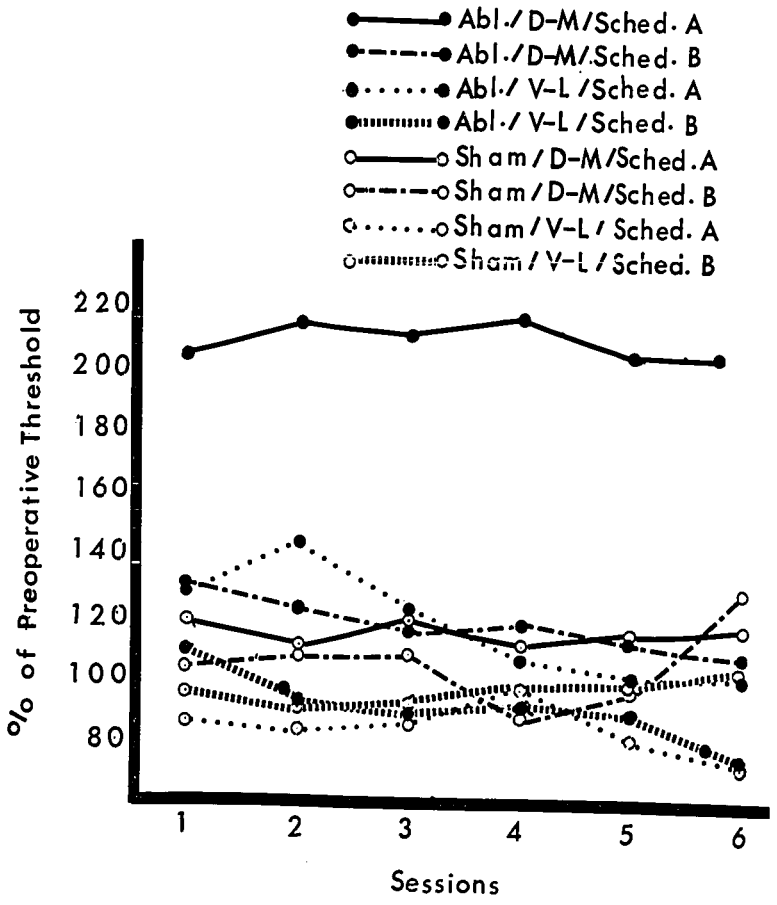

Figure 8. Mean thresholds across six postoperative sessions for ablated and sham-ablated subjects divided according to schedule and electrode placement: Bilateral ablation data.

TABLE 15

Two-Way Analysis of Variance of Postoperative Thresholds in Sessions 1-6 with Electrodes Grouped According to Location and Testing Schedule

Source	df	MS	F
Between subjects	66		
Groups (A)	7	62755.63	6.85**
Subj. w. groups	59	9156.84	
Within subjects	335		
Sessions (B)	5	199.09	0.50
AB	35	454.09	1.14
B X Subj. w. groups	295	399.67	

** $p < .01$

TABLE 16

Within Group Changes in Threshold: Bilateral Ablation Data

Groups	df	t Sessions: 1-3	t Sessions: 4-6
Ablat.-Dorsal-A	5	1.85	2.63*
Ablat.-Dorsal-B	10	3.05**	3.82***
Ablat.-Ventral-A	6	1.53	0.36
Ablat.-Ventral-B	10	0.10	2.03
Sham-Dorsal-A	10	0.35	0.29
Sham-Dorsal-B	4	0.69	1.87
Sham-Ventral-A	3	0.61	1.03
Sham-Ventral-B	11	0.81	0.24

* $p < .05$ ** $p < .02$ *** $p < .01$

TABLE 17

Variation in Performance due to Variations in Ablation Size and Location: Bilateral Ablation Data

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Anterior-posterior	1.47	Total	0.03	33	0.02
		Frontal	-0.53	33	12.78*
		Parietal	0.12	33	0.50
		Occipital	0.16	33	0.88
		Temporal	0.05	33	0.07

Variables Deleted: Preop. Perform., Schedule, DM/LV, Net Deviation

* $p < .01$

was the measure of damage to the frontal cortex ($r_{part} = -0.53$, $p < .01$).

In the second analysis (Table 18) the interaction between electrode location and postoperative performance was tested. Variance in performance due to frontal damage ($F = 14.78$) and testing schedule ($F = 2.06$) was first partialed out. None of the resulting partial correlations between performance change and the electrode location variables were statistically significant.

A third analysis (Table 19) tested for interactive effects of variation in testing schedule and preoperative performance levels. Neither of these variables significantly influenced performance.

The results of these three analyses indicated that performance decreased following bilateral ablations in proportion to the amount of frontal cortex removed, while the degree of damage in parietal, occipital, and temporal cortex, or total cortical damage was unrelated to variations in performance. No interactions with variations in non-ablation variables were detected.

In order to study further the relationship between the frontal ablations and performance change, subjects were divided into three groups as in the analysis of unilateral ablations: (1) Those with ablations not involving the frontal cortex, (2) those with larger than the median amount of frontal damage, and (3) the remaining with a smaller than the median amount of frontal damage. The mean performance-change scores for each ablation group and the sham group in each post-operative session are presented graphically in Figure 9. Table 20

TABLE 18

Variation in Performance due to Variations in

Electrode Location: Bilateral Ablation Data

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Frontal	14.78	Anterior-posterior	-0.15	31	0.70
Schedule	2.06	Net Deviation	0.03	31	0.03
		DM/VL	-0.23	31	1.66

Variables Deleted: Total, Parietal, Occipital, Temporal, Preop. Perform.

TABLE 19

Variation in Performance due to Variations in Testing Schedule and Preoperative Performance: Bilateral Ablation Data

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Frontal	12.63	Schedule	0.24	32	2.06
		Preop. Perform.	0.03	32	0.02

Variables Deleted: Total, Parietal, Occipital, Temporal, Anterior-Posterior, DM/VL

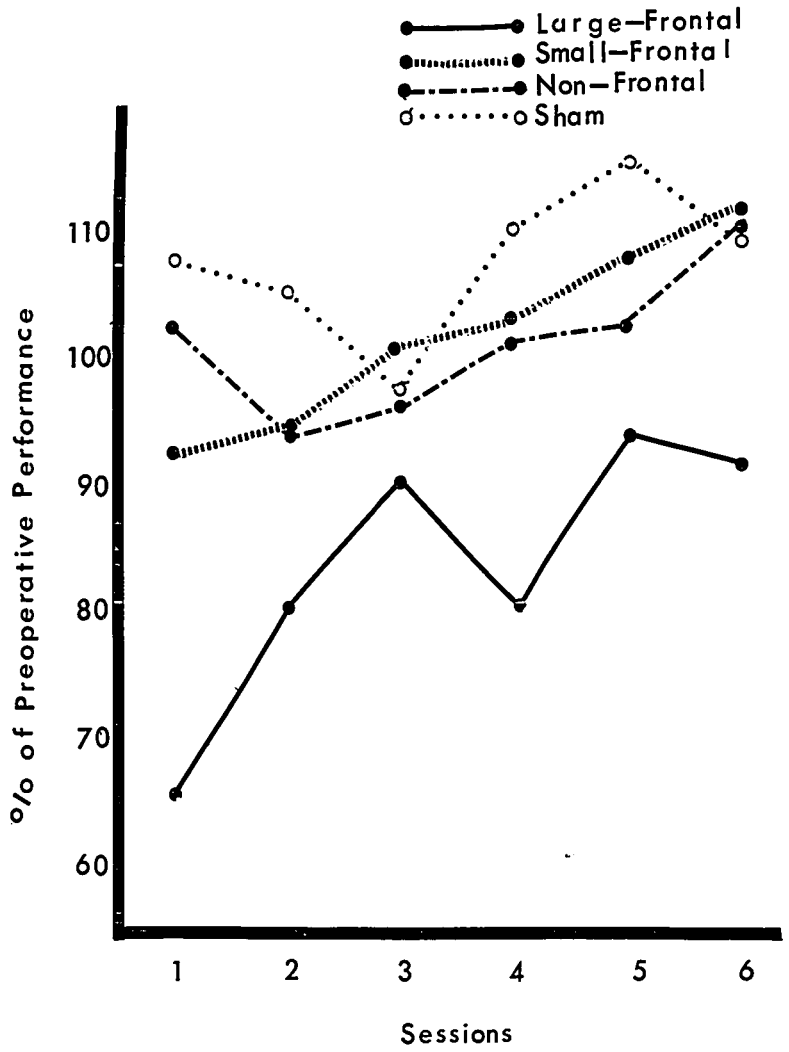

Figure 9. Mean performance across six postoperative sessions for subjects with large-frontal, small-frontal, non-frontal, and sham ablations: Bilateral ablation data.

summarizes the analysis of variance of these data. Significant group ($p < .05$) and sessions ($p < .05$) main effects were obtained. All groups showed an improvement in performance across sessions, however, subjects in the large-frontal group had consistently lower performance scores than subjects in the other three groups.

Comparison of pre- and postoperative performance within groups (Table 21) indicated a significant decrement in performance for the large-frontal group ($p < .05$) in the first block of postoperative sessions but not in the second.

Disrupted Feeding

Stimulation-elicited feeding was completely disrupted in 8 bilaterally ablated rats at 12 stimulation sites (A1R, A2R, A3L, A3R, A5L, A10L, A10R, A11L, A11R, B18L, B19L) and in two unilaterally ablated animals at two stimulation sites (A4L, A1L). At no time during disruption were these rats completely aphagic since in every case feeding was observed in the testing box prior to the stimulation session, and occasionally, between stimulation trials.

During disruption, stimulation produced orientation and general exploratory responses, but not feeding. In the first postoperative session stimulation in several subjects (A2R, A1RL, A11L, B47L) evoked what appeared to be an incomplete appetitive sequence of responses. At intensities that generally were well above the preoperative threshold, stimulation initiated orientation and direct approach to the food cup. Upon reaching the cup, however, the subject only sniffed the contents briefly and then proceeded to explore the testing box.

TABLE 20

Two-Way Analysis of Variance of Postoperative Performance in Sessions 1-6 with Electrodes Grouped According to Ablation Location: Bilateral Ablation Data

Source	df	MS	F
Between subjects	66		
Groups (A)	3	8661.39	2.86*
Subj. w. groups	63	3024.40	
Within Subjects	335		
Sessions (B)	5	1494.42	2.93*
AB	15	394.82	0.77
B X Subj. w. groups	315	510.60	

* $p < .05$

TABLE 21

Within Group Changes in Performance: Bilateral Ablation Data

Groups	df	t Sessions: 1-3	t Sessions: 4-6
Large-Frontal	8	2.61*	1.34
Small-Frontal	8	0.09	1.17
Non-Frontal	16	0.4280	1.1530
Sham	31	0.49	1.76

* $p < .05$

While stimulation-elicited feeding was absent in the free-moving animal, some facilitatory influence of hypothalamic stimulation on food intake could still be demonstrated, if attempts were made to hand feed these animals liquid food with a medicine dropper. At certain minimum stimulation intensities, food was readily accepted while at lower intensities, or in the absence of stimulation, food was rejected.

In general, the vigor of these responses was related to the intensity of stimulation. At the lower effective intensities, lapping responses were only maintained if the dropper tip were held constantly in contact with the mouth. If the dropper was withdrawn by even a few millimeters, the response terminated but could be reinstated if the dropper was again touched to the mouth. The subject made no attempts to relocate or to follow the dropper when it was moved away. At higher intensities, lapping was more vigorous and the subject tracked the dropper as it was slowly withdrawn. At still higher current levels, lapping changed to biting and gnawing, although food was still ingested.

The range of stimulation intensities for evoking "dropper-feeding" in each disrupted subject is shown in table 22. The minimum intensity was higher than the preoperative feeding threshold in all cases but one. In that one (A5L) feeding was elicited at an intensity clearly below the previous feeding threshold. In a few cases where hand feeding was sampled in nondisrupted electrodes the minimum effective intensities were equal to or somewhat below the normal feeding threshold.

In most cases disruption was transient, and feeding reappeared after a period of days or weeks (Table 23). Disruption usually occurred

TABLE 22

Dropper-Feeding and Preoperative Thresholds

in Cases of Disrupted Feeding

Electrode Number	Preoperative Threshold (uA)	Range of Dropper-Feeding Thresholds (uA)
A 1R	117	220 -
A 1L	272	600 - 700
A 2R	203	160 - 270
A 3L	69	
A 3R	136	100 - 130
A 4L	56	60 -
A 5L	161	80 - 100
A 5R	133	
A10L	138	350 -
A10R	96	
A11L	116	240 - 300
A11R	158	220 - 260
B18L	86	150 -
B19L	52	80 - 200

TABLE 23

Disrupted Electrodes: Duration of Disruption

Electrode Number	First Disruption			Duration	
	Stage	Session	Day	Session	Day
A 1R	II	2	2	4	9
A 1L	I	1	1	5	5
A 2R	II	1	1	5	10
A 3L	II	2	2	1	1
A 3R	II	2	2	8	30+
A 4L	I	1	1	1	1
A 5L	II	1	1	6	10+
A 5R	II	4	4	2	2
A10L	II	1	1	9+	23+
A10R	II	1	1	9+	23+
A11L	II	1	1	7	21
A11R	II	1	1	7	21
B18L	II	1	8	4	15
B19L	II	1	8	6	25

in the first postoperative session, with some notable exceptions. Rats A1R and A3LR ate food on Day 1 but not on Day 2. For subject A3LR the right electrode remained ineffective throughout the remainder of testing (30 days). The right electrode in Rat A1 elicited feeding in the sixth session after a 9-day disruption. The left electrode in subject A5 was effective in the first three sessions, but in the fourth and fifth (postoperative days 8 and 9) feeding occurred so infrequently that a threshold could not be measured. In the sixth session feeding was elicited frequently enough to allow thresholds to be measured.

In the two cases where feeding was disrupted following the unilateral ablation (A1L, A4L), the affected electrode was in the same hemisphere as the ablation. In subject A1LR both the left and right electrodes were studied, and although stimulation on the left failed to elicit feeding for five days, the electrode contralateral to the ablated hemisphere showed only a slight increase in threshold. Unfortunately, subject A4L had only a single electrode so the specificity of the deficit to ipsilateral stimulation could not be tested.

In the cases where stimulation-elicited feeding recovered, the new threshold was generally higher than before the ablation but still well below the maximum currents sampled during the period of disruption (Table 24). "Recovered" thresholds in most cases were also higher than the minimum currents that had been found to be effective in the dropper-feeding experiments (Table 24). Performance scores for recovered subjects were variable but tended to be below preoperative values.

Since threshold and performance data for disrupted subjects were either lacking or incomplete, a scoring system was adopted to enable

TABLE 24

Disrupted Electrodes: Recovery of Feeding

Electrode Number	Preoperative Measures		Disruption		Recovery	
	Thresh. (uA)	Perform. (sec.)	Range of Dropper-Feeding Thresh. (uA)	Range of Max. Intensity (uA)	Thresh. Range	Perform. Range (sec.)
A 1R	117	10.4	220 -	600 - 800	380 -	5.8 -
A 1L	272	7.3	600 - 700	900 -1000	430 - 725	4.2 - 6.9
A 2R	203	12.5	160 - 270	300 - 350	210 - 250	8.3 -13.4
A 3L	69	9.1		240 -	72 - 90	4.1 -10.1
A 3R	136	6.6	100 - 130	200 - 380		
A 4L	56	9.1	60 -	300 -	140 - 214	1.0 - 5.5
A 5L	161	9.3	80 - 100	190 - 440		
A 5R	133	7.8		440 - 500	165 - 200	4.1 - 8.5
A10L	138	9.7	350 -	600 - 850		
A10R	96	10.1		640 - 840		
A11L	116	10.3	240 - 300	300 - 500	195 - 280	6.8 -11.0
A11R	158	9.5	220 - 260	380 - 560	188 - 212	7.4 - 9.6
B18L	86	15.9	150 -	200 - 300	132 - 180	7.9 - 9.2
B19L	52	13.0	80 - 200	220 - 260	130 -	10.2 -

multiple regression analyses of performance, using all operated subjects. In sessions where disruption occurred, performance was scored as zero. Performance change for all subjects, disrupted and nondisrupted, was expressed as the difference between the raw scores averaged on post-operative days 8-10 and the average preoperative score. Of course, a comparable analyses for the threshold data was not feasible.

Multiple regression analysis of performance data: Disrupted and nondisrupted subjects combined. In the first analysis (Table 25a) two nonablation variables, DM/VL ($F = 3.18$) and preoperative performance ($F = 2.57$) were added to the regression equation to control for variation in performance attributable to the variables. Significant partial correlations were found between performance and total damage ($r_{part} = -0.41$, $p < .01$), frontal damage ($r_{part} = -.77$, $p < .001$) and parietal damage ($r_{part} = -0.41$, $p < .01$).

In order to partial out the influences of differences in total ablation size, the total damage variable was added to the regression dquation of uncontrolled variables (Table 25b). As a result, significant partial correlations were obtained for frontal damage ($r_{part} = -0.75$, $p < .001$), occipital damage ($r_{part} = -.58$, $p < .001$), and temporal damage ($r_{part} = 0.40$, $p < .01$). The direction of these correlations suggests that the results attributed to occipital and temporal damage were solely a function of their negative intercorrelation with frontal damage. Consequently, in a third step of the analysis (Table 25c) the variance in performance due to frontal damage was partialed out by adding that variable to the regression equation. The resulting partial correlations in the three remaining cortical region variables were not significant, indicating that their apparent importance

TABLE 25

Variation in Performance due to Variation in

Ablation Size and Location: Bilateral Ablation

Data, Non-Disrupted and Disrupted Subjects Combined

a. Before adding Total to equation

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
DM/VL	3.18	Total	-0.41	41	8.55*
Preop. Perform.	2.57	Frontal	-0.77	41	60.08**
		Parietal	-0.41	41	8.62*
		Occipital	0.22	41	2.06
		Temporal	0.09	41	0.32

Variables Deleted: Anterior-Posterior, Net Deviation, Schedule

b. After adding Total to equation

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
DM/VL	1.22	Frontal	-0.75	40	45.58**
Preop. Perform.	1.69	Parietal	-0.19	40	1.37
Total	8.55	Occipital	0.58	40	17.89**
		Temporal	0.40	40	6.67**

Variables Deleted: Anterior-Posterior, Net Deviation, Schedule

c. After adding Total and Frontal to equation

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Total	2.73	Parietal	0.07	41	0.18
Frontal	45.58	Occipital	0.03	41	0.04
		Temporal	-0.04	41	0.06

Variables Deleted: DM/VL, Preop. Perform.

*$p < .01$ **$p < .001$

in the preceding analysis was, in fact, due to their high negative correlation with the frontal cortex measure.

Also associated with the addition of the frontal cortex variable was a reduction in the F value associated with the total damage variable already in the regression equation. This result indicated that the apparent importance of total ablation size was due only to its intercorrelation with the frontal cortex measure. Additional multiple regression analyses showed that variation in electrode location (Table 26) and initial performance and testing schedule (Table 27) did not interact with the effect of frontal damage.

In summary, the results of these analyses showed that maximum performance decreases occurred most reliably in subjects with ablations that destroyed comparatively large amounts of frontal cortex. This relationship is seen most clearly by comparing the amount of frontal damage in the disrupted and nondisrupted group. The mean frontal damage in the disrupted group was 26.4% while that for frontally damaged but not disrupted subjects was 11.9% ($t = 4.48$, $df = 22$, $p < .001$).

Changes in Body Weight

In several ablated subjects normal, daily food intake appeared to be markedly reduced in the first few days following the second operation, although in no case was complete aphagia observed. A few subjects (A1LR, B18L, B19L) had difficulty holding and gnawing dry Purina pellets but ate readily when optional liquid diets were offered.

Although food intake was not measured, daily body weights were recorded in 30 ablated and 20 sham-ablated rats from the day of the first operation to 10 days after the second. The data for the ablated animals

TABLE 26

Variation in Performance due to Variation in Electrode Location: Bilateral Ablation Data, Disrupted and Nondisrupted Subjects Combined

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Frontal	59.99	DM/VL	0.13	40	0.73
Total	4.23	Anterior-posterior	0.02	40	0.01
Schedule	5.18	Net Deviation	0.05	40	0.13

Variables Deleted: Preoperative Performance, Occipital, Temporal, Parietal.

TABLE 27

Variation in Performance due to Variation in Preoperative Performance and Testing Schedule: Bilateral Ablation Data, Disrupted and Nondisrupted Subjects Combined

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Frontal	57.51	Preop. Perf.	0.07	39	0.20
Total	1.54	Schedule	-0.24	39	2.52
DM/VL	1.83				
Net Deviation	1.64				

Variables Deleted: Parietal, Occipital, Temporal, Anterior, Posterior

were analyzed by the multiple regression method with the five ablation measures and preoperative weight as independent variables. The dependent measure was the percent change in body weight averaged over postoperative days 8-10.

Multiple regression analysis of body weight data. The results of two steps of the multiple regression analysis are shown in Table 28a and 28b. The first analysis (Table 28a) showed that when the influence of total cortical damage was removed, only damage to the frontal cortex was significantly correlated with weight change ($r_{part} = -0.71$, $p < .001$).

In a second analysis both the total and the frontal damage variables were partialed out. The resulting partial correlation for the remaining ablation variables (occipital, temporal, parietal) were negligible (Table 28b). It is worth noting that addition of the frontal damage variable to the regression equation did not markedly reduce the F value associated with total damage ($F = 9.55$). This result indicated that although weight loss was correlated highest with frontal damage, large ablations, regardless of location, also lead to a loss of weight.

In order to compare ablated animals to controls, subjects were divided into large-frontal, small-frontal, non-frontal, and sham-ablated groups. The daily group means from the time of the first operation to 10 days after the second operation are plotted in Figure 10. The analysis of variance (Table 29) revealed a significant groups ($p < .001$) and a significant sessions ($p < .001$) main effect. In addition, the interaction between these two variables was significant ($p < .001$). Thus, the groups differed in the percentage of weight lost immediately following both operations; however, observation of Figure 10 suggests that this loss was greater after the second operation. Although in all groups

TABLE 28

Variation in Body Weight due to Variation in Sizes and Location of the Cortical Ablation: Bilateral Ablation Data

a. After adding Total to equation

Variables in Equation		Variables not in Equation			
Variable	F	Variable	Part. Corr.	df	F
Total	9.55	Frontal	-0.71	26	26.16**
		Parietal	-0.26	26	1.89
		Occipital	0.60	26	14.63*
		Temporal	0.34	26	3.30

b. After adding Total and Frontal to equation

Variable	F	Variable	Part. Corr.	df	F
Total	8.52	Parietal	-0.08	25	0.14
Frontal	28.23	Occipital	0.18	25	0.80
		Temporal	-0.15	25	0.63

* $p < .01$ ** $p < .001$

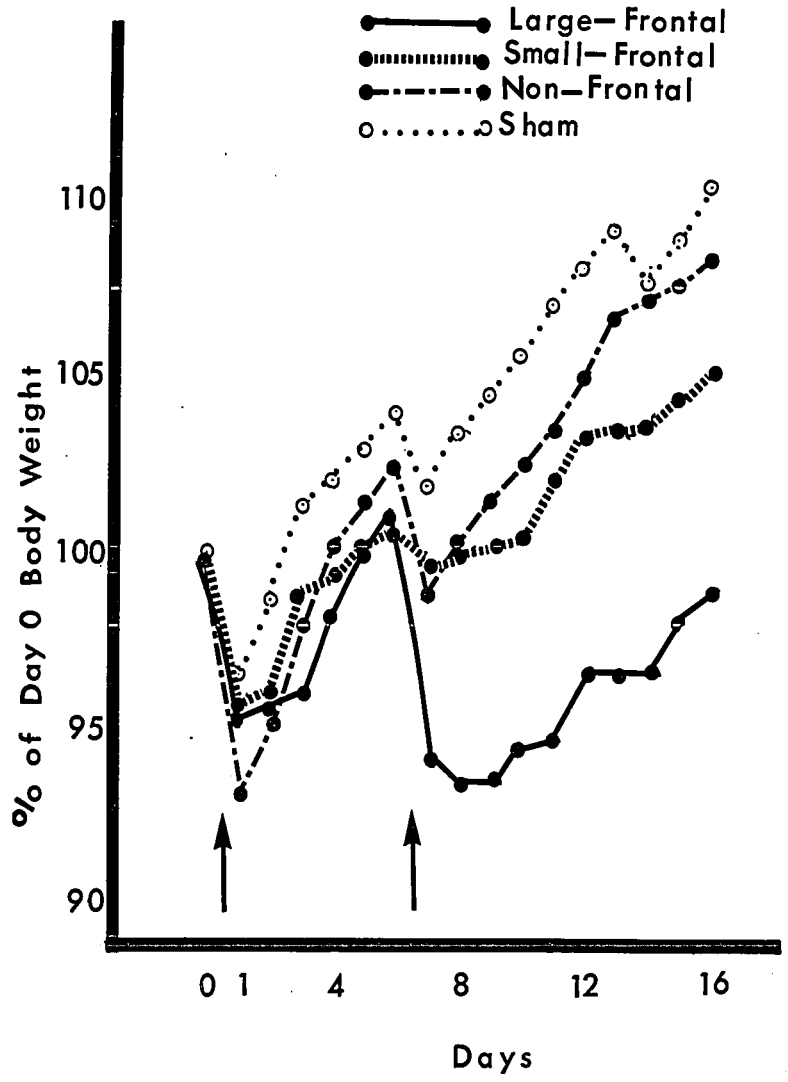

Figure 10. Mean percent preoperative body weights from the first operation to 10 days after the second operation for subjects with large-frontal, small-frontal, non-frontal, and sham ablations.

TABLE 29

Two-Way Analysis of Variance of Body Weight Change

Source	df	MS	F
Between Subjects	45		
Groups (A)	3	1623.68	5.71**
Subjects w. groups	42	284.34	
Within Subjects	690		
Days (B)	15	372.67	44.54***
AB	45	34.21	4.09***
B X subj. w. groups	630	8.37	

** $p < .01$ *** $p < .001$

there was a gradual increase in body weight following the operations, the rate of weight gain in the large-frontal group was slower in comparison to that of the other three groups.

Summary of Results

1. Unilateral cortical ablations resulted in increases in feeding threshold and decreases in feeding performance. These changes occurred whether the stimulating electrode was ipsilateral or contralateral to the ablated hemisphere. The percent increase in threshold was correlated significantly with the total amount of cortical damage; and percent decrease in performance was correlated significantly with the amount of damage in the frontal cortex but not in the parietal, occipital, or temporal cortex. Threshold and performance changes were greater in the first three-day block of postoperative testing session than in the second three-day block.

2. Feeding was disrupted in two subjects following unilateral ablations, one for a period of one day and the other for five days. In both cases the ablation was comparatively large and centered in the frontal region on the same side as the stimulating electrode; but in only one case was the effect demonstrably unilateral.

3. Bilateral ablations resulted in increases in threshold and decreases in performance. Threshold increases were largest in ablated subjects tested according to schedule A and where the site of stimulation was in the dorsal-medial part of the hypothalamus. Variations in the size or location of the ablation did not affect the degree of threshold change. Performance decreased in proportion to the percent destruction of the frontal cortex, but not the other three cortical

areas. This relationship was not influenced by variations in electrode location or testing schedule.

4. Following bilateral ablation, feeding was disrupted in 8 out of 36 subjects, or in 12 of the 48 stimulation sites examined, for periods ranging from one day to when the animals were sacrificed 30 days later. None of these subjects lost the ability to feed spontaneously in the absence of stimulation, and in most cases stimulation continued to elicit feeding when the animals were restrained, and offered liquid food with a medicine dropper. The deficit therefore appeared to be limited primarily to the food-seeking component of the stimulation-elicited behavior. Considered as a group, subjects displaying this deficit had ablations that destroyed greater amounts of frontal cortex than did subjects for which hypothalamically-elicited feeding was intact.

5. Although ablated animals were never aphagic, their rate of body weight gain following the second stage operation was slower than that observed in sham-operated control animals. These differences were greatest in subjects with large frontal ablations, but large ablations not centered in this area also produced this result.

DISCUSSION

Possible Artifacts

Before considering the importance of the results of the present study for the understanding of the nature of cortical-hypothalamic interaction, the possibility that the impairment and complete disruption of feeding observed were artifacts of the operative procedure must first be considered. Surgical procedures, apart from the ablation of neural tissue per se, have the potential of determining the observed effects in a number of ways. First, the ablations were made only after the electrodes were implanted and tested; thus any change in the electrode tip tissue interface that occurred as a result of subsequent surgical procedures might have altered the stimulation field. Conceivably, such a change could be produced by a shift in brain tissue due to the removal of parts of the cortex. However, since neither all subjects with large removals of cortex nor all subjects with ablations of cortex nearest to the hypothalamus, were adversely affected, it is unlikely that tissue movement made an important contribution to the obtained results.

A second possibility is that instead of the tissue shifting, the electrode tip might have changed position slightly as a result of loosening of the electrode assembly anchorage to the skull. To control for this occurrence the junction between the electrode assembly and skull was carefully examined at the time of sacrifice. Unless all four anchor screws of the assembly had remained firmly embedded in the skull, the animal's data were not included in the analysis.

A third consideration is that even in the absence of brain or electrode movement, the tissue at the tip of the electrode might have

been altered by seepage of blood or cerebrospinal fluid down the electrode shaft as a result of hemmorrhage during surgery. Histological examination showed that at the time of sacrifice no blood was present in the electrode tip region in any subject, including those in which stimulation-elicited feeding had not recovered.

In view of the transiency of the phenomenon in some subjects, a fourth source of disruption, surgical shock, must also be considered. Although feeding was never disrupted in the sham-operated subjects, it is not unreasonable to suppose that the surgical trauma associated with the ablation operation was greater than that resulting from the sham procedures. Two findings argue against the importance of surgical trauma as the primary determinant of disruption. First, assuming that surgical shock is related directly to the total amount of tissue damaged, then, statistically, that measure would most likely have been the highest correlate of performance decrease and disruption. Instead, the percent damage to the frontal cortex, but not other areas, was found to be the most closely related to these deficits. Second, in the majority of subjects where disruptions occurred, the deficit persisted for more than a week, by which time the secondary effects of the operation would have attenuated.

An additional control for "non-ablation" factors was made by assessing the effects of spreading depression. Seven subjects, (B48R, B51LR, B52LR, B53LR, B54LR, B55LR, and B56LR) which had previously served as sham-operate controls were fitted with nylon canulae. In a subsequent experiment, KCl was injected onto the dural surface of the brain bilaterally or unilaterally to induce spreading depression. Unfortunately, the canulae quickly became clogged, and therefore only a few observations were made.

The results of the spreading depression experiment were in keeping with the ablation findings. In two subjects (B54L and B55LR) hypothalamically-elicited feeding was disrupted when unilateral depression occurred in the same hemisphere as the stimulating electrode. In both cases, responses elicited by the contralateral electrode were unimpaired and spontaneous feeding was also observed. When the "dropper-feeding" technique was tried, subjects ate greedily in response to stimulation. Feeding continued as long as a minimum current was maintained and food was kept in contact with the mouth. These results were clearly analogous to those of subjects A1LR where feeding was disrupted by an ipsilateral ablation of the fronto-lateral cortex.

In the remaining five subjects, unilateral spreading depression had little effect on feeding threshold or performance regardless of the site of stimulation. These negative findings could not be attributed to failure of the canulae since in each case cortical depression was confirmed by the loss of placing reflexes in the contralateral limbs. However, when the cortex was depressed bilaterally both hypothalamically-elicited and spontaneous feeding were disrupted. In spite of the complete absence of feeding, stimulation continued to evoke ingestive responses when food was placed in contact with the animal's mouth. In summary, the spreading depression data, together with the points discussed above, support the view that disruptions of stimulation-elicited feeding were the direct result of the cortical ablations.

Interpretation of Major Results

The major aim of the present study was to assess the influence of the neocortex on the lateral hypothalamus in the control of feeding.

On the basis of spreading depression studies, which show a facilitatory influence of the cortex on the lateral hypothalamus (Bureš et al., 1961; Huston & Bureš, 1970; Teitelbaum & Cytawa, 1962), it was thought that subtotal ablations would lead to a reduction of hypothalamic activity and, as a consequence, would impair the feeding function. Consistent with this expectation, the threshold for electrically-elicited feeding increased and the feeding performance decreased. Further, the degree of impairment in feeding performance was directly related to ablation size. There were, however, several additional findings, which require consideration.

1. Dissociation of consummatory acts and instrumental action. The animals showing a complete disruption of feeding performance reflected a deficit in the food-seeking component of the hypothalamically-elicited feeding since the consummatory component continued to be elicited by contact of food to the mouth. In this respect, the disruption was similar to the aphagic behavior of decorticate rats; in these preparations, food placed in the mouth is readily ingested although voluntary feeding is absent (Braun, 1966; DiCara et al., 1970; Sorenson & Ellison, 1970). Thus, it appears that electrical stimulation of the hypothalamus by itself is capable of only producing consummatory eating acts in the presence of food-contact stimuli (tactual or gustatory); cortical input is required for generating instrumental, goal-directed approach in relation to distal food stimuli.

The above finding also suggests that one effect of hypothalamic stimulation is the facilitation of consummatory responses. This conclusion is supported by the finding that ingestion could be evoked by the dropper

technique and that the vigor and ease of initiation of the ingestion response increased as a function of stimulus intensity. The similarity of this "reflexive" feeding to that described by Woods (1964) in decerebrate rats further suggests that the consummatory eating responses are probably organized at a lower level of the brain stem and that facilitation reflects a downstream influence from the hypothalamus.

The notion that the hypothalamus controls feeding behavior by facilitation of these reflexes is not new (e.g., Brobeck, 1969). However, with one other notable exception (Flynn, 1969), this view has received little direct experimental support. In Flynn's experiment, hypothalamic stimulation facilitated reflexive biting, a component of the predatory attack sequence in the cat.

2. Causes of Feeding Impairment. In attempting to understand the deleterious effects of frontal ablations on hypothalamically-elicited feeding it is important to take into account some basic features of electrically-elicited feeding. One important consideration is that electrical stimulation probably activates only a part of the circuitry that normally controls feeding. At the same time, it may also activate circuits that are normally unrelated to feeding. For instance, locomotor, or exploratory behavior is a consistent concomitant of hypothalamically-elicited feeding (Glickman & Schiff, 1968). Although such behaviors superficially appear to be related to food seeking, some observations suggest that they interfere with feeding.

During initial testing sessions of the present experiment several animals behaved as if they were trying to locomote and eat simultaneously. They often transported food pellets in their mouths between short bouts of feeding or nibbled crumbs off the floor while continually moving about

the box. As testing continued over several days exploration gradually attenuated and all subjects ate in a more sedentary manner. Even after nine sessions exploratory bouts generally preceded feeding for several seconds and dominated approximately 10% of the suprathreshold stimulation trials.

Observations by Mendelson (1966) offer a stronger demonstration that this exploratory behavior is unrelated to food seeking. When food-sated rats were taught a T-maze problem motivated by hypothalamic stimulation and reinforced by food, they learned in fewer trials and ran faster if stimulation was given only in the goal boxes and not in the alleyways. When stimulation commenced in the start box, running times increased up to five times their previous duration primarily because the rats explored the path to the correct goal box.

Disruption of electrically-elicited feeding therefore may be due to a deficit in the ability to suppress these inappropriate behaviors. Other experimenters have also concluded that frontal damage leads to a deficit in the ability to inhibit locomotor or exploratory responses (Campbell & Lynch, 1969; Lynch, 1970). Although in these studies the frontally-damaged animals were never aphagic, less extreme forms of disruption were apparent; frontally-damaged animals exhibited slower rates of lever-pressing for food and maintained lower body weights than controls. This latter finding is consistent with the finding of the present study that animals with large frontal ablations exhibited slower rates of weight gain following surgery than animals with smaller ablations and controls. Thus, even in the naturally-occurring feeding situation some relatively minor deficits in food-seeking behavior were probably involved.

It is possible that an inbitory deficit (associated with frontal damage) might be more disruptive to elicited feeding than to spontaneous feeding. In order to feed during stimulation, animals have to inhibit competing exploratory responses within a set time period. The time element is less critical to the performance of the naturally-occurring response since it is presumably a consequence of central processes which are active over a much greater time range. Unfortunately, since prolonged stimulation trains often become aversive (Valenstein, 1966; Grastyán, Czopf, Ángyan, & Szabó, 1965), it is doubtful whether adoption of longer stimulation trials would help to clarify this issue. To test whether disruption was due to impaired suppression of locomotor activity it would be necessary to compare disrupted and control subjects on a task on which feeding behavior and suppression of locomotor activity can be dissociated.

The above considerations raise some interesting problems for further research. Since it was suggested that disruption of feeding may involve more general deficits in inhibitory control or locomotor behavior--effects that have been shown to result from ablations limited to the frontal pole (Campbell et al., 1969; Thompson, 1963, 1964)--it would be pertinent to determine the limits of the cortical region necessary to produce the disruption syndrome. It was not clear in the present experiment whether removal of the frontal poles alone was sufficient to produce disruption. In seven subjects damage was restricted to the frontal poles (B17L, B20L, B21R, B23R, B26L, B27R, and B28LR) although in none of these cases was the entire region destroyed. Feeding was not disrupted and only one subject (B28LR) showed a marked decrement in performance. Disrupted subjects all sustained frontal pole damage, but in each

case the ablation was large and involved the posterior part of the frontal cortex and the anterior parietal cortex.

3. Recovery from Disruption. With the exception of three electrodes in two subjects (A3R, A10L, A10R), electrically-elicited feeding recovered after complete disruptions of from 1 to 25 days. Where disruption lasted only one or two days (A3L, A4, and A5R), behavioral recovery might have been due to recovery of cortical tissue bordering the ablated area whose functioning was only temporarily impaired. Similarly, the three instances where disruption occurred after a one-day (A1R, A3L, and A3R) or three-day latency (A5R), can perhaps be attributed to degenerative changes or to transient dysfunctions due to edema. Either event, but particularly the latter, would be expected to have a delayed onset.

The cases where hypothalamically-elicited feeding recovered after disruptions of five to 25 days are more difficult to interpret. There is some suggestion, however, that recovery was dependent on the nature of the stimulation experience during disruption. In these subjects feeding was readily elicited by the dropper in several sessions. In contrast, in the two subjects that did not recover, feeding was always more difficult to elicit by this technique, and in later sessions, could not be elicited at all. As a consequence, they had fewer feeding experiences during stimulation than the subjects which recovered.

4. Changes in Feeding Threshold. Following unilateral damage, thresholds increased in proportion to the amount of cortex destroyed; but since these effects were studied in only the first six days postoperatively the result must be interpreted with caution due to the possible contributing factor of surgical shock. Although sham-ablated animals showed

no significant change in threshold the surgical procedures in these animals were no doubt less traumatic and therefore constitute a limited control. The finding that the threshold increases in subjects with large ablations attenuated somewhat over the six-day period could be interpreted as due either to the remission of shock effects or to some manifestation of recovery of function. However, the failure of unilateral spreading depression to elevate thresholds suggests that the ablation effects were complicated by factors related to the surgical procedure.

In the case of bilateral ablations, the influence of surgical shock was less likely since the animals were studied over a longer period. Unlike the unilateral results, the size of the threshold increases were unrelated to ablation size. Instead, the degree of postoperative threshold change in ablated subjects appeared to be determined by the locus of stimulation and the schedule of postoperative testing.

The finding that the thresholds of subjects tested under schedule A increased more than those of the subjects tested under schedule B is most puzzling. (Schedule A animals were given threshold tests on the six days following the first ablation, and were tested for the three days immediately following the second ablation. Schedule B subjects were not tested until seven days after the second ablation.) Statistically, this result could not be attributed to differences in electrode location, ablation size and location, or differences in preoperative thresholds. The data appear to indicate that the procedure of testing immediately after the operation had a deleterious effect on subsequent thresholds. Schedule A animals had nine days of additional threshold tests prior to comparison with animals tested under schedule B. If the elevation in thresholds

seen following unilateral ablations were related to surgical trauma, stimulation would appear to retard the processes that normally lead to recovery.

Regardless of the testing schedule, the effect of the ablation on threshold showed a marked interaction with electrode location. The statistical analyses indicated that threshold increases were greatest in electrodes located in the dorsomedial part of the sample distribution and that those located ventrolaterally were unchanged. As in the case of the schedule variable, the differences in postoperative thresholds attributable to variation in the electrode dimension were independent of variation in ablation size, location, testing schedule, and preoperative threshold. Clearly, the problem is to determine in what way feeding elicited from these dorsomedial electrodes differed from that elicited from lateral and ventral sites. Data from the present experiment offer no clues other than that the thresholds for these two regions are differentially affected by cortical ablations--preoperative thresholds and performance were unrelated to variations in electrode location in all dimensions evaluated.

Two observations in the literature may bear on the present findings. Morgane (1961) has demonstrated differences in the motivational properties of midlateral and far lateral hypothalamic stimulation loci. Behaviorally, stimulation of the far lateral sites appeared to be more drive-inducing; stimulated rats lever-pressed at high rates and would cross an electrified grid in order to obtain food. Stimulation of more medial sites produced feeding when food was readily available, but the animals would not cross the electrified grid to obtain it. Olds (1969) has also mentioned that motivational differences can be observed in the effects of stimula-

tion at different loci. He reported that certain feeding sites in the dorsal part of the medial forebrain bundle would not sustain self-stimulation behavior, a phenomena previously held to be a consistent correlate of electrically-elicited feeding. Unfortunately, in the present study the motivational qualities of the elicited behavior were not measured. The findings of Morgane and Olds, however, could suggest that subjects with dorsomedial electrodes were initially less motivated to eat than those with ventrolateral placements. Even granting that these motivational differences are present it remains unclear how this factor would account for the differential effects of cortical ablations on thresholds. Because of the tendency in the literature to treat all stimulation sites which elicit feeding as equivalent, with the exception of the two experiments noted above, it is important that in further studies more attention be paid to variations in electrode location.

5. Locus of Corticohypothalamic Interactions. The purpose of testing subjects following the first stage of the ablation was to assess separately the importance of cortical regions ipsilateral and contralateral to the side of the stimulating electrode. The results indicated that with the exception of two subjects (A1LR and A4L), ablations that damaged the frontal cortex in either hemisphere were equally effective in producing performance deficits in feeding elicited by stimulating in either of the two hypothalami. This result is consistent with earlier work by Murphy and Gelhorn (1945). They found that movements evoked by cortical stimulation could be facilitated equally by hypothalamic stimulation in either hemisphere. Together these findings suggest that the locus of interaction between cortical and hypothalamic influences is at

a level of the neuroaxis where information from either source is mediated bilaterally. If the interaction was "unilateral" then frontal ablations should have affected only the responses elicited by stimulation in the ipsilateral hypothalamus.

One potential site of interaction is the pontine reticular formation in which bilateral fiber degeneration has been reported following unilateral frontal cortical ablations (Rossi & Brodal, 1956). An equally likely candidate is the midbrain reticular formation; though lacking strong contralateral cortical input (Auer, 1956; Knook, 1965; Leonard, 1969) it contains contralateral fibers of lateral hypothalamic origin that probably descussate in the supramammillary commisure (Millhouse, 1969).

Data for the two atypical subjects (A1R and A4L) mentioned above will now be considered in light of these hypothesized sites of cortical-hypothalamic interaction. In these subjects, and two additional ones from the spreading depression experiment (B54LR and B55LR), feeding elicited from the hypothalamus ipsilateral to the impaired cortex was abolished. In the three of these subjects with bilateral electrodes (A1LR, B54LR, and B55LR), contralaterally elicited responses were unimpaired, implying a purely unilateral phenomenon.

A most interesting result was obtained in two of these subjects where spreading depression was studied. When the opposite hemisphere was depressed, unilateral disruption did not occur. This finding suggested that the occurrence of unilateral disruption is specific to particular stimulation sites. Subsequent examination of the electrode tip locations offered confirmatory evidence. Electrodes A4L and A1L were both in the lateral half of the medial forebrain bundle and in the most

caudal plane of all electrodes sampled (Appendix C). Electrode B55L was also quite caudal and lateral, and B54R, though near the center of the sample distribution rostrocaudally, was one of the most lateral sites tested.

According to the anatomical work of Millhouse (1969) the fibers in the region of these electrode tips would be least likely to decussate in the supramammillary commissure; only the medial third of the medial forebrain bundle appears to contribute to this commissure. Thus, the downstream effects of stimulation at these sites would be limited primarily to the ipsilateral midbrain. At the pontine level, fibers from the intact contralateral cortex are present (Rossi & Brodal, 1956) but do not seem to be involved since in spite of this available avenue of contralateral cortical influence, hypothalamically-elicited feeding was abolished. Therefore, by elimination, the more probable site of cortical-hypothalamic interaction is the midbrain.

Further experiments are obviously needed to strengthen this conclusion. In addition to verifying the post hoc hypothesis developed here--that feeding elicited by electrodes in the lateral half of the medial forebrain bundle is subject to disruption only by ipsilateral cortical insult, experiments should be designed to investigate the importance of the supramammillary commisure in the bilateral mediation of these unilaterally elicited responses. For example, if the commissure were severed by a discrete midline lesion or knife cut, then the downstream influences of lateral hypothalamic stimulation would be limited to the ipsilateral midbrain where input is only available from the ipsilateral cortex. Unilateral depression of that cortex should then disrupt feeding elicited from the ipsilateral hypothalamus.

The finding that the majority of disruptions in feeding occurred only after bilateral ablations or during bilateral spreading depression suggests another experimental approach to determining the locus of cortical-hypothalamic interaction. In these animals, unilateral destruction or depression of the cortex ipsilateral to hypothalamic stimulation did not result in disruption. The influence of the contralateral cortex was sufficient to maintain the behavior. When this remaining source of cortical control was eliminated by a suitable ablation or spreading depression, then hypothalamic elicitation of feeding was blocked. However, instead of eliminating this cortical influence at its source, lesions or knife cuts could be made at different points along its cortiofugal trajectory. Failure to disrupt feeding following one of these cuts would indicate that the severed fibers did not mediate the critical cortical influence. By this technique it might be possible to isolate the corticofugal pathway involved in the cortical-hypothalamic interaction.

SUMMARY

Lesion and stimulation studies of the hypothalamus have firmly established that this structure plays a major role in the central regulation of feeding behavior. More recently, theoretical considerations have pointed to the possible influences of extrahypothalamic brain areas in feeding. The purpose of the present experiment was to study the interaction between one of these areas, the neocortex, and the lateral hypothalamus in the control of feeding in the rat.

The general approach of the experiment was to determine electrical current thresholds for elicitation of feeding from the lateral hypothalamus before and after cortical ablations. In addition, a number of variables which might potentially influence the cortical-hypothalamic interaction were considered.

The most provocative finding was that large bilateral removals of frontal cortex abolished hypothalamically-elicited feeding while leaving the naturally-occurring behavior comparatively intact. This failure to eat during stimulation reflected a deficit in the food-seeking component of the behavior since the consummatory behavior could be elicited by contact of food to the mouth. Thus, hypothalamic stimulation by itself appears capable only of producing consummatory responses in the presence of food-contact stimuli. On the other hand, cortical input appears to be necessary for generating goal-directed approach in relation to distal food stimuli. It was suggested that the deficits in food-seeking were related to an inability to inhibit competing exploratory or locomotor responses that generally accompany hypothalamic stimulation.

Most subjects in which ablations resulted in the disruption of stimulation-induced feeding eventually recovered. Behavioral recovery which occurred within five days of surgery was probably due to recovery of cortical tissue bordering the ablated area where functioning was only temporarily impaired. Recovery after longer periods of disruption appeared to be related to the amount and type of intervening stimulation experience rather than the total time since the ablation.

Changes in current thresholds were also observed but appeared to be unrelated to disruption or performance decrements. Following unilateral ablations thresholds increased in proportion to the total amount of cortex destroyed. However, these threshold elevations may have been a secondary effect of surgical trauma, or shock since unilateral spreading depression generally did not affect thresholds. Following bilateral ablations threshold increases were most marked in subjects where stimulation occurred in the dorso-medial part of the lateral hypothalamus. Size or location of the ablation were not correlated with the degree of threshold change. This latter result suggested that certain parts of the hypothalamus may be more dependent on cortical input than others.

Finally, the result of unilateral ablation and spreading depression on the performance of hypothalamically-elicited feeding suggested that the locus of the cortical-hypothalamic interaction is at a level of the neuroaxis where information from one or both structures is mediated bilaterally. The midbrain reticular formation was considered a likely substrate.

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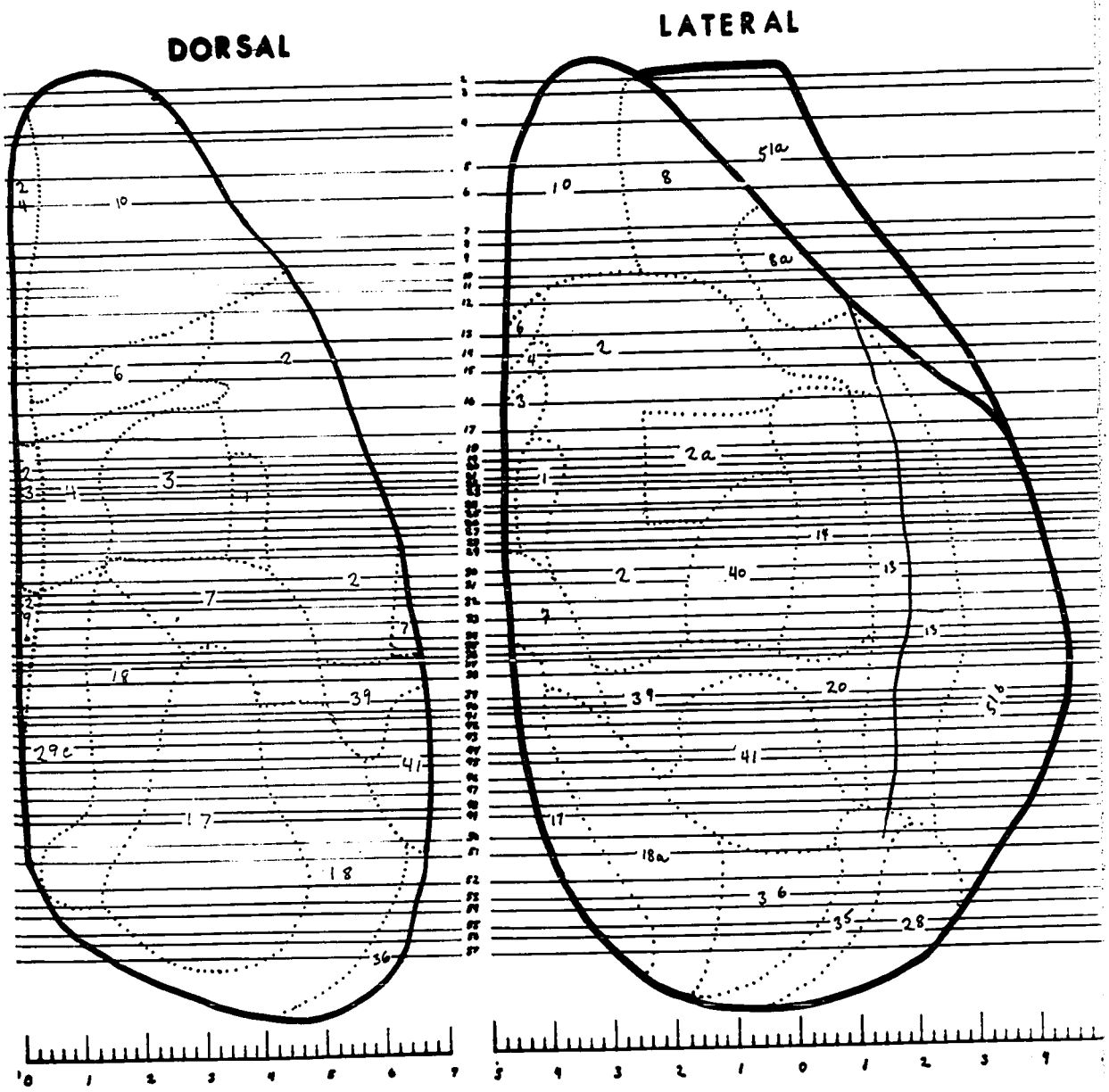
APPENDIX B

Cortical Reconstruction



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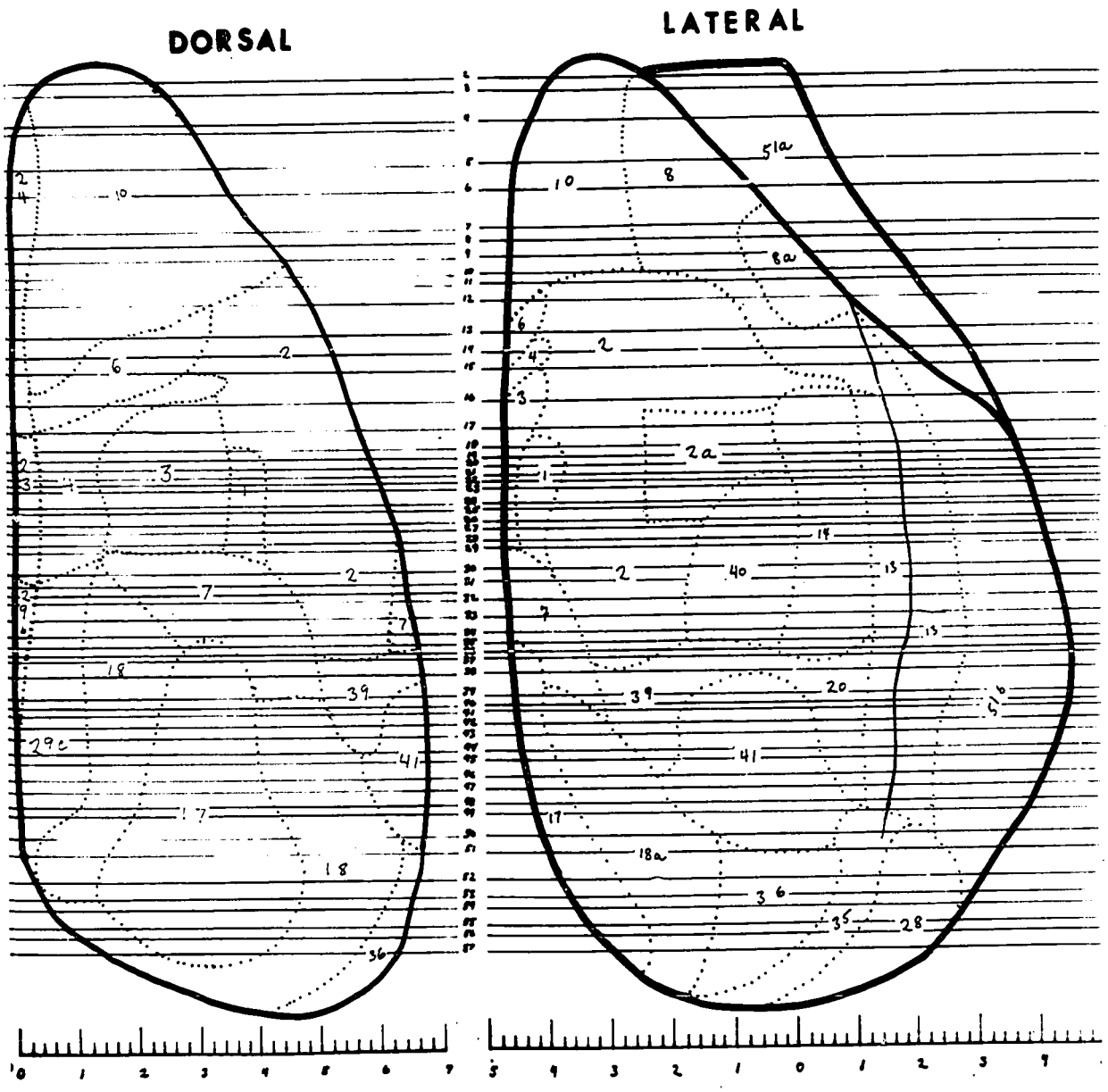

(The numbered lines refer to the frontal plane drawings of Konig & Klippel, 1963)

APPENDIX C

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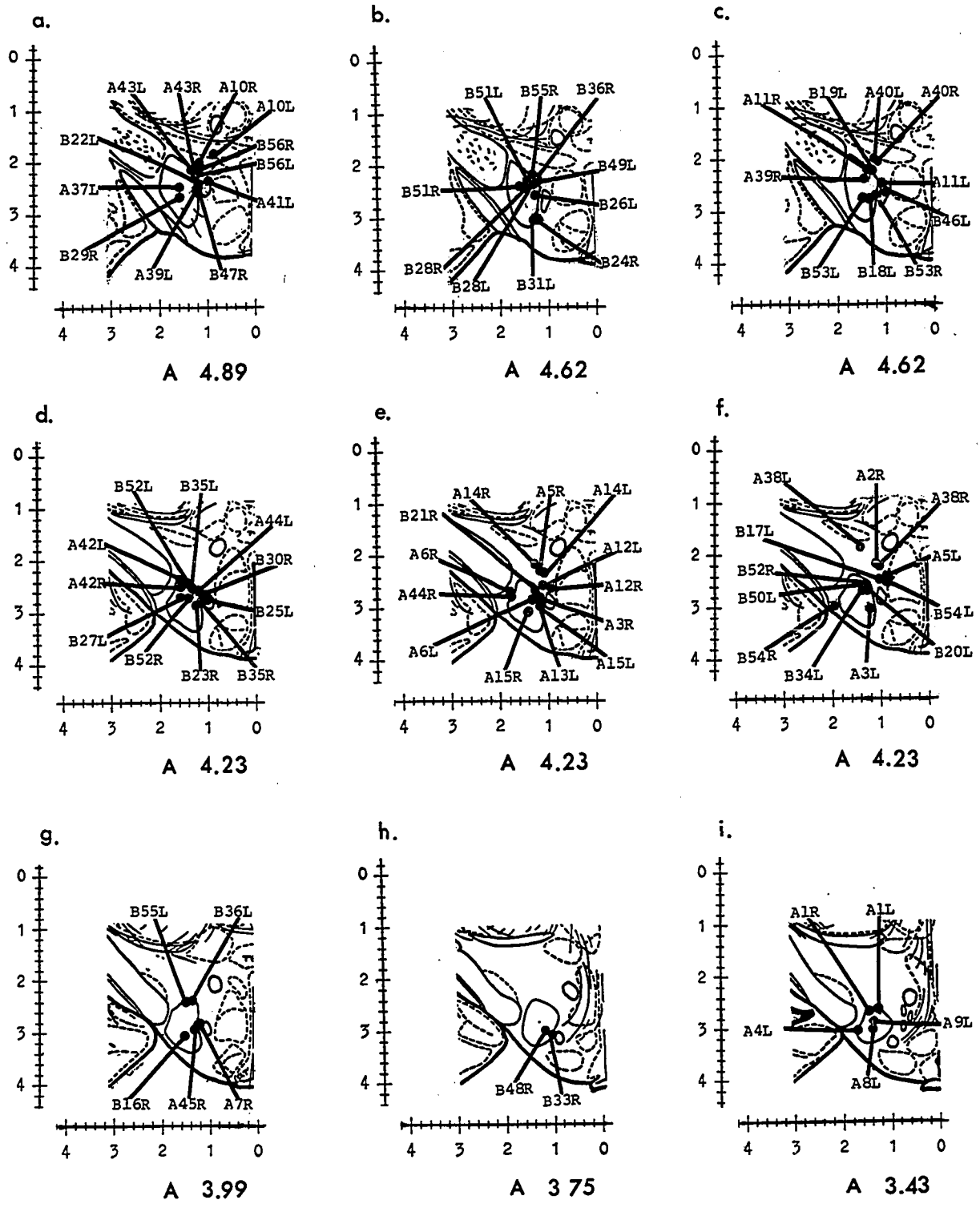
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A37L A41L
B29R A39L B47R
A 4.89
b.
B51L B55R B36R
B49L
B51R B26L
B28R B24R
B28L B31L
A 4.62
c.
A11R B19L A40L A40R
A39R A11L
B46L
B53L B18L B53R
A 4.62
d.
B52L B35L
A44L
A42L B30R
A42R B25L
B27L
B52R B23R B35R
A 4.23
e.
A14R A5R A14L
B21R A12L
A6R
A44R A12R
A3R
A6L A15L
A15R A13L
A 4.23
f.
A38L A2R A38R
B17L A5L
B52R
B50L B54L
B54R B20L
B34L A3L
A 4.23
g.
B55L B36L
B16R A45R A7R
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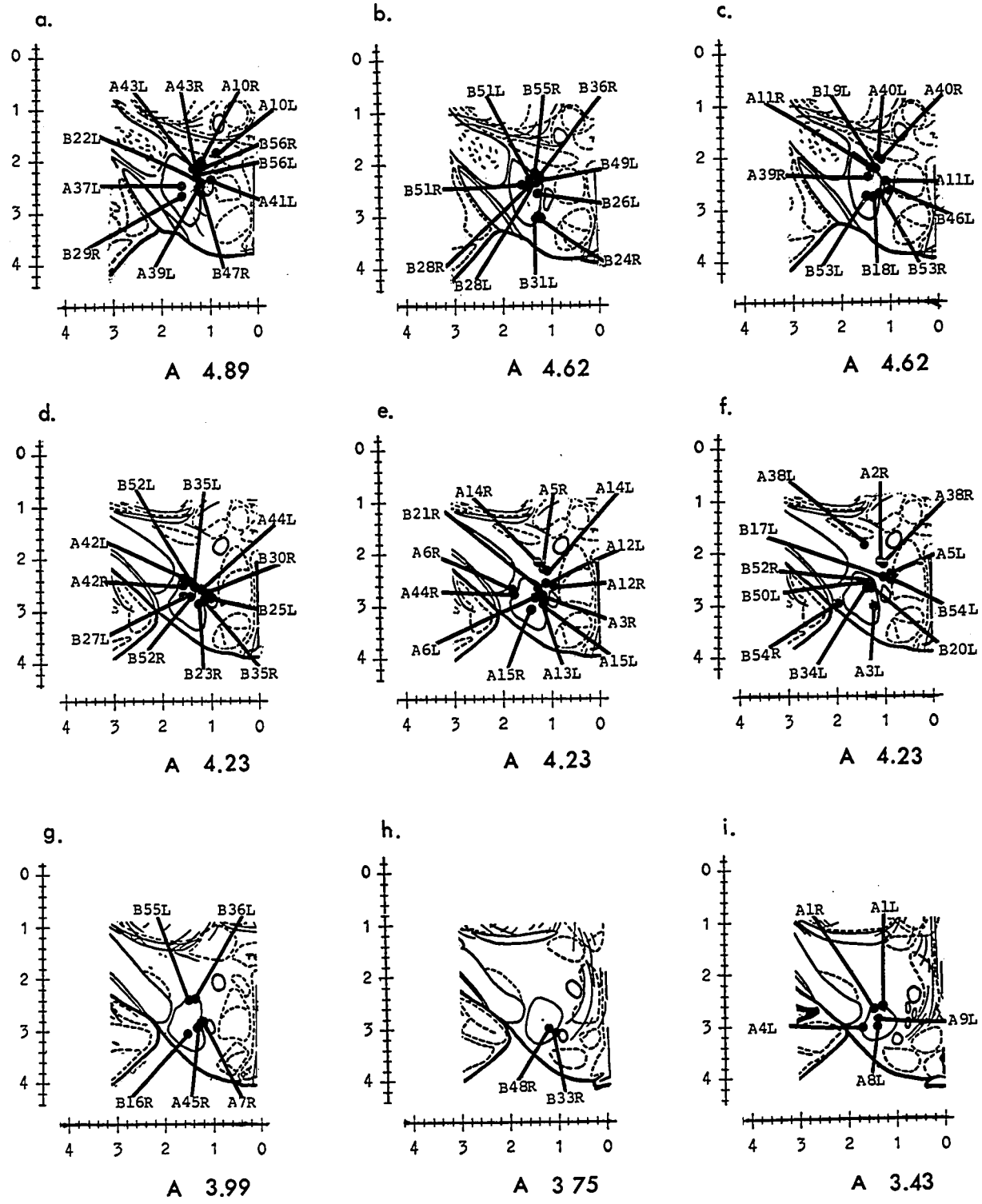
h.
B48R B33R
A 3 75
i.
A1R A1L
A4L A9L
A8L
A 3.43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b.
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c.
A11R
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f.
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B17L
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B54R
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A 4.23
g.
B55L
B36L
B16R
A45R
A7R
A 3.99
h.
B48R
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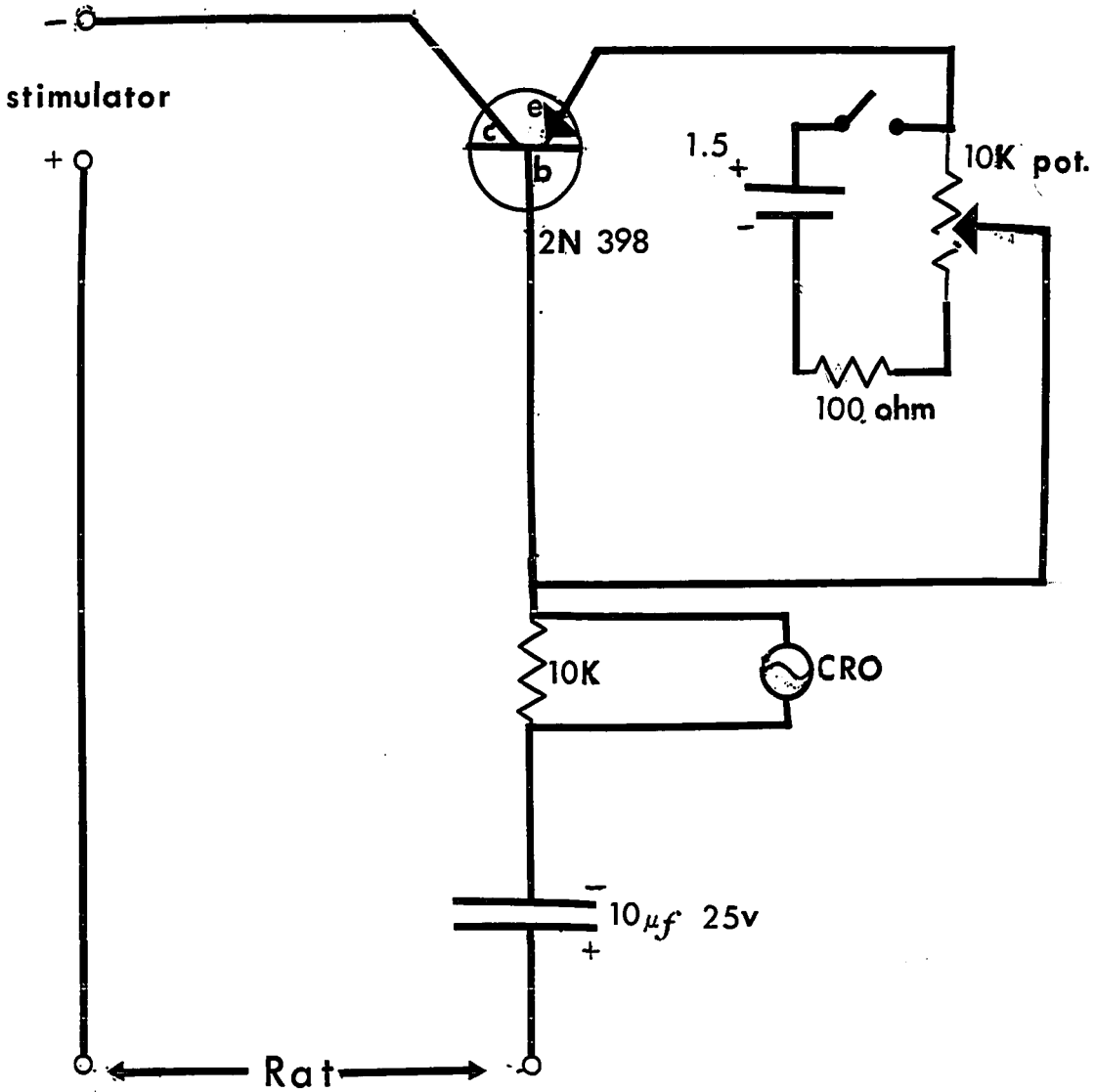
i.
A1R
A1L
A4L
A9L
A8L
A 3.43

APPENDIX A

Constant Current Circuit


stimulator
+
e
c
b
2N 398
1.5
+
-
10K pot.
100 ohm
10K
CRO
10μf 25v
Rat

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APPENDIX D

Reconstruction of Individual Cortical Ablations

The number to the left of the reconstruction refers to the subject number. The number to the right refers to the percentage of total cortical damage.

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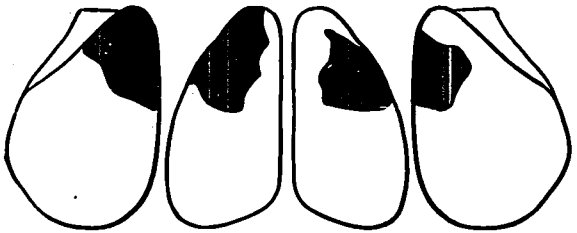

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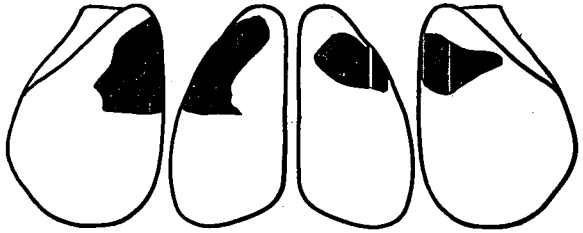

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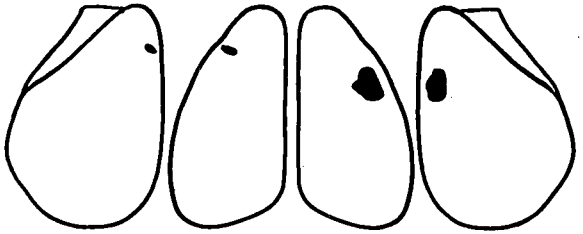

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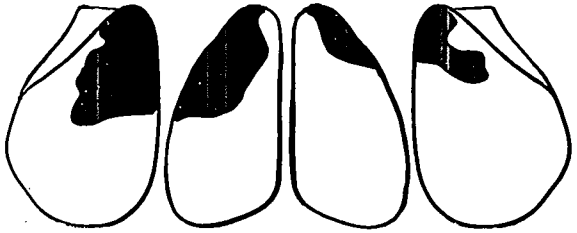

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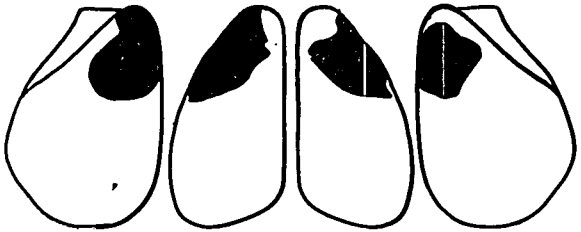

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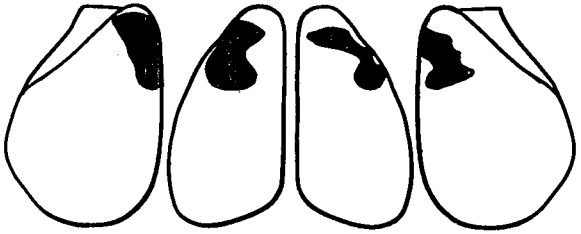

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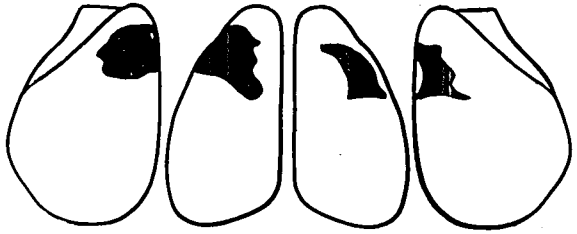

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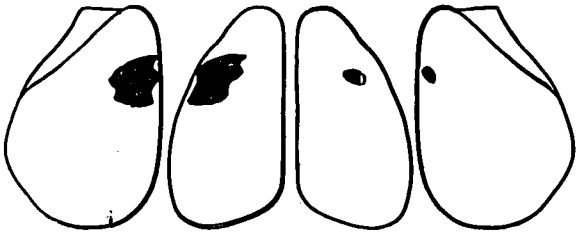

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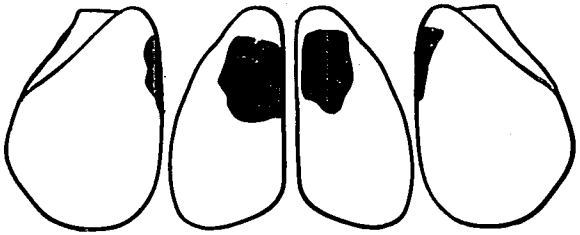
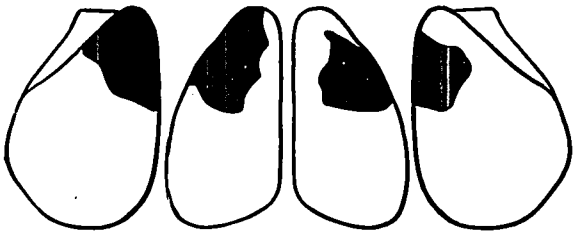
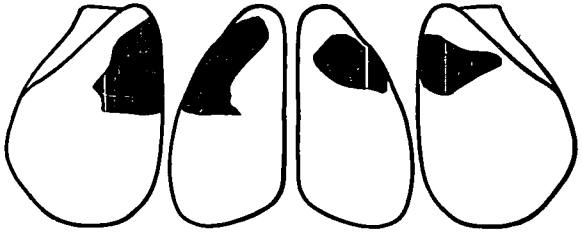


A1LR 13.5



A4L 11.5



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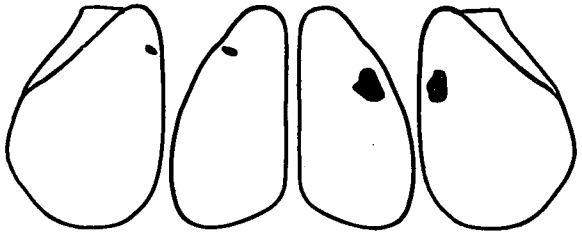

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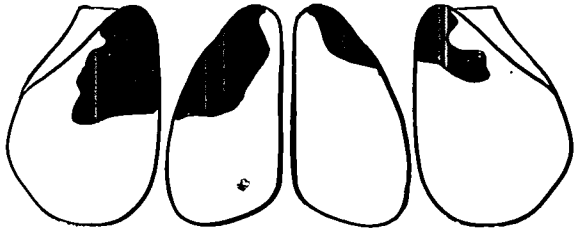
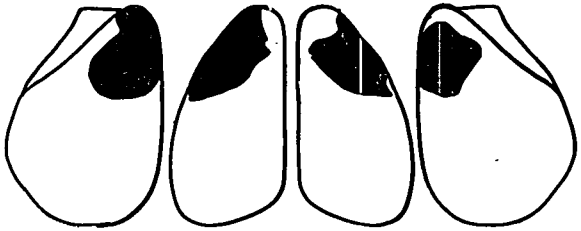


A5LR 11.7



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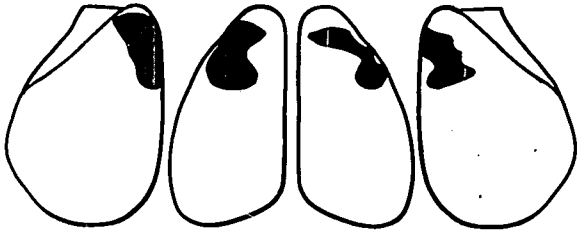

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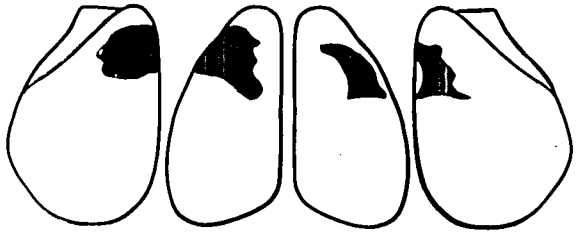
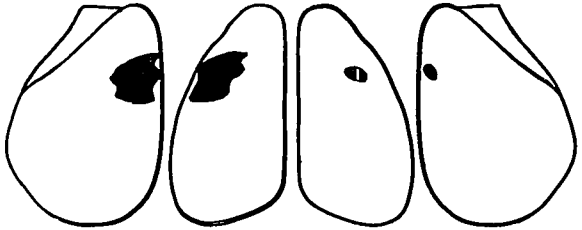
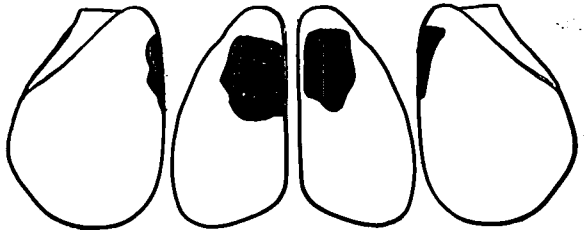


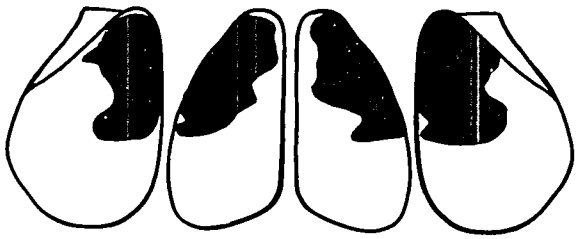
A6LR 1.8



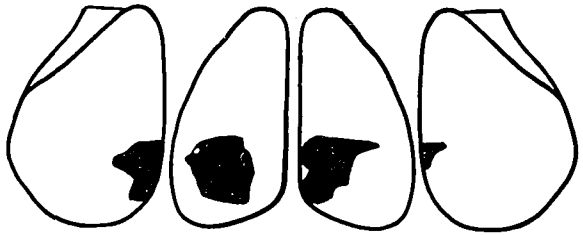
A9L 7.6



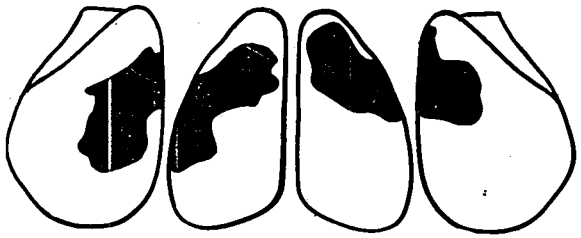
A10LR 21.3



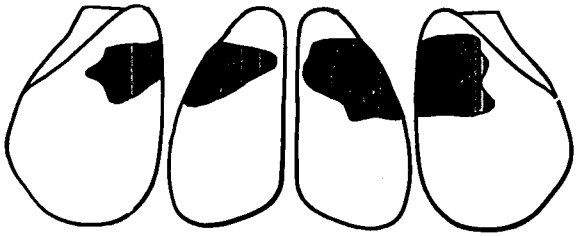
A13L 10.5



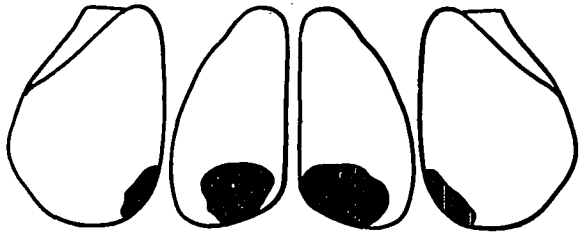
B16R 13.7



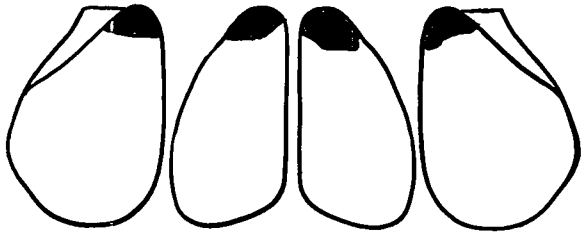
A11LR 13.0



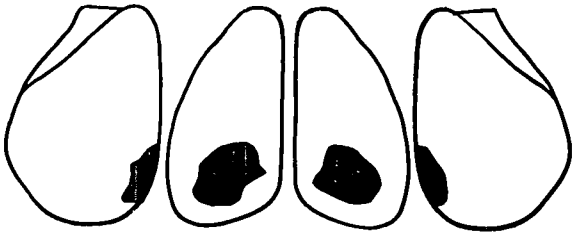
A14LR 6.5



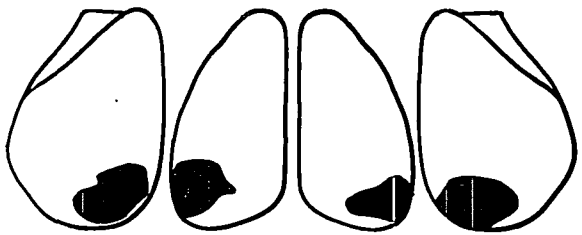
B17L 4.7



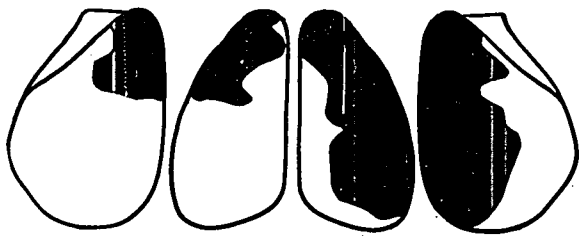
A12LR 7.5



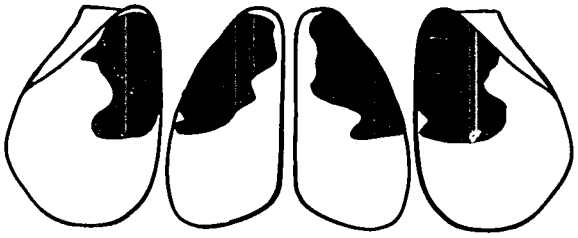
A15LR 5.3



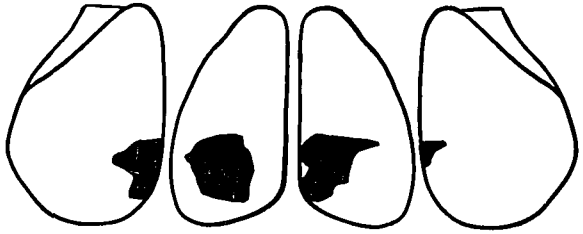
B18L 31.8



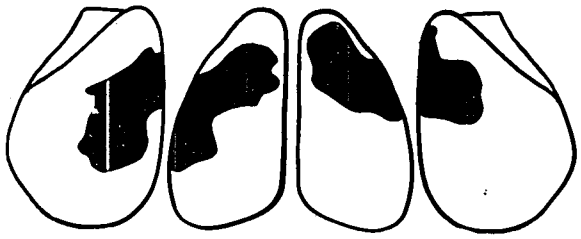
A10LR 21.3



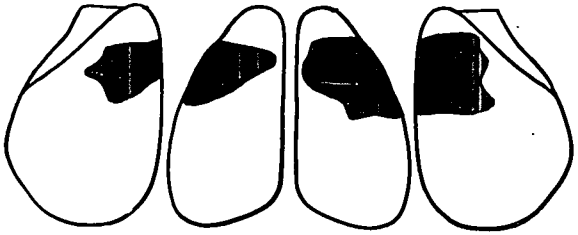
A13L 10.5



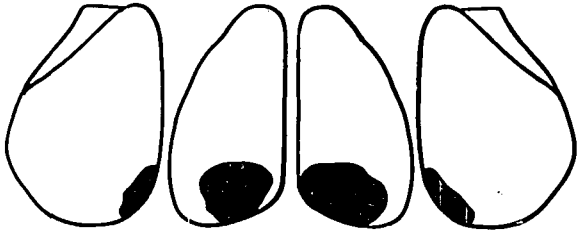
B16R 13.7



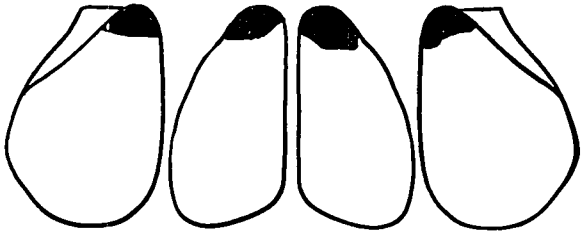
A11LR 13.0



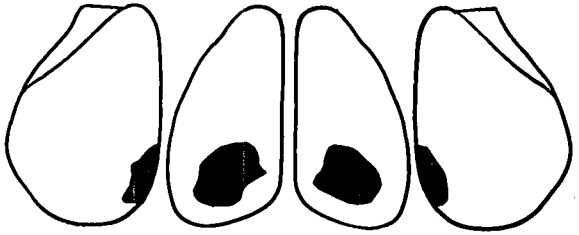
A14LR 6.5



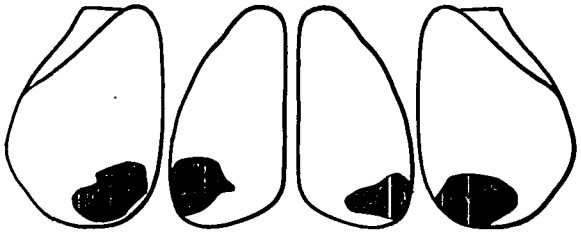
B17L 4.7



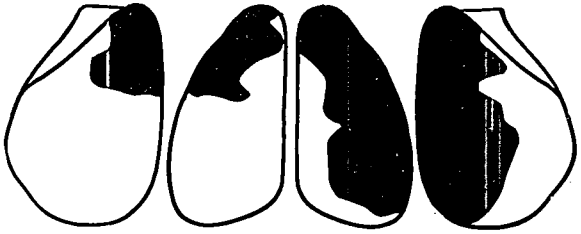
A12LR 7.5



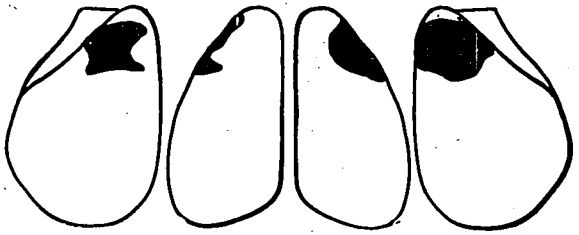
A15LR 5.3



B18L 31.8



B28LR 8.4



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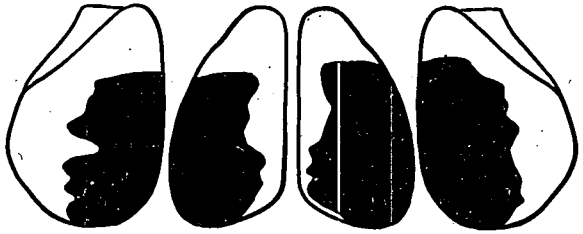

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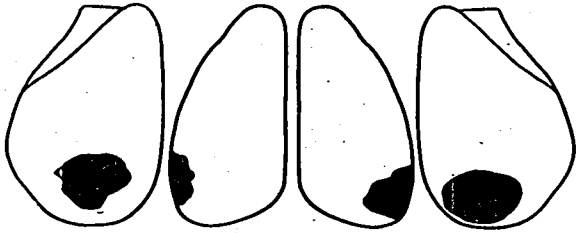
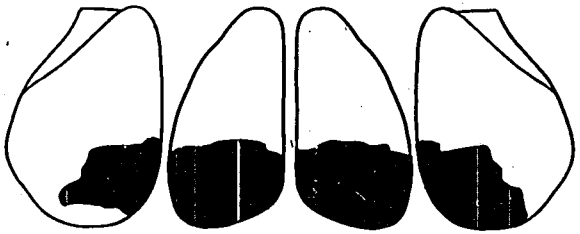
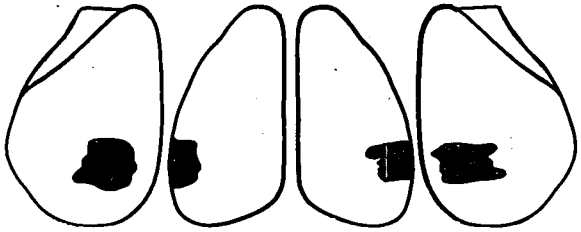


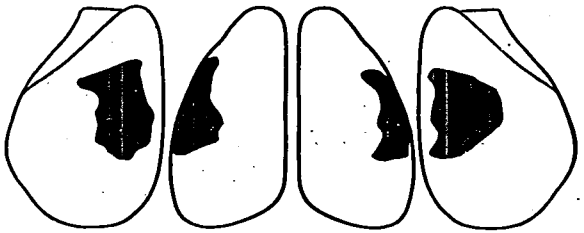
B29R 22.0



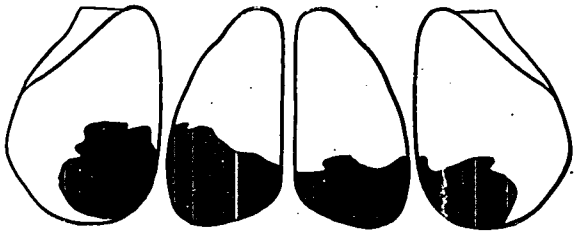
B32L 14.6



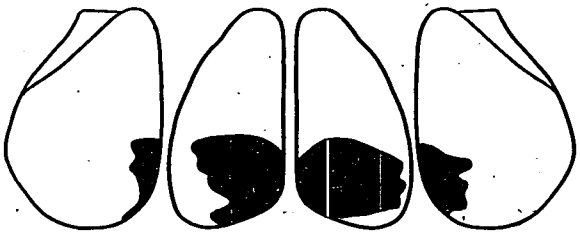
B35LR 11.3



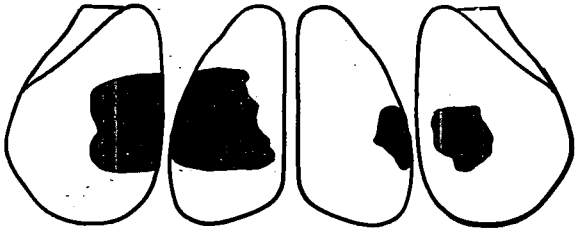
B30R 20.8



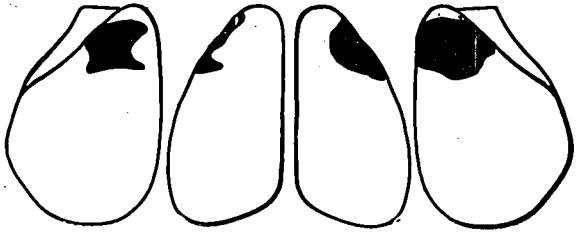
B33R 14.6



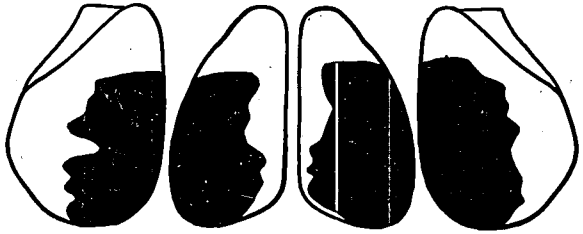
B36LR 14.4



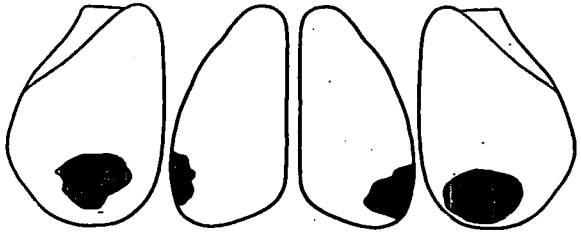
B28LR 8.4



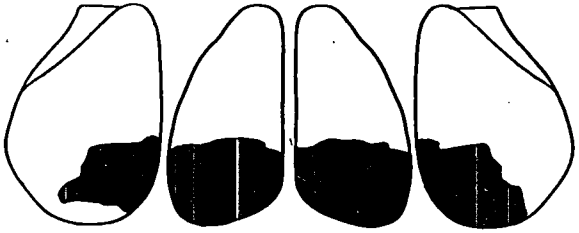
B31L 43.0



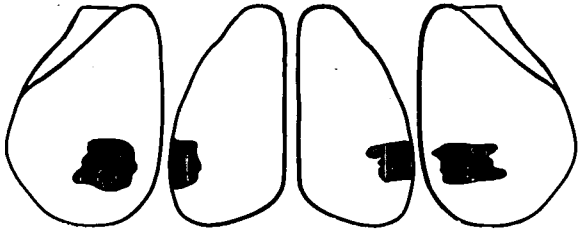
B34L 5.8



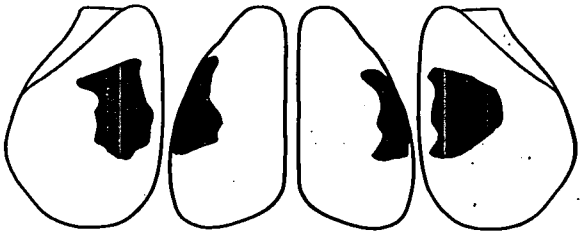
B29R 22.0



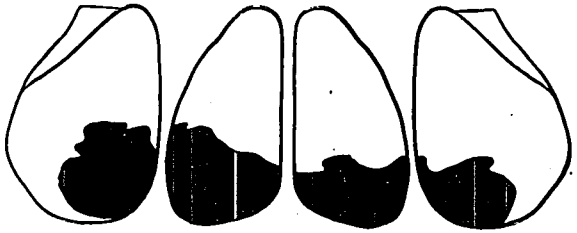
B32L 14.6



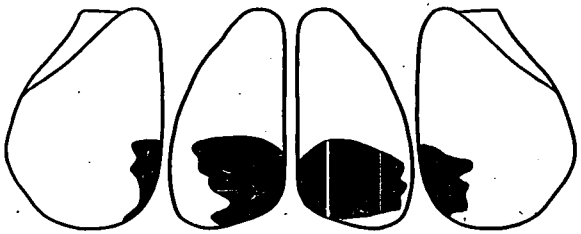
B35LR 11.3



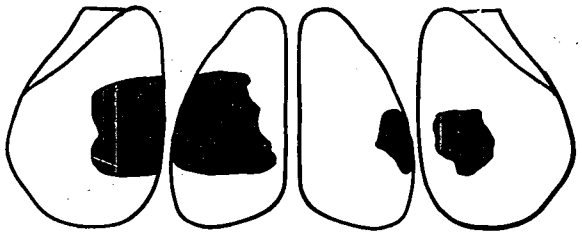
B30R 20.8



B33R 14.6



B36LR 14.4



APPENDIX E

Percent Damage to Total Neocortex and to Four Cortical Areas

Subject	Total (r=0.69)*	Frontal (r=0.67)	Parietal (r=0.59)	Occipital (r=0.91)	Temporal (r=0.88)
A1LR	13.5	21.1	23.1	0.0	0.0
A2R	15.4	27.6	23.4	0.0	0.0
A3LR	5.8	12.1	6.9	0.0	0.0
A4L	11.5	16.9	20.8	0.0	0.0
A5LR	11.7	25.0	12.9	0.0	0.0
A6LR	1.8	1.8	4.1	0.0	0.0
A7R	0.4	0.0	1.5	0.0	0.0
A8L	5.9	11.2	8.2	0.0	0.0
A9L	7.6	20.1	5.4	0.0	0.0
A10LR	21.3	33.9	35.8	0.0	0.0
A11LR	13.0	22.9	19.8	0.0	0.0
A12LR	7.5	0.0	0.0	35.6	0.0
A13L	10.5	0.0	0.0	36.9	0.0
A14LR	6.5	0.0	0.0	28.4	0.0
A15LR	5.3	0.0	0.0	17.0	17.8
B16R	13.7	12.7	29.8	1.4	3.4
B17L	4.7	15.9	0.0	0.0	0.0
B18L	31.8	38.2	38.5	34.4	10.8
B19L	23.6	39.8	37.7	0.0	0.0
B20L	5.8	19.5	0.0	0.0	0.0
B21R	4.3	14.6	0.0	0.0	0.0
B22L	15.4	12.2	37.5	0.0	0.0
B23R	1.3	4.5	0.0	0.0	0.0
B24L	18.3	13.3	43.3	0.6	0.0
B25L	18.2	3.6	32.5	8.8	4.4
B26L	3.1	11.9	0.0	0.0	0.0
B27L	2.2	7.5	0.0	0.0	0.0
B28LR	8.4	23.9	4.2	0.0	0.0
B29R	22.0	0.0	0.0	71.6	70.1
B30R	20.8	0.0	3.2	57.2	74.5
B31L	43.0	6.5	62.0	69.0	72.6
B32L	14.6	0.0	0.0	56.5	27.5
B33R	14.6	0.0	0.0	61.4	0.0
B34L	5.8	0.0	0.0	5.7	46.7
B35LR	11.3	0.0	33.1	4.3	0.0
B36LR	14.4	0.0	28.8	16.4	19.2

* Correlation between percent damage in each hemisphere

APPENDIX F

Means and Standard Deviations for the Variables Included in the Stepwise Multiple Regression Analyses: Unilateral Ablation Data

Variables	Mean	Standard Deviation
Independent Variables		
Total	8.01	4.74
Frontal	9.93	11.46
Parietal	7.78	10.72
Occipital	9.80	14.07
Temporal	1.81	5.57
Dorso-Ventral	30.75	13.23
Medio-Lateral	47.75	9.66
Antereo-Posterior	35.90	5.66
Net Deviation	14.41	8.68
Laterality	.40	.50
Dependent Variables		
Threshold Change	169.65	144.30
Performance Change	95.05	24.68

APPENDIX G

Correlation Matrix: Unilateral Ablation Data

	TV	FC	PC	OC	TC	D-V	M-L	A-P	ND	Lat.	T	P
Total Cortex	1.000	.821	.847	-.169	-.105	.653	.416	-.347	.236	.141	.598	-.278
Frontal cortex		1.000	.847	-.636	-.296	.399	-.359	-.147	.223	.054	.426	-.491
Parietal cortex			1.000	-.532	-.248	.457	-.259	-.220	.330	.104	.612	-.188
Occipital cortex				1.000	.313	.188	.019	-.117	-.129	.055	-.077	.245
Temporal cortex					1.000	-.394	.204	-.054	.072	.068	-.163	.325
Dorso-ventral						1.000	-.418	-.463	.293	.111	.398	-.042
Medio-lateral							1.000	.216	.019	-.618	-.163	.191
Antereo-posterior								1.000	.174	.244	-.174	.063
Net deviation									1.000	.073	.133	.320
Laterality										1.000	.088	-.065
Threshold change											1.000	-.109
Performance change												1.000

APPENDIX H

Means and Standard Deviations for the Variables Included in the Stepwise Multiple Regression Analyses: Bilateral Ablation Data

Variables	Mean	Standard Deviation
Independent Variables		
Total	9.71	8.03
Frontal	6.34	7.98
Parietal	10.98	16.54
Occipital	16.36	22.71
Temporal	10.66	21.76
Dorso-Ventral	25.97	10.74
Medio-Lateral	50.08	7.54
Antereo-Posterior	34.83	1.85
Net Deviation	10.75	6.66
Test Schedule	.63	.49
Preoperative Threshold	81.00	46.90
Preoperative Performance	9.73	3.47
Dependent Variables		
Threshold Change	130.20	58.40
Performance Change	94.26	21.28

APPENDIX I

Correlation Matrix: Bilateral Ablation Data

	FC	PC	OC	TC	IT	TS	D-V	M-L	A-P	ND	Thresh.	Perf.
Total cortex	-.120	.607	.669	.695	-.150	.360	-.136	-.063	-.064	.110	-.091	.064
Frontal cortex		.058	-.507	-.311	.246	.230	-.168	.083	-.071	-.214	-.122	-.526
Parietal cortex			-.019	.163	-.292	.358	-.252	.048	-.169	.065	-.244	.152
Occipital cortex				.672	.020	.036	.010	-.182	.100	.280	.143	.191
Temporal cortex					-.261	.284	-.032	.066	-.215	.063	-.095	.096
Initial threshold						-.170	-.120	-.104	.169	-.166	.124	-.108
Testing schedule							-.080	.033	-.179	-.312	-.405	.083
Dorso-Ventral								-.369	-.227	-.081	.442	-.136
Medio-Lateral									-.123	.153	-.393	.028
Antereo-Posterior										.277	-.119	-.077
Net deviation											-.059	.015
Threshold												-.190