chemical and spectroscopic techniques in the rose, pea, greenbug, and cotton aphids (*9*). The effectiveness of *trans*-β-farnesene against six other aphid species (*10*) indicates that this compound is perhaps the most interspecifically active pheromone to be discovered.

Since exposure to the alarm pheromone causes aphids to escape rapidly from their feeding sites, especially by dropping from the host plant, an interesting and novel method of insect control may be realized.

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6. *trans*-β-Farnesene was also synthesized by dehydration of farnesol and nerolidol with both basic and acidic catalysts [see (*7*) for review]. Our procedure is somewhat more convenient and gives a better yield of the desired isomer.
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8. Bioassays were performed by applying 30 ng of the active compound in 3 μl of methanol to filter paper disks (6 mm in diameter) and presenting them to 10 to 20 apterous aphids at a distance of 0.5 to 1 cm. A positive response was indicated by 50 to 100 percent of the aphids walking or dropping from feeding sites on plants. Aphids exposed to disks treated with methanol or untreated did not respond.
9. Rose aphid, *Macrosiphum rosae* (L.); pea aphid, *Acyrthosiphon pisum* (Harris); greenbug aphid, *Schizaphis graminum* (Rondani); and cotton aphid, *Aphis gossypii* Glover.
10. Potato aphid, *Macrosiphum euphorbiae* (Thomas); English grain aphid, *Macrosiphum avenae* (Fabr); foxglove aphid, *Acyrthosiphon solani* (Koltenbach); green peach aphid, *Myzus persicae* (Sulzer); corn leaf aphid, *Rhopalosiphium maidis* (Fitch); and oat birdcherry aphid, *Rhopalosiphum padi* (L.).

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Relation between REM Sleep and Intracranial Self-Stimulation

Abstract. *Depriving rats of rapid eye movement (REM) sleep was shown to lower their thresholds and raise their response rates for rewarding brain stimulation. Conversely, allowing rats to self-stimulate while they were being deprived of this sleep form reduced the amount of REM rebound during recovery from deprivation. These results demonstrate a reciprocal relation between rewarding brain stimulation and REM sleep.*

Although traditionally sleep has been thought of as a state of relative quiescence, at least one type of sleep, rapid eye movement (REM) sleep, is a state of extreme activation of the central nervous system (*1*). Dement and others (*2*, *3*) have shown that there is a lowering of threshold of many neural and behavioral activities following REM deprivation (*3*). Their data suggest a generalized neural hyperexcitability after REM deprivation, which in turn is hypothesized to be reflected in heightened behavioral activity.

In the first experiment, we chose to look at the effect of REM deprivation on positively reinforcing electrical brain stimulation, also called intracranial self-stimulation (ICSS) (*4*). This is of particular interest in that ICSS measures activity of the central nervous system (CNS) through behavioral methods. In addition, some of the "drive" behaviors that Dement and his associates (*3*) have elicited as a result of REM deprivation have also been elicited from hypothalamic regions that are ICSS areas (*5*). Our specific prediction in the first experiment was that thresholds for ICSS would be lowered following REM deprivation. In other terms, we predicted that subjects would be more sensitive to ICSS following REM deprivation.

To test this hypothesis, 12 male albino Holtzman rats weighing approximately 250 grams at the start of the study were used as subjects. Two pairs of insulated stainless steel electrodes were implanted in each rat with the use of a stereotaxic device while the animal was under sodium pentobarbital and chloral hydrate anesthesia. One pair of electrodes was aimed at the medial forebrain bundle, a structure yielding strong self-stimulation effects. A second pair recorded activity from the dorsal hippocampus. Two cortical screws were implanted to record from the frontal and occipital cortex. After completion of the experiment, animals were killed by perfusion. Histological sections stained according to the Luxol fast blue and cresyl violet method were made and confirmed the electrode placements.

Electrical brain stimulation consisted of biphasic rectangular waves. Each pulse pair consisted of two 0.2-msec waves, opposite in polarity and separated by an interval of 0.2 msec. Pulse pairs were delivered at a frequency of 100 per second, and train duration was held constant at 0.25 sec. Current was varied according to the demands of the experiment and was continuously monitored on an oscilliscope.

Subjects were taught to self-stimulate; ICSS was delivered when the subject pressed a lever in an experimental chamber. The range of current intensities that would support responding on a continuous reinforcement schedule was explored, and rate-intensity functions (*6*) were collected for 10 days. Then, ascending rate-intensity functions were collected during 1-hour sessions conducted at the same time during each of 4 consecutive days (baseline data). Immediately after the 1-hour session of the 4th day, six subjects (REM deprivation group) were deprived of REM by the platform method (*7*), and six subjects were placed on a larger platform (13 cm) and used as a yoked control group (*8*). The REM deprivation and yoked control subjects were on their respective platforms approximately 23 hours. After this period, all subjects were placed in a self-stimulation test chamber, and ascending rate-intensity functions were again obtained. The cycle of 23 hours on the platform followed by 1 hour of ICSS testing was continued for 4 days. After the 4 days of REM deprivation, subjects were returned to their home cages, and rate-intensity functions were again ascertained each day for an additional 4 days (recovery period). Following a 2-week rest period, four subjects that originally were in the REM deprivation group were placed on the large platform and used as a nonyoked control group (*8*).

In general, both control groups showed a lowering of response rates and a rise in ICSS threshold, while the REM deprivation group showed the opposite, increased response rates and lowered ICSS threshold. In all respects, these control animals were treated identically to animals that were on the REM deprivation platform, and both yoked and nonyoked controls fell off

their platforms at least as often as did REM deprivation animals.

Figure 1 gives rate-intensity data for control sessions, sessions during REM deprivation, and REM recovery sessions for a representative animal. Deprivation of REM generally lowered ICSS thresholds and increased rates of responding. This was not the case for the highest intensity; when this was used, response rates after REM deprivation were lower for all subjects. We interpret the lowering of self-stimulation rates at the highest intensity as further evidence that REM deprivation lowers self-stimulation thresholds. Thus, REM deprivation has not altered the shape of the self-stimulation curve, but has shifted the entire curve toward the lower intensities. This was not true during the REM recovery phase. When animals were again allowed to obtain REM sleep, self-stimulation rates approximated control rates.

No animals tested on the large platform demonstrated either a lowering of threshold or an increase in self-stimulation rates. If anything, control subjects seemed to show an opposite (although not statistically significant) effect. This effect was slightly more pronounced in the yoked controls.

For each subject, a repeated-measure analysis of variance was performed. Rate-intensity data after REM deprivation were significantly different from baseline data for all subjects ($F = 4.63$, $P < .05$ level). Both the REM deprivation and intensity effects were significant, as was their interaction. In addition, grouped differences (one-way analysis of variance) were significant at the .01 level (that is, comparing data for nonyoked or yoked control subjects to that for REM deprivation subjects).

Two lines of evidence indicate that the lowering of self-stimulation thresholds by REM deprivation is not an artifact due to a nonspecific increase in general activity. First, response rate at zero intensity of stimulation did not increase. Even more conclusive is the fact that the observed shift of the entire rate-intensity function to the left for all subjects represents an increase in response rate at lower intensities, but a decrease in response rate at the highest intensity. The decrease in response rate at the highest intensity during REM deprivation occurred in all subjects and is significant at the .05 level (sign test).

In the experiment just described, we looked at the effect of REM deprivation on ICSS thresholds; in the second experiment, we examined the effect of ICSS on REM rebound. Dement and his associates (*9*) have shown that if an animal is deprived of REM sleep, then on subsequent days, when the animal is allowed to sleep uninterruptedly, the amount of REM sleep will be 50 to 60 percent greater than normal; this increase is REM rebound.

Table 1. Procedure for measuring effect of ICSS (1½ hours per day) on REM rebound.

Consecutive days	Treatment
10	ICSS testing
5	Rest
4	24-Hour sleep records (baseline)
3	REM deprivation; ICSS to AB animals; no ICSS to BA animals
4	24-Hour sleep records (REM recovery)
14	Rest
3	REM deprivation; ICSS to BA animals; no ICSS to AB animals
4	24-Hour sleep records (REM recovery)

Cohen and Dement (*3*) have demonstrated that REM deprived animals will not show a REM rebound if treated with electroconvulsive shock, but that electric shock below convulsive levels will not alter amounts of REM sleep. In previous experiments, electroconvulsive shock was administered both through external and intracranial routes. In the present experiment, we presented the animal with subconvulsive ICSS to the lateral hypothalamus, in an attempt to see if subconvulsive ICSS could reduce REM rebound.

Electrodes were implanted and placements verified histologically as described in the first experiment. Six male albino Holtzman rats trained to self-stimulate were subjects. Rate-intensity functions were generated. Animals were always observed when they received stimulation to insure that there were no behavioral signs of convulsion (*10*).

Subjects were tested in two conditions. Condition A consisted of REM deprivation with 1½ hours of ICSS per day; and condition B consisted of REM deprivation without ICSS, with subjects being kept awake 1½ hours per day. The order of testing was counterbalanced in a simple AB, BA design; REM deprivation was accomplished in three animals by the platform method (*7*), and in three animals (two tested in the AB order, one in the BA order) by hand awakenings. (That is, every time a subject would enter REM, it would be awakened by the experimenter.)

Animals were first tested for ICSS responses for 10 days and allowed to rest for 5 days. Then 24-hour sleep records were kept for 4 days to serve as baselines. Animals were deprived of REM sleep for the next 3 days (those tested in the AB order received ICSS daily). In the 4-day recovery period that followed, 24-hour sleep records were kept. After a rest of 2 weeks, the REM deprivation and recovery periods were repeated with animals tested in the BA order receiving daily ICSS during deprivation. Table 1 outlines the procedure.

Sleep records were scored for awake, light, or transition slow-wave sleep, deep slow-wave sleep, and REM sleep. A bipolar dorsal hippocampal electrode and two sets of cortical electrodes were used to score these states. The scoring technique used is described by Fishman and Roffwarg (*11*). Subjects were frequently monitored visually.

All of the animals, when tested in the B condition (REM deprivation without self-stimulation), displayed marked REM rebound (significant at the .005 level by analysis of variance). The REM rebound varied from 39 to 59 percent of total REM time on baseline days. The subjects that were deprived of REM by hand showed lower REM rebound, which was probably due to some experimental error (hand awakening may not be as efficient a procedure for REM deprivation as the platform method). In contrast, subjects tested in the A condition (REM deprivation with ICSS) had markedly lower REM rebounds, ranging from 13 to 23 percent of baseline REM. The effect of allow-

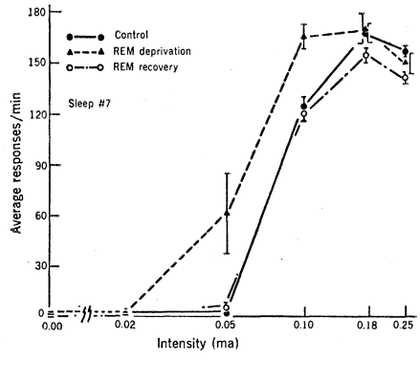

Fig. 1. Average response rate as a function of current intensity (plotted on a logarithmic scale) for a representative animal under three different conditions. Data were averaged for the 4 days of baseline conditions (solid circles), the 4 days of REM deprivation (triangles), and the 4 days of recovery (open circles).

ing subjects 1½ hours of ICSS is to reduce REM rebound by at least 50 percent in each subject. This effect was significant at least at the .01 level (one-way analysis of variance). Amounts of slow-wave sleep were almost identical in conditions A and B.

In these two experiments, we maintain that we have demonstrated that a waking behavior can reduce REM rebound patterns, and the corollary, that depriving an organism of REM sleep can affect a waking behavior. Explicitly, an organism deprived of REM sleep will be more sensitive to and select more ICSS. More specifically, we have demonstrated a reciprocal relation between REM sleep and ICSS. It is our view that the ICSS neural network is part of the neural network activated during REM sleep. From this we hypothesized that nuclei in the hindbrain that are involved in initiating aspects of REM sleep are ICSS sites. Ellman *et al.* (*12*) confirmed this hypothesis.

Our results can be explained on at least one other level. Dement and his colleagues (*9*) have maintained that REM sleep is triggered by, and in turn dissipates, a neurohumoral substance. When subjects are deprived of REM, this hypothetical substance is thought to accumulate. Jouvet has proposed (*13*) that norepinephrine is one of the biogenic amines involved in triggering and maintaining REM sleep. Stein (*14*), on the other hand, has implicated norepinephrine as an agent involved in mediating ICSS. One may explain the changes in ICSS as being potentiated by the release of norepinephrine as a result of REM deprivation. In a similar way, one could explain the reduction in REM rebound by ICSS as a partial depletion of norepinephrine. This explanation is extremely tentative, because it is not absolutely clear how norepinephrine is involved in either REM sleep or ICSS.

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6. In ICSS experiments, the subject is placed in a chamber, and electrical stimulation is delivered whenever the animal presses the lever. The subject is tested over a range of different intensities of stimulation, and rates of lever pressing are recorded for each intensity (rate-intensity function). In this situation, one can determine a threshold for electrical self-stimulation as well as a rate-intensity function.
7. Deprivation of REM was accomplished by placing the subject on a circular platform situated in the center of a vessel filled with water. The REM deprivation platform was 7 cm in diameter and protruded less than 1 cm above the level of the water. Loss of tonus from the neck muscles, which occurs at the onset of REM sleep, causes loss of balance, immersion in water, and consequent awakening. This procedure effectively deprives the subject of almost all REM sleep. Electroencephalographic recordings confirmed that this procedure prevented the subject from going into REM sleep, while allowing 65 percent of baseline slow-wave sleep to occur.
8. Two controls were run, because the results of our experiment might be due to the nonspecific stressful effects of being placed on the circular platform. Control subjects in both groups were placed on a 13-cm platform. Recordings demonstrated that animals on the large platform were not deprived of REM. Yoked control subjects were tested simultaneously with animals from a REM deprivation group, and every time a subject deprived of REM fell into the water, the corresponding yoked control subject was simultaneously dunked into the water (by tipping over its platform). Animals in the nonyoked control group were simply placed on a 13-cm platform. All subjects showed about a 35 percent reduction in slow-wave sleep.
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10. If there was any evidence of convulsion, even signs such as teeth grinding, standing in a fixed glazed position, and so forth, then the intensity of stimulation that produced this behavior was judged too high for use during the experiment. Subjects were tested as described (*6*) until an intensity was found which produced reliable subject response for stimulation and which was at least 20 mv below the intensity that produced even partial signs of convulsive behavior.
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Behavioral Changes of Chronic Schizophrenic Patients Given L-5-Hydroxytryptophan

Abstract. *Oral administration of the serotonin precursor* L-*5-hydroxytryptophan with a peripheral decarboxylase inhibitor produced mild to moderate improvement in six of seven chronic undifferentiated schizophrenic patients who were resistant to phenothiazine treatment, as compared to an oral administration of a placebo. Two of four chronic paranoid schizophrenic patients who were resistant to phenothiazine treatment became worse with 5-hydroxytryptophan, one improved. It is presumed that these psychological changes were directly or indirectly produced from increases in brain serotonin. Indirect data from animals and humans indicate that there may be an abnormality in serotonin metabolism in some schizophrenics. While our data are consistent with this hypothesis, other explanations for our data must be entertained.*

There are three lines of investigation supporting the hypothesis that some schizophrenic patients have an abnormality in serotonin metabolism (*1*). Two of these, sleep and psychotomimetic drug research, approach the problem indirectly. Animal and human sleep data indicate that serotonergic neurons may exert their influence by suppressing phasic events such as rapid eye movements (REM's) and pontine geniculate occipital spiking during nonrapid eye movement (NREM) sleep and perhaps during waking. These phasic events are thus normally forced to appear during REM or dreaming sleep (*2*). Some schizophrenic patients seem to have an abnormal frequency of REM's during NREM sleep (as defined by the electroencephalogram and the electromyogram), few during REM sleep, and, as opposed to most normal subjects, do not have REM compensation after REM deprivation (*1*). Cats given *p*-chlorophenylalanine, a drug that inhibits the synthesis of serotonin, have features of sleep and behavior similar to those of schizophrenic patients (*2*). This also appears to be true of the sleep of humans given *p*-chlorophenylalanine for medical purposes. In addition, a small number of such patients have had psychotic episodes while on this drug (*3*).

A possible endogenous substance that might produce these changes is the hallucinogen dimethyltryptamine. An enzyme capable of synthesizing di-