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## Hypothalamic Stimulation Facilitates Contralateral Visual Control of a Learned Response

Abstract. *Rats that ate during hypothalamic stimulation were trained to press a lever for food only while receiving light signals from head-mounted lights. During stimulation, they pressed if the signal was visible to the eye contralateral to the electrode, but ignored the signal if it was visible only to the ipsilateral eye.*

Behavioral studies using both electrical stimulation and lesions have provided evidence suggesting that the lateral hypothalamus influences behavior, in part, by controlling the utilization of sensory information by systems that release and guide responses. One example is Bandler and Flynn's (*1*) demonstration, in cats, that unilateral hypothalamic stimulation facilities lunging toward a mouse seen by the contralateral eye. Another is Marshall and Teitelbaum's (*2*) report that unilateral hypothalamic lesions produce a contralateral neglect of olfactory, tactile, and visual stimuli.

In most of these studies, a sensory stimulus is presented to one side of the animal, evoking a reflex response directed toward the same side. Thus, it is difficult to determine whether it is really the sensory input or only the motor system that has been affected by the hypothalamic manipulation. By using an arbitrary, learned, stimulus-response connection, we have been able to show that lateral hypothalamic stimulation in rats produces a contralateral visual facilitation that cannot be attributed to motor potentiation. Rats were trained to use a visual discrimination to control a lever press response. During brain stimulation, the animal's responding was controlled solely by information received through the eye contralateral to the electrode.

We used four male albino rats that were induced to eat when stimulated through electrodes implanted in the lateral hypothalamus. Two of the rats had two electrodes each, bilaterally placed. The others had one electrode each. The stereotaxic coordinates for the six electrode sites, verified by subsequent histology as lateral hypothalamus, were 1.5 to 2.8 mm posterior to bregma, 1.5 mm lateral to the midline, and 8.5 mm below the level skull surface. Stimulation consisted of monophasic negative pulses, 0.2 msec in duration, delivered through monopolar stainless steel electrodes at a frequency of 100 pulses per second (*3*).

While deprived of food, the animals were trained to press a lever for 45-mg food pellets on a fixed ratio of three presses for each pellet. Then, while being stimulated, they were taught to press only while signal lights were on. Two tiny light bulbs (*4*) on stiff wire stalks were attached to the top of the rat's head. They were mounted on the miniature electrical connector between the electrodes and wires from the stimulator. For each animal, the stalks were bent to position the bulbs approximately 8 mm lateral to each eye. The bulbs were painted opaque black except for a 1.5-mm spot aimed at a point on the rat's head 5 mm below and 5 mm behind each eye, to ensure that each eye could receive light only from its own bulb (*5*). The visual discrimination was established by making food available only when both lights were on. Training continued until the rats pressed eight times as often when the lights were on as they did when the lights were off.

After this training, each animal was tested with only one light at a time. The hypothalamus was stimulated for 30-second periods separated by 60-second intervals. Left and right lights were presented in random order, switched while stimulation was off. Each electrode was tested in one continuous session of 20 stimulation periods, 10 with each light.

The results were the same for all six of the electrodes. During stimulation, the rats pressed the lever only when the contralateral light was on. When the stimulation was off, they made few or no responses. Lever press rates for the unilateral light test were compared with rates for the last session of the two-light discrimination training (Fig. 1). The animals performed the discrimination during stimulation as though they were using only the eye contralateral to the electrode. If the contralateral light was on, they pressed. If the contralateral light was off, they did not press, regardless of whether the ipsilateral light was on or off.

This finding is not a result of one light's being more visible than the other, because the animals with two bilateral electrodes (5L,R; 17L,R) used the left eye during stimulation through the right electrode, and the right eye during stimulation through the left electrode. In addi-

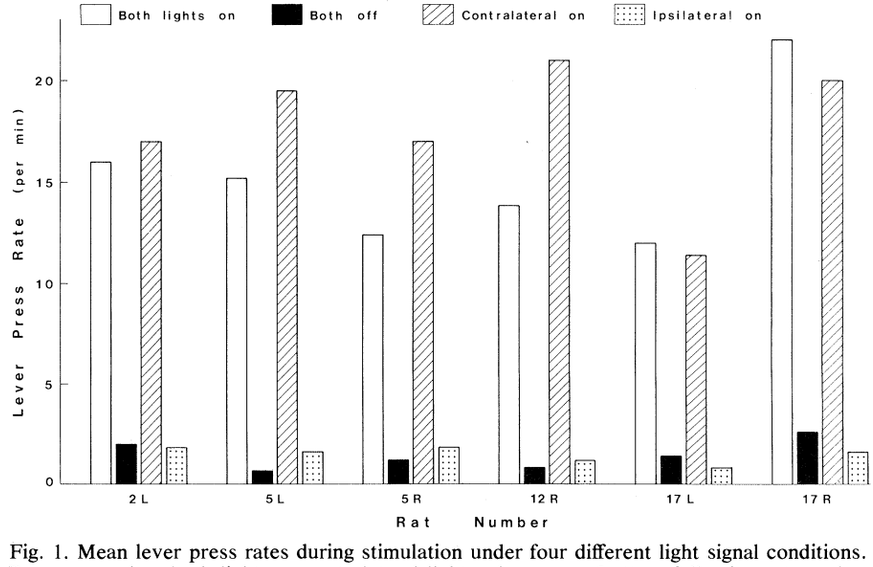


Fig. 1. Mean lever press rates during stimulation under four different light signal conditions. Rats press when both lights or contralateral light only are on. Letters following rat number indicate whether the electrode was on the left or right side of the brain. Each bar represents either 5 or 6 minutes of responding.

tion, when rat 2 was subsequently tested under hunger rather than stimulation, he used either eye equally well.

As neither the brain stimulation nor the response requirement changed when the light was switched from right to left, the change in response rate must be due to a difference in sensitivity to stimuli. This result confirms that the contralateral facilitation produced by stimulation is at least partially a sensory (input) effect.

This, of course, does not mean that the hypothalamus exerts only sensory control. Turner (*6*) concluded, on the basis of lesion-produced deficits in conditioned escape, that he had destroyed tissue that normally connected sensory and motor systems. As the animals in our experiment were not constrained to use one paw exclusively, the results do not bear on the issue of possible motor effects. We have observed, however, that rats trained to press a lever generally prefer one paw over the other regardless of which side of the hypothalamus is being stimulated or which eye sees the light signal.

The evidence we have presented supports the conclusion that hypothalamic stimulation produces functional behaviors such as eating and drinking in part through altering the animal's sensitivity to the sensory stimuli that trigger them (*7*). It also demonstrates that lateralized sensory facilitation produced by stimulation is not limited to the control of reflexes or stereotyped actions, such as orientation or biting, but can also affect the performance of a learned response.

WALTER K. BEAGLEY
*Department of Psychology,*
*Alma College,*
*Alma, Michigan 48801*
TERRY L. HOLLEY
*Developmental Studies, Georgia*
*State University, Atlanta 30303*

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## Alzheimer's Disease, Trisomy 21, and Myeloproliferative Disorders: Associations Suggesting a Genetic Diathesis

Abstract. *Relatives of probands with Alzheimer's disease had excessive incidences of trisomy 21 and myeloproliferative disorders. Microtubules are structures that are likely to be affected by a genetic defect causing a predisposition to Alzheimer's disease, trisomy 21 and, possibly, to myeloproliferative disorders.*

Among 301 first-degree and 556 second-degree relatives of 30 probands with histopathologically proven Alzheimer's disease, 22 had Alzheimer's disease, 6 had trisomy 21 (Down's syndrome, mongolism), and 13 had a myeloproliferative disorder. The incidence of trisomy 21 and myeloproliferative disorders is notably excessive compared to what one would expect in a general population (Table 1). Alzheimer's disease has a known genetic component (*1*). The morbid risks to relatives found in this study (parents 0.23 ± .07 and siblings 0.10 ± .04) are higher than those previously reported, probably because the number of probands with histologically proven disease was much larger in this study and the search for secondary cases was intense. The evidence adds to a set of relationships implicating a single genetic defect in the etiology of some proportion of all three disorders and suggests faulty organization of microtubules as a cause of the pathology.

Alzheimer's disease is one of the presenile dementias present in about 70 per 100,000 persons over age 40 dying in Minnesota (*2*). Starting in late middle age the victim exhibits a loss of memory for recent events, and this decline in mentation relentlessly progresses until a vegetative state is reached. The cases of Alzheimer's disease for this study came from a series of 2204 consecutive autopsies done between 1952 and 1972 in Minnesota state hospitals and a state nursing home. Brain tissue changes characteristic of Alzheimer's disease were found in 30 persons: 12 males and 18 females whose illness began before age 65. The mean age of onset was 55.9 years, the remaining life expectancy was 7.9 years, and all were of North European origin.

From their relatives and from records, a medical history was obtained for the probands' parents, siblings, and children, and for all relatives of probands and their siblings through second-degree genetic relationships to an affected person (proband or relative who had Alzheimer's disease). At least one interview was conducted per family and there were usually four or five interviews. All birth and death certificates and medical records were reviewed. Special effort was directed at obtaining autopsy results or obtaining autopsies of relatives who died while the study was in progress.

In 6 of the 22 relatives with Alzheimer's disease, the disease was confirmed by autopsy. Diagnoses for 11 cases were based on medical records and, for five cases, on family history. All cases of trisomy 21 were diagnosed in medical facilities. In two cases a karyotype demonstrated the trisomy and in four cases the diagnosis was based on clinical evidence. A clinical diagnosis of trisomy 21 is based on relatively unambiguous physical criteria and is considered quite valid. However, the possibility of translocations and mosaics causing the disorder cannot be excluded. In addition, five persons, all deceased, had phenotypes suggesting autosomal aberrations, and there was an excess of neonatal deaths [from 50 to 300 percent depending on the group used for comparison (*3*)]. These findings suggest that aberrations other than trisomy 21 were present in excess.

All of the myeloproliferative disorders were diagnosed in medical facilities, although in four cases the only written rec-

Table 1. Expected and observed incidences of trisomy 21 and myeloproliferative disorders among relatives of 30 probands with Alzheimer's disease (*14*).

| Disorder | Persons at risk | Number of cases | | *P** |
|---|---|---|---|---|
| | | Expected | Observed | |
| Trisomy 21 | 777 | 1.20 | 6 | < .0001 |
| Myeloproliferative disorders | | | | |
| First- and second-degree relatives | 837 | 5.90 | 13 | < .01 |
| First-degree relatives | 301 | 3.06 | 10 | < .001 |

*Probability of observed result or one more extreme.