Lateral Hypothalamus: Reevaluation of Function in Motivated Feeding Behavior

Abstract. *In contrast to the existing views of lateral hypothalamic function, food motivated behavior appears to be greatly enhanced in animals that have recovered from lateral hypothalamic lesions. In a familiar environment, these rats begin eating 4.8 times sooner than normal controls, 5.6 times faster than hyperphagic rats that have received ventromedial hypothalamic lesions, and 4.7 times faster than animals with septal lesions. The same relation holds for latencies to eat in a novel environment and for rate of acquisition of a simple food-rewarded discrimination task. The concept of a lateral hypothalamic "hunger center" is questioned.*

The historical coincidence of two scientific events contributed significantly to contemporary views on the neural regulation of food intake. Shortly after the numerous reports of hyperphagia and obesity produced by destruction of the ventromedial hypothalamus (*1*), Anand and Brobeck (*2*) found that lesions placed lateral to the ventromedial hypothalamus resulted in a severe aphagia. These findings were quickly synthesized into a theory in which food motivated behavior was regarded as a result of the relative activity of these two hypothalamic mechanisms (*2, 3*). The medial "satiety center," that is, the ventromedial hypothalamus, was assumed to exert an inhibitory influence over the lateral hypothalamus excitatory "hunger center." Electrical (*4*) and chemical (*5*) stimulation of these areas provided complementary evidence. Stimulation of the lateral area dramatically increases food intake, whereas ventromedial hypothalamic stimulation abruptly inhibits food motivated behavior.

In spite of the fact that animals with lateral hypothalamic lesions (LH) will eventually recover the ability to eat if forced intragastric feeding is maintained (*6*), and regardless of suggestions that the lateral hypothalamic syndrome might be due to the interruption of fibers projecting to "extrahypothalamic" structures (*7*), or the possibility of feeding apraxia (*8*), the theory of hypothalamic "hunger" and "satiety" centers has been generally accepted and included in recent textbooks (*9*).

Our experiments suggest that, if motivation is assessed by measures more sensitive to hunger and less sensitive to other deficits which have been reported to impair the LH's behavior (such as, motor), a totally different picture of the behavior of animals that have received lateral hypothalamic lesions emerges.

Lateral hypothalamic, ventromedial hypothalamic, and septal lesions were placed (*10*) in albino rats approximately 100 days old. All animals sustaining lateral hypothalamic damage (see Fig. 1) exhibited a period of aphagia for 7 to 43 days, during which forced intragastric feeding was necessary. In order to assure complete recovery, testing was not begun for at least 21 days after voluntary eating and drinking were resumed by these animals. Animals with ventromedial hypothalamic lesions (VMH) displayed an acute dynamic and a chronic dynamic period (*11*) during which an accelerated weight gain was observed. All VMH animals were tested 21 to 35 days after surgery while they were still in the dynamic stage of hyperphagia (*11, 12*). Rats with septal lesions (SPT) exhibited the characteristic hyperreactivity-rage syndrome (*13*) which gradually subsided. The animals were completely tractable at the time of testing.

Two latency tests, separated by 7 days, were run in a counterbalanced design as a control for order effects. One-half of the animals in each of the four groups was tested in a familiar environment (home cage) first, while the other was exposed to a novel environment (open field) first. One of the LH animals died before it could be tested in the novel environment. No differences attributable to order effects were observed, so the data for each group were pooled.

The animals were tested for their latency to eat in a novel open field situation. After being deprived of food (but not water) for 21 hours, each animal was placed in the center of an enclosed, square open field, which was divided into 25 squares (16 by 16 cm), with a standard laboratory food pellet (Teklad) in the center of each of the 25 squares. Latency to pick up a pellet and to begin eating was recorded for each animal. If a feeding response did not occur within 300 seconds, testing for that animal was terminated.

The procedure for testing in the familiar environment (home cage) was as follows: A handful of standard laboratory pellets was placed in the animal's cage. The period of time elapsing between placement of food and the initiation of an eating response defined the latency measure in this experiment.

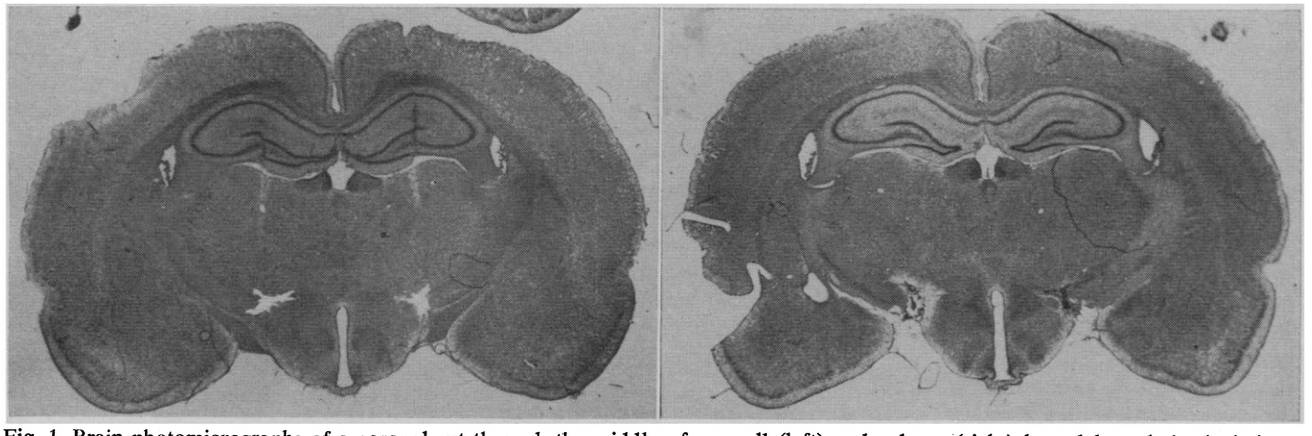

Fig. 1. Brain photomicrographs of a coronal cut through the middle of a small (left) and a large (right) lateral hypothalamic lesion.

Table 1. Acquisition of a left-right discrimination.

Pair	Trials to criterion	
	LH†	Control
1	16	46
2	16	33
3	11	50*
4	35	50*
5	29	50*

* Testing was terminated if the animal did not reach criterion in 50 trials. † LH = rats with lateral hypothalamic lesions.

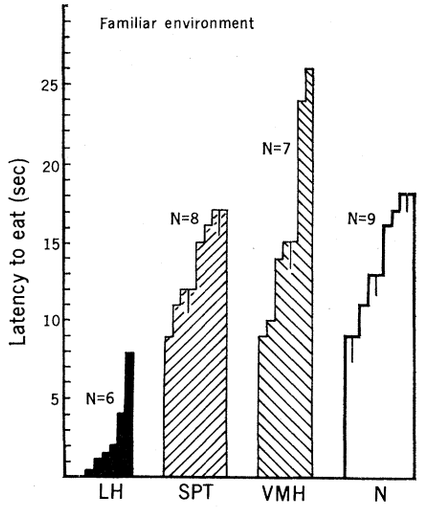

Fig. 2. The effect of brain lesions in rats on the latency to eat standard food in a familiar environment. LH, lesions in lateral hypothalamus; SPT, lesions in septal nuclei; VMH, lesions in ventromedial hypothalamus; N, normal (no lesions).

As can be seen in Figs. 2 and 3, LH animals begin eating almost immediately in both the novel and familiar environments. These results were analyzed by the nonparametric Mann-Whitney U test (*14*). Not only are LH animals significantly faster than normal controls in all conditions ($P < .001$), but they are considerably quicker than starved VMH hyperphagics ($P < .001$).

The fact that LH animals eat much more readily than normal controls, VMH hyperphagics, and SPT animals in the familiar environment should obviate any "response disinhibition" or "reduced fear" interpretation as to why LH animals respond more quickly in the novel environment (although there is no experimental precedence for such an interpretation). No fear or inhibition of responding should prolong the latencies of normal controls or VMH's in their home cages, while such factors could conceivably be operative in the novel environment. But again, there is no reason to believe that LH animals would not be subject to the same inhibitory influences. Nevertheless, SPT animals were included in these experiments as a further control for such an interpretation. The SPT's display a lack of response inhibition as evidenced by passive avoidance deficits (*15*). If disinhibition contributes to the short latencies of LH animals, SPT's should be at least as fast. This was not the case. The LH animals responded more quickly than their SPT controls ($P < .001$). Thus, response disinhibition should be discounted as a factor responsible for the short latencies of LH animals. In general, SPT's respond more quickly in the novel environment than normal controls or VMH's, but not in the familiar environment. This observation lends further support to the response disinhibition theory of septal lesions (*15*).

If latency to eat is a valid measure of motivation (*16*), then it must be concluded from these experiments that LH animals are more highly motivated to eat than normal controls, VMH's, and SPT's. In view of the nature of our findings, an additional test was instituted. If LH's are more motivated than controls, this enhanced motivation should facilitate the learning of a simple discrimination task. Therefore, LH animals were compared to normal controls in their rate of learning a left-right discrimination for food reward.

After a 36-hour deprivation period, each LH and his control were trained, in one session, to run to the positive [food-containing (*17*)] arm of a Y-maze (*18*). The positive side for any particular animal was determined as the side opposite to which the animal ran in a preliminary (unrewarded) trial. Therefore, if the animal ran to the left arm of the maze on this pretrial, the right arm would subsequently be the rewarded (correct) side. During each session, trials were alternated between an LH and his normal control. A maximum of 60 seconds was allowed for each animal to make a response, after which the animal was removed and caged while his partner was run. When the animal reached the goal dish, he was allowed to eat approximately 2 seconds and then was removed. If an animal did not meet the learning criterion of nine out of ten consecutive correct responses by the 50th trial, training for that animal was terminated. A total of six LH's and six controls were run. One LH had to be eliminated. This animal suffered from severe skeletal motor deficit.

The LH's reached the 90 percent

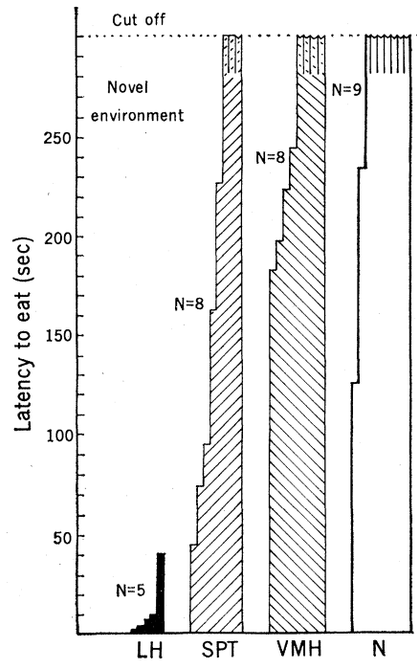

Fig. 3. The effect of brain lesions in rats on the latency to eat standard food in an unfamiliar environment. LH, lesions in lateral hypothalamus; SPT, lesions in septal nuclei; VMH, lesions in ventromedial hypothalamus; N, normal (no lesions).

correct criterion very quickly, usually by the 16th trial (Table 1). In contrast, only two of the normal controls learned the correct response in less than 50 trials. Because there is no reason to believe that lateral hypothalamic lesions enhance learning in general (*19*), it must be concluded that their superior performance reflects an enhanced motivational state.

As a result of our experiments, we question the notion of a lateral hypothalamic "hunger center." The LH animals in these experiments had suffered severe destruction of the alleged "center" yet exhibited a strong food motivation. Earlier studies (*2, 6*) included only the amount eaten, or the weight gained in animals that had received lateral hypothalamic lesions, which of course is commonly observed to be less than that of controls. But such measures may also be highly sensitive to motor, metabolic, or other deficits resulting from the lesion.

Our LH animals never achieved a body weight equivalent to that of matched-age normal controls and remained at approximately 70 percent of normal weight when maintained on a free-access diet of standard laboratory chow. The factors responsible for the failure of LH's to regain weight are still not clear. It could be that because

of a motor, metabolic, arousal, or other deficit, these animals could be considered to be in a chronic state of deprivation. In that food motivation appears to bear a fairly direct relation to body weight (*20*), it could be hypothesized that the strong food motivated behavior exhibited by animals that have recovered from lateral hypothalamic lesions is due to their chronic state of "lesion-imposed" deprivation. They readily approach and begin eating food, yet they may be unable to consume sufficient amounts and metabolize it efficiently (*21*).

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10. Lesions were produced by passing anodal current through a stainless steel electrode 0.015 inch in diameter. Current parameters were: LH, 2 ma per 10 seconds; VMH, 1.5 ma per 10 seconds; SPT, 2 ma per 20 seconds. Animals in the LH group sustained bilateral damage to the medial part of the internal capsule, lateral hypothalamus, and zona incerta at the level of the VMH. The VMH animals received discrete bilateral lesions of the ventromedial hypothalamic nuclei. The SPT animals sustained damage of both medial and lateral septal nuclei.
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21. After this report was submitted for publication, results have been gathered indicating that LH animals are also efficient in performing a food-reinforced position reversal task.
22. We thank Andrea Murray for collaboration. John Kelsey provided some of the septal animals. Supported by NIH grant MH-14596 to S.B.

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Amnesia Produced by Spreading Depression and ECS: Evidence for Time-Dependent Memory Trace Localization

Abstract. *Rats were given electroconvulsive shock and bilateral cortical spreading depression, either alone or in combination, at various times after a single passive avoidance training trial. Assessment of retention deficits, 24 hours after training, revealed a U-shaped amnesic function for cortical spreading depression as compared with the short linear function consistently obtained with electroconvulsive shock in this situation. Induction of cortical spreading depression immediately after training resulted in an extension of the amnesic gradient produced by electroconvulsive shock, presumably by disruption of the subcortically confined memory trace. In addition to indicating a subcortical locus of action for the amnesic effects of electroconvulsive shock, these results are interpreted as favoring a hypothesis of time-dependent memory trace localization in short-term memory processing, which involves an initial subcortical localization of the trace followed by a phase involving either direct or indirect cortical participation in a multistage memory fixation process.*

Past research has demonstrated that electroconvulsive shock (ECS) administered shortly after training produces behavioral performance deficits on a subsequent 24-hour retention test. This phenomenon, commonly referred to as retrograde amnesia, is generally attributed to a disruption of memory consolidation (*1*). A number of recent studies have attempted to localize areas within the brain specifically responsible for this amnesia in the belief that such findings will lead to a better understanding of the neurobiological basis of the memory storage process (*2*).

Our purpose in the experiments reported here was to investigate the temporal and sequential role of the cortex and subcortex in the memory fixation process as well as the amnesic action of ECS. This was done by studying the memory disruptive effects of ECS and cortical spreading depression (CSD), alone and in combination, on learning of a single-trial passive avoidance task in rats. The results of these experiments may be summarized as follows: (i) confirmation of a previously reported U-shaped function between degree of amnesia and time elapsed between training and initiation of CSD; (ii) delay of the period of vulnerability for memory disruption to CSD by induction of CSD immediately after training; (iii) extension of the ECS-induced temporal gradient of amnesia as a result of functional decortication by induction of CSD immediately after training. In addition to indicating a subcortical locus of action for the amnesic effects of ECS, these data are interpreted as favoring a hypothesis of time-dependent memory trace localization in short-term memory processing, which involves an initial subcortical localization of the trace followed by a phase that involves either direct or indirect cortical participation in a multistage memory fixation process.

Subjects were 194 male rats (*3*), 90 to 100 days old; they were maintained in individual stainless steel cages with free access to food and water.

The one-trial passive avoidance apparatus (*4*) consisted of a small compartment separated from a larger compartment by a guillotine door. Animals were given a single training trial followed by a single retention trial 24 hours later. During training each animal was placed in the small compartment, the guillotine door was opened, and the latency to enter the large compartment was measured to the nearest 0.1 second. After entry, the guillotine door was closed and the various treatment procedures were initiated. For animals receiving aversive training, closing of the door automatically triggered the presentation of a 60-cycle a-c electric shock of 1.0-ma intensity