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Sensory Neglect Produced by Lateral Hypothalamic Damage

Abstract. *Unilateral lateral hypothalamic lesions in rats produce deficits in orientation to contralateral visual, olfactory, whisker-touch, and somatosensory stimuli. This syndrome of sensory neglect appears to be involved in some of the deficits in feeding and attack which follow bilateral lateral hypothalamic lesions.*

The lateral hypothalamus is important in both feeding and attack behavior. Electrical stimulation of this region can produce overeating (*1*) and stimulation-bound killing (*2*). Lateral hypothalamic lesions produce deficits in both behaviors (*3*). MacDonnell and Flynn (*4*) found that touching the contralateral upper or lower lip of a cat during unilateral hypothalamic stimulation elicited reflexive mouth opening. Furthermore, touching a discrete area in the contralateral maxillary snout region of the cat elicited reflexive head turning toward the stimulus. These reflexes, head turning and mouth opening, are involved in the cat's integrated biting attack on a rat. Increasing the intensity of lateral hypothalamic stimulation enlarged the effective sensory field around the mouth. In the absence of any hypothalamic excitation, touch around the mouth did not elicit the attack reflexes. MacDonnell and Flynn therefore suggested that lateral hypothalamic control over attack behavior may act partly through sensory systems, since hypothalamic excitation facilitates the action of sensory stimuli involved in eliciting such behavior.

Lateral hypothalamic control of sensory mechanisms has also been suggested by Turner's unpublished observations. Turner found that unilateral lesions in the amygdalo-lateral hypothalamic system of rats produced contralateral deficits in responding to visual and somatosensory stimuli. This experiment was undertaken, therefore, in order to extend Turner's observations and to determine the extent to which sensory deficits might contribute to the syndromes of aphagia and loss of attack.

Twelve female Sprague-Dawley albino and two male hooded rats were used. All rats were housed individually. Water in Richter tubes and food pellets on the cage floor were available at all times. Most rats received the tests described below for at least 1 week preoperatively. This provided a baseline against which to measure the effect of lateral hypothalamic damage. Rats were then anesthetized with Equithesin or Nembutal and placed in a stereotaxic instrument (David Kopf Instruments) with the skull level. Unilateral or bilateral lesions were made by passing 1 to 2 ma of direct current for 10 to 30 seconds through an insulated stainless steel anodal electrode (0-0 insect pin), bared to a 0.5-mm conical tip (*5*). All animals were tested on the day after the operation to evaluate initial deficits. Thereafter, the animals were tested two or three times per week in order to assess recovery of function.

Three sets of tests were used to measure sensory and motor functions. The first set measured head orientation to sensory stimuli. A normal rat investigates a stimulus by orienting its head toward it. As shown in Fig. 1, this natural response was used to determine the responsivity of rats before and after lateral hypothalamic damage. For example, to test vision on each side of the body, a 2 by 2 inch (5 by 5 cm) piece of white or yellow cardboard was moved in front of each eye. Normal

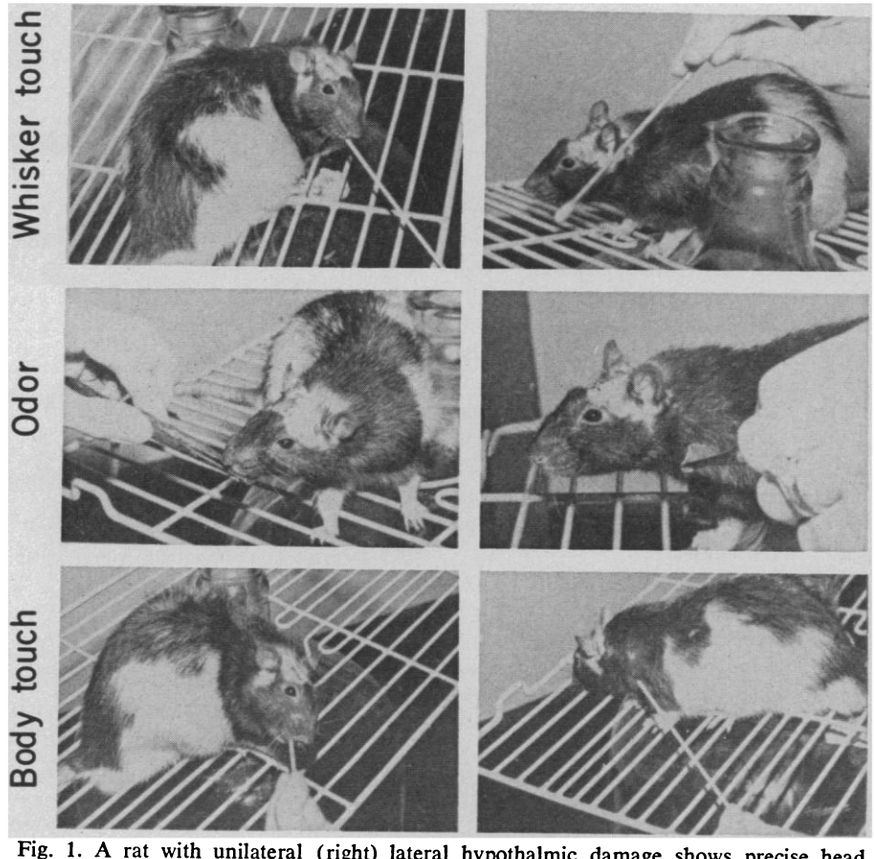

Fig. 1. A rat with unilateral (right) lateral hypothalmic damage shows precise head orientation and biting to various kinds of stimuli (whisker touch, odor, body touch) on the ipsilateral side (pictures at left) while neglecting the same stimuli presented contralaterally (pictures at right).

rats typically turn their heads toward this visual stimulus.

To test olfaction, we looked for head orientation to a ¼-inch cube of chocolate held in forceps or to a cotton swab soaked in Mennen shaving lotion (both of which elicited approach) or to an ammonia-soaked swab (which elicited approach followed by turning the head away).

In response to whisker-touch by a cotton swab on each side of the face, normal rats will orient toward and often bite the swab. Similarly, sensitivity of the entire body surface on each side was explored by noting whether the rat would orient toward or bite stimuli of several intensities (touch of the rat's body hair with a cotton swab; Von Frey hairs of 1, 2, 4, 8, and 16 g of pressure; pinprick; and pinch with forceps) applied systematically to several areas along the body surface.

When testing for the rat's response to olfactory and whisker-touch stimuli, we generally attempted to avoid entering the visual field by moving stimuli toward the snout from the rear of the animal. Also, the olfactory and visual stimuli were held far enough away from the rat's snout to avoid contact with the whiskers.

The second set of tests measured limb coordination. Several tasks were used to test the righting response, resistance to gravitational pull, and cage climbing. Normal rats, when placed in a supine position in the experimenter's hand, will use their limbs to right themselves to a prone position. When normal rats are placed on a laterally tilted platform, they use their limbs effectively in resisting the pull of gravity to either side. Normal rats use all four limbs effectively when climbing around on the rungs of a wire cage on which they have been placed. The cage used in this test was a wire box (14 by 12 by 10 inches) of the type used to carry milk bottles.

The third set of tests measured feeding and attack behaviors. Daily measures of food and water intake and body weight were taken. Tube-feeding and special diets (chocolate-chip cookie, pablum, Sustagen) were required to maintain rats with bilateral lateral hypothalamic lesions and to assess their stage of recovery (*6*). Normal rats were able to maintain their body weight on Purina lab pellets and water. Some rats also were tested for a preferred side for obtaining food, by placing cups containing lab pellets on both the right and left sides of the cage and then measuring the amount of food taken from each cup daily.

The rat's attack behavior was evaluated in two ways. First, rats were tested to see whether they would bite at a pair of forceps used to pinch the forepaws or a wooden probe used to rub the snout on each side. Normal rats typically bite these stimuli. Second, all rats were tested to see whether they would kill a mouse put in the home cage overnight. If the rat did kill the mouse, then additional mice were offered in order to determine latency to kill. Three rats were found which killed mice preoperatively. After a few days of testing, all three killed a mouse within 20 seconds of its introduction into the home cage.

The most obvious and dramatic effect of damaging the lateral hypothalamus (*7*) on one side was to impair profoundly the rat's ability to orient to stimuli on the side contralateral to that of the lesion. Rats with unilateral lesions initially showed no orientation to contralateral visual, olfactory, whisker-touch, or somatosensory stimulation, whereas they responded promptly to the same stimuli presented ipsilaterally (see Fig. 1). Rats with bilateral lesions showed impaired responsivity to sensory stimuli on either side.

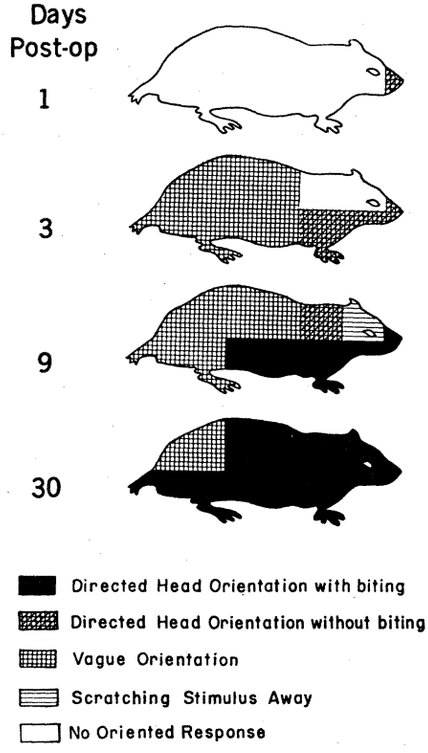

Fig. 2. Pattern of recovery (after left lateral hypothalamic damage) of orientation to tactile stimulation (HT) of various points of the contralateral body surface. (HT stimulus means touch of the hairs along the body surface with a cotton swab.) During the course of recovery, direct orientation and biting to rostral points occurs prior to orientation and biting to more caudal points.

In the tests of limb coordination, rats with unilateral lateral hypothalamic damage showed great difficulty in using their contralateral limbs to right themselves and to brace themselves against the pull of gravity. The rats missed the cage rungs with these limbs during cage climbing and were often defective in grasping food pellets with the contralateral limbs. Since they seemed to use all limbs quite well during locomotion on a flat surface, during scratching, and during grooming, the observed deficits in limb use were apparently caused by a loss of proprioceptive information rather than by motor dysfunction. However, the possibility of a motor deficit cannot be excluded, since no systematic effort was made to separate proprioceptive loss from motor impairment in limb use.

Reponsiveness to sensory stimuli gradually recovered after lateral hypothalamic damage. During the first post-operative week, the rats showed progressively greater orientation to whisker-touch and to olfactory stimuli. Generally, direct head orientation to visual stimuli and accurate limb use recovered more slowly. These rats also showed a pattern of increasing localization of somatosensory stimuli on the contralateral body surface during recovery. Somatosensory responsivity progressed rostrocaudally during recovery (see Fig. 2). Directed orientation generally occurred first to stimulation of the snout and face regions, later to stimulation of the midsection, and finally to stimulation of the flanks. In some animals, this rostrocaudal pattern of recovery was quite marked, giving the impression of a wave of sensitivity slowly progressing down the animal's body day by day.

Bilateral lateral hypothalamic lesions produced total aphagia and adipsia lasting from 1 to 9 days, followed by the usual syndrome of recovery (*6*). Analysis of the relationship between recovery of feeding and recovery of orientation to sensory stimuli revealed a striking finding. In all five animals with bilateral lesions, transition from stage

1 (complete aphagia) to stage 2 (accepting only highly palatable foods) occurred on the same day that direct head orientation to olfactory stimuli first appeared. Furthermore, in all animals, direct orientation to whisker-touch had preceded or was coincident with transition from stage 1 to stage 2. Rats with unilateral lesions which were tested for side preference in feeding generally took more food from the container located in the ipsilateral field, though preoperatively no such preference had existed. Thus, it seems that the effect of the lesion was to produce a neglect for the sensory stimuli signaling the presence of food on the contralateral side.

Damage to the lateral hypothalamus also drastically affected oriented biting and attack. Initially, rats with unilateral lesions would not bite either a pair of forceps used to pinch the contralateral forepaw or a probe used to rub the contralateral snout region, whereas responsiveness to the same stimuli presented ipsilaterally was normal. Rats with bilateral lesions showed impairments in biting to stimuli presented on both sides. When a mouse was placed in the cage, all three mouse-killing rats (with unilateral lateral hypothalamic lesions) ignored the mouse when it was in the contralateral field. But as soon as the mouse moved into the ipsilateral field, the rats showed oriented biting attack on the mouse. They did not succeed in killing a mouse for at least 1 week postoperatively, largely because the mouse would escape to the defective contralateral side. This indicates that some integration of sensory input from both sides of the body is necessary for a rat to kill a mouse.

In summary, then, lateral hypothalamic lesions produce severe deficits in orientation to sensory stimuli, which in turn appear to have profound consequences for feeding and attack behavior. After receiving unilateral lesions, rats do not use information from the contralateral side of the body either to initiate attack or to accept food placed there. Furthermore, after bilateral damage, the early stages of recovery from aphagia are correlated with recovery of direct orientation to olfactory and whisker-touch stimuli. Additional support for the idea that sensory information from the snout region contributes to feeding comes from Welker's (*8*) finding that section of the trigeminal afferent branches produced great deficits in the ability of rats to locate food pellets in their cages. Trigeminal nerve section also eliminates biting attack in cats (*9*).

The results of this experiment are consistent with Hess's finding (*10*) that unilateral hypothalamic and subthalamic lesions in cats produce inattention to visual, tactile, and proprioceptive stimuli on the opposite side. Hess also reported that bilateral damage produced deficits on both sides. Also, Ellison *et al.* (*11*) mentioned briefly that they observed bilateral deficits in attending to sensory stimuli in rats following neural isolation of the entire hypothalamus from the rest of the brain.

The precise nature of the observed deficit in orientation to sensory stimuli observed in this experiment needs further clarification. Our observations suggest that the impairment after lateral hypothalamic damage is not simply motor, since rats with unilateral lesions have been observed to turn contralaterally during locomotion in an open field situation as well as during grooming. In the normal act of grooming, a rat typically starts by grooming its face and head with its paws, turns to one side and grooms its side and flank, then terminates the sequence by grooming the opposite side and flank. Thus, during normal grooming, the rat's head is turned and oriented to one or the other side just as it is during normal orientation to tactile stimuli from that side. After unilateral lateral hypothalamic damage, the rat grooms the contralateral side of the body only after it has groomed the ipsilateral side. It grooms its face and head with its paws, simultaneously and rhythmically, turns to groom the ipsilateral side and flanks, then often completes the grooming sequence by grooming the contralateral side in the normal manner. However, even seconds after grooming the side contralateral to the lesion the rat ignores tactile stimuli to that side and fails to turn contralaterally toward those stimuli. Such failure to respond to stimuli even when the animal clearly can perform the necessary head movements makes us believe that the deficit is not motor, but rather a lack of responsiveness to sensory stimuli.

Similarly, the differential rate of recovery of sensory systems (for example, recovery of orientation to olfactory stimuli before orientation to visual stimuli) seems to preclude a simple motor impairment. Nor does the deficit resemble deafferentation, because autonomic (respiratory changes) and skeletal reflex (eyeclosure, tooth chattering) behaviors often occurred when a stimulus was presented on the contralateral side. Instead, the deficit seems more an inability of the rat to integrate sensory information with motor patterns in performing localized, adaptive responses. In this respect, the syndrome described here seems similar to syndromes in the cat following brainstem lemniscal lesions (*12*) and in macaques and humans following parietal lobe damage (*13*).

The nature of the deficit requires exploration in more detail. It is clear from this experiment, however, that damage to the lateral hypothalamus which produces aphagia and loss of killing also produces impairments in the ability of rats to respond to sensory information. These impairments seem to be causally implicated in the loss of mouse-killing as well as in the initial stages of the aphagia syndrome.

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