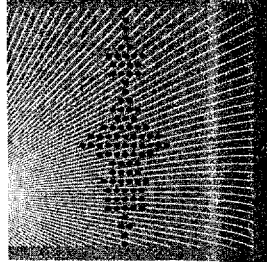


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# Microwave Irradiation Affects Radial-Arm Maze Performance in the Rat

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After 45 min of exposure to pulsed 2450 MHz microwaves (2  $\mu$ sec pulses, 500 pps, 1 mW/cm<sup>2</sup>, average whole body SAR 0.6 W/kg), rats showed retarded learning while performing in the radial-arm maze to obtain food rewards, indicating a deficit in spatial "working memory" function. This behavioral deficit was reversed by pretreatment before exposure with the cholinergic agonist physostigmine or the opiate antagonist naltrexone, whereas pretreatment with the peripheral opiate antagonist naloxone methiodide showed no reversal of effect. These data indicate that both cholinergic and endogenous opioid neurotransmitter systems in the brain are involved in the microwave-induced spatial memory deficit. ©1994 Wiley-Liss, Inc.

**Key words:** microwaves, radial-arm maze, learning, memory, cholinergic systems, endogenous opioids

## INTRODUCTION

In previous research, we have found that rats acutely exposed (45 min) to pulsed 2450 MHz microwaves [power density = 1 mW/cm<sup>2</sup>, average whole body specific absorption rate (SAR) = 0.6 W/kg] showed a deficit in learning to perform in the radial-arm maze [Lai et al., 1989]. This behavioral task involves spatial memory functions, i.e., the ability to remember and learn to use spatial cues in the environment. Study of spatial memory functions in rodents has been suggested as a model for the investigation of cognitive and memory functions in humans [Gallagher and Pellemounter, 1988; Upchurch and Wehner, 1989]. Deficit in memory functions, even transient, can lead to serious detrimental consequences. Thus, it is important to understand further this behavioral effect of microwaves and, especially, the underlying neural mechanisms involved. The present series of experiments was carried out with these goals.

From the data of our research on the effects of low-level microwave irradiation on the neurochemical changes in the brain of the rat, we have hypothesized

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that acute low-level microwave exposure activated endogenous opioids which in turn caused a decrease in cholinergic activity in the hippocampus and frontal cortex [Lai, 1992; Lai et al., 1987a, 1989]. Cholinergic systems are known to play an important role in memory functions and also in performance in the radial-arm maze [cf. Levine, 1988]. It is also well established that radial-arm maze performance involves central, but not peripheral, cholinergic functions [Beatty and Bierley, 1985; Eckerman et al., 1980; Levy et al., 1983; Okaichi and Jarrard, 1982]. In the present research, we investigated whether cholinergic systems and endogenous opioids played a role in the microwave-induced spatial memory deficit in the radial-arm maze. A series of experiments was carried out to study whether pretreatment with the cholinergic agonist physostigmine or the opiate antagonist naltrexone could reverse this behavioral effect of microwaves. In addition, since the origin (peripheral or central) of the endogenous opioid effect was not known, we also studied the effect of pretreatment with the peripheral opiate antagonist naloxone methiodide. If the behavioral effect involves only endogenous opioids inside the central nervous system, treatment with naloxone methiodide would have no significant effect on the microwave-induced spatial memory deficit.

## METHODS

### Animals

Male Sprague-Dawley rats (250–300 g at the start of an experiment) purchased from Tyler Laboratories (Bellevue, WA) were used in our experiments. During these experiments they were housed in a room adjacent to the microwave exposure room and were maintained on a 12 h light-dark cycle with the light on between 7 AM and 7 PM. The ambient temperature of the experimental environment was 23 °C.

### Microwave Exposure

The 2450 MHz cylindrical waveguide exposure system of Guy et al. [1979] was used. The waveguide system consists of eight individual cylindrical exposure tubes connected through a power divider network to a single microwave power source. Each tube consists of a section of circular waveguide constructed of galvanized wire screen in which a circularly polarized  $TE_{11}$  mode field configuration is excited. The tube also contains a plastic chamber to house a rat. The floor of the chamber is formed of glass rods, allowing waste to fall through plastic funnels into a collection container outside of the waveguide.

Both experimental and control animals were subjected to either microwave or sham exposure simultaneously. The microwave-exposed rats were irradiated with pulsed (2  $\mu$ sec pulses, 500 pps), circularly polarized 2450-MHz microwaves at a spatially averaged power density of 1 mW/cm<sup>2</sup> (average whole body SAR was 0.6 W/kg). Study measuring local SAR in eight regions of the brain of rats exposed in this waveguide system showed that the values vary from 0.5–2.0 W/kg per mW/cm<sup>2</sup> [Chou et al., 1985].

For sham exposure, animals were placed in similar waveguides for the same period of time and exposure schedule as the microwave-exposed animals, but they did not receive irradiation. All exposures were done between 8–10 AM to control for possible circadian variation in response.

### Radial-Arm

A wooden circular central platform with eight arms (68 cm diameter) was used. The end of each arm was marked with a black line.

Rats were trained to enter the maze to 90% of a platform. They were given ad lib weight gain during the training for 10 min. The maze was used for 10 min. The animals were trained to enter the maze. In the next experiment, the animals receive either hub, and the maze was recorded when they entered adjacent rooms and the performance in the maze was recorded. Each animal was given a score of 1 into an arm and a score of 0 into an arm.

### Drug Treatments

Before the experiment, the rats were given intraperitoneal (i.p.) injections of physostigmine (PHYSO) (0.5 mg/kg) or naloxone methiodide (0.5 mg/kg) in pyrogen-free saline (SAL), micrococcal nucleus (NMI), and saline (SAL) groups.

### Data Analysis

The data were analyzed using a one-way ANOVA. The training session errors made by the one-way ANOVA were considered.

## RESULTS

Results of the different groups are shown in Table 1.

### Radial-Arm Maze Training

A wooden 12-arm radial maze was used in this experiment. It consisted of a circular center hub (86 cm in diameter, 20 cm high) surrounded by 12 equally spaced arms (68 cm long, 10 cm wide) with a food wall (2 cm diameter) situated at the end of each arm.

Rats were maintained on a restricted food schedule to reduce their body weight to 90% of ad libitum level before experiment. When the rats reached 90% of their ad lib weights, they were sham-exposed (45 min) in the waveguides and then placed for 10 min each in the maze with pieces of rat chow (0.1 g each) scattered within the maze. This procedure was repeated for 4 more days and was designed to get the animals used to the experimental procedures of exposure and maze running. In the next session (start of learning session), the rats were randomly assigned to receive either microwaves (45 min) or sham exposure and then placed in the center hub, and allowed to explore the maze and obtain food bait placed at the food wells. All 12 food wells were baited. Each rat remained in the maze until it made 12 arm entries or 10 min had elapsed, whichever occurred first. An entry was recorded when an animal placed all four paws inside an arm. An experimenter in the adjacent room observed the performance, using a closed circuit television system, and the performance was also recorded on videotape for detailed data analysis. The maze was cleaned with 2.5% cider vinegar after each training session. Each animal was given 10 consecutive daily training sessions. In data analysis, the first entry into an arm during a training session was scored as a correct choice, whereas a reentry into an arm was scored as an error.

### Drug Treatments

Before exposure in each training session, rats were given one of the following intraperitoneal injections: physiological saline (SAL) (1 ml/kg), physostigmine (PHYSO) (1 mg/kg); naltrexone hydrochloride (NAL) (1 mg base/kg); or naloxone methiodide (NMI) (1 mg base/kg). All drugs were dissolved daily before injection in pyrogen-free physiological saline and injected in a volume of 1 ml/kg. Thus, the experiment consisted of the following eight treatment groups: microwave/SAL, sham/SAL, microwave/PHYSO, sham/PHYSO, microwave/NAL, sham/NAL, microwave/NMI, and sham/NMI. There were eight animal subjects in each of these treatment groups.

### Data Analysis

The learning curves of the treatment groups (i.e., average errors made in each training session versus training sessions) were analyzed by trend analysis. Total errors made by each treatment group in the ten training sessions were analyzed by the one-way analysis of variance (ANOVA) and the difference between two treatment groups was compared by the Newman-Keuls test. A difference at  $P < .05$  was considered statistically significant.

## RESULTS

Results of the radial-arm training sessions (errors made) of rats subjected to the different treatments are shown in Figures 1-4. Figure 1 shows the data of

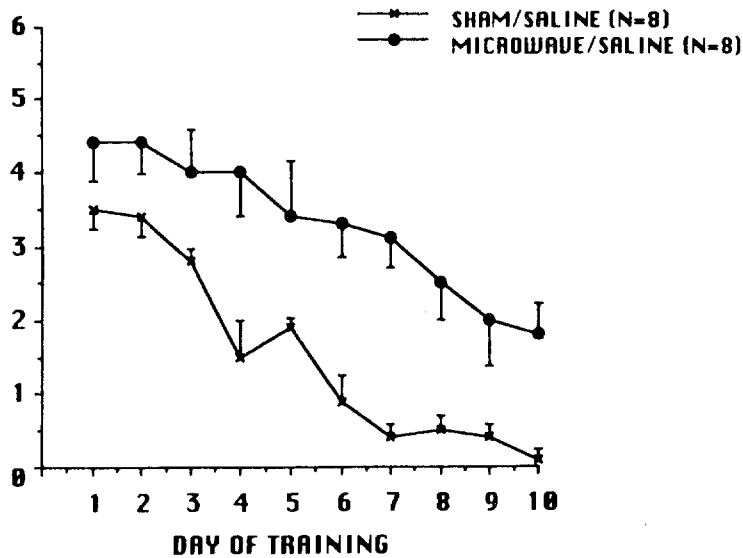


Fig. 1. Performance of the microwave/saline and sham/saline treated rats during the ten training sessions. N = 8 in each group. Treatment effect:  $F[1,14] = 14.84, P < .005$ ; training effect:  $F[9,63] = 12.67, P < .005$ .

microwave- and sham-exposed animals pretreated with physiological saline before each training session. The trend analysis of the data showed significant treatment (microwave or sham) effect ( $F[1,14] = 14.82, P < .005$ ). The microwave-exposed rats learned significantly slower than the sham-exposed animals (i.e., they made more errors during the training sessions). Pretreatment with physostigmine (Fig. 2) or naltrexone (Fig. 3) attenuated the effects of microwaves. There was no significant difference in performance between the microwave- and sham-exposed animals under these drug-treatment conditions (treatment effect for physostigmine:

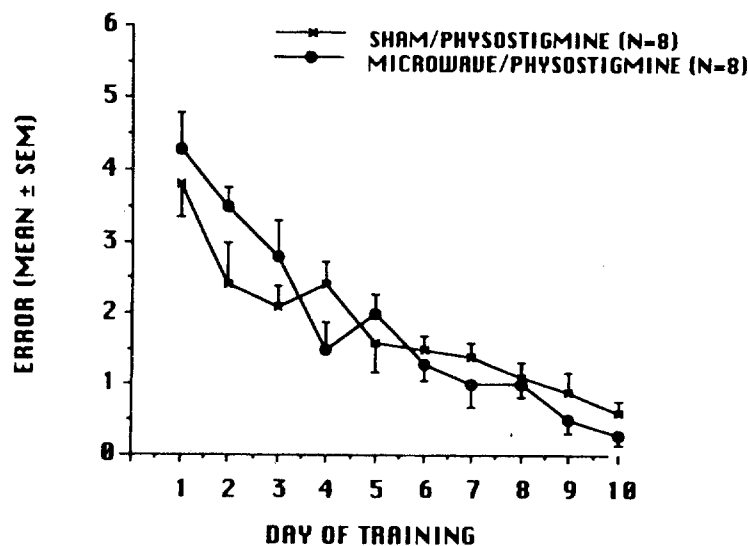


Fig. 2. Performance of the microwave/physostigmine and sham/physostigmine rats during the ten training sessions. N = 8 in each group. Treatment effect:  $F[1,14] = 1.14$ , nonsignificant; training effect:  $F[9,63] = 15.2, P < .005$ .

Fig. 3. Performance of the microwave/naltrexone and sham/naltrexone treated rats during the ten training sessions. N = 8 for each group. Treatment effect:  $F[1,14] = 1.1$ , nonsignificant; training effect:  $F[9,63] = 12.67, P < .005$ .

$F[1,14] = 1.1$ . However, in the microwave-exposed group, there was a significant learning effect ( $F[9,63] = 12.67, P < .005$ ). The microwave-exposed rats learned significantly slower than the sham-exposed animals (i.e., they made more errors during the training sessions).

Data from the microwave-exposed group under these drug-treatment conditions (treatment effect for naltrexone:

Fig. 4. Performance of the microwave/naltrexone and sham/naltrexone treated rats during the ten training sessions. N = 8 in each group. Treatment effect:  $F[1,14] = 1.1$ , nonsignificant; training effect:  $F[9,63] = 15.2, P < .005$ .

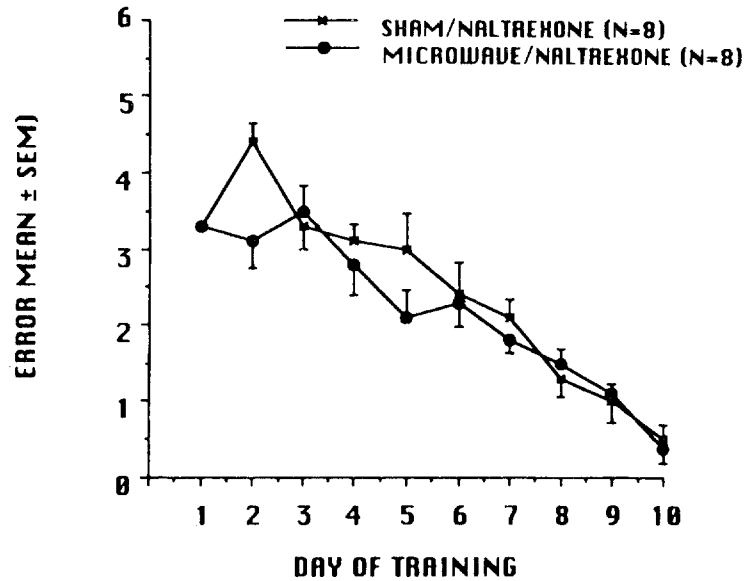


Fig. 3. Performance of the microwave/naltrexone and sham/naltrexone rats during the ten training sessions. N = 8 for each group. Treatment effect:  $F[1,14] = 2.35$ , nonsignificant; training effect:  $F[9,63] = 12.19$ ,  $P < .005$ .

$F[1,14] = 1.14$ , nonsignificant; and for naltrexone:  $F[1,14] = 2.35$ , nonsignificant). However, in rats treated with naloxone methiodide, the microwave-exposed rats learned significantly slower than the sham-exposed animals (Fig. 4) ( $F[1,14] = 175.4$ ,  $P < .005$ ). Thus, the effect of microwaves was not significantly blocked by naloxone methiodide.

Data from the sum of errors made in the ten training sessions by the different treatment groups are shown in Figure 5. One-way ANOVA showed a significant treatment effect ( $F[7,56] = 18.99$ ,  $P < .005$ ) and the Newman-Keuls test

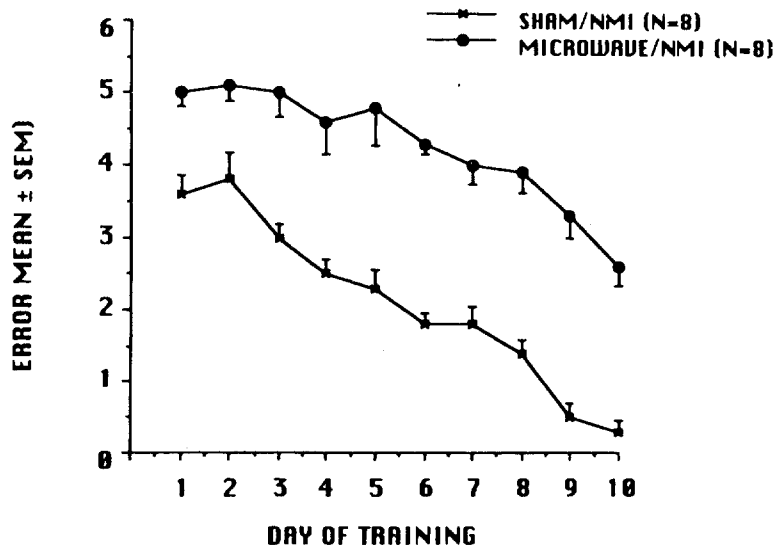


Fig. 4. Performance of the microwave/naloxone methiodide (NMI) and sham/naloxone methiodide treated rats. N = 8 in each group. Treatment effect:  $F[1,14] = 175.4$ ,  $P < .005$ ; training effect:  $F[9,63] = 13.9$ ,  $P < .005$ .

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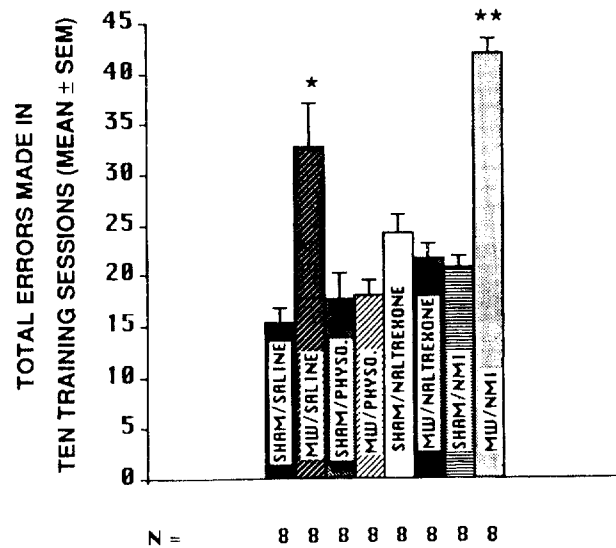


Fig. 5. Total errors made in the ten training sessions of the different treatment groups. \*,\*\* indicate difference between the sham/saline vs. microwave/saline groups, and sham/NMI vs. microwave/NMI groups, respectively, at  $P < .01$  (Newman-Keuls test). MW, microwave; PHYSO, physostigmine; NMI, naloxone methiodide

comparing treatment groups showed a significant difference between the microwave/saline vs sham/saline ( $P < .01$ ) and microwave/NMI and sham/NMI ( $P < .01$ ) groups, whereas no significant difference was found between the microwave/physostigmine vs. sham/physostigmine and microwave/naltrexone vs. sham/naltrexone groups.

Thus, these data show that the microwave-induced learning deficit in the radial-arm maze was blocked by pretreatment with the cholinergic agonist physostigmine or the opiate antagonist naltrexone, but not by the peripheral opiate antagonist naloxone methiodide.

## DISCUSSION

Data from the present experiment indicate that both cholinergic and endogenous opioid neurotransmitter systems within the central nervous system are involved in the microwave-induced deficit in learning in the radial-arm maze. Since the effect is reversed by a cholinergic agonist or an opiate antagonist, these data are in agreement with our hypothesis that low-level microwaves activate endogenous opioids which in turn cause a decrease in cholinergic activity in the brain [Lai, 1992], and the decrease in cholinergic activity is responsible for the behavioral deficit observed. In our experiments, since all the arms of the radial maze were baited, this allowed us to study "working" memory function, a memory function similar to short-term memory. During each training session, the rat has to remember its previous arm choices in order to obtain food from the arms and not to re-enter an arm. Since the pattern of arm choices varies from session to session, the "working" memory is not fixed and changes with each session. Our data imply that acute microwave irradiation affects "working" memory in the rat.

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Involvement of central cholinergic systems in the performance in the radial-arm maze is well known [cf. Levin, 1988]. Deficits in maze learning have been reported in animals after disruption of cholinergic functions, for example, after administration of cholinergic antagonists [Okaichi and Jarrard, 1982; Stevens, 1981; Watts et al., 1981; Wirsching et al., 1984], or lesioning of the hippocampal or cortical cholinergic pathways [Altman et al., 1985; Jarrard et al., 1984; Murray and Fibiger, 1985; Olton and Papas, 1979]. Furthermore, similar to our results, deficits in maze performance caused by lesioning of the cholinergic pathways is reversible by treatment with the cholinergic agonist physostigmine [Murray and Fibiger, 1985].

Since endogenous opioids play a modulatory role on the activity of the cholinergic systems in the brain, they have also been implicated in radial-arm maze performance. However, it seems that whether the endogenous opioid systems in the brain play a role in the performance in the radial-arm maze depends on the complexity of the training and testing procedures used. For example, Beatty [1983] showed that opiate agonists and antagonists had no significant effect on spatial memory of rats performing in an 8-arm radial maze. Gallagher et al. [1983, 1985] also found no significant effect of the opiate antagonist naloxone in the rat on the rate of learning in an 8-arm radial maze. However, they did show in rats, which had been previously trained in the maze, that post-training treatment with opiate antagonists improved the rate of learning when these animals were retrained in a similar maze arranged in novel spatial environments. They have further demonstrated that the medial septal areas of the brain mediated the effect of the opiate antagonists [Bostock et al., 1988]. This is significant because the medial septum contains the cholinergic cell bodies which send innervations to the hippocampus. More recently, Canli et al. [1990] reported that the opiate antagonists, naloxone and naltrexone, enhanced the "working" memory component of the performance when a significantly more complex 12-arm radial maze, the type of maze used in our experiments, was used.

In our previous research, we have found in the rat that acute exposure to pulsed low-level microwaves decreased the activity of cholinergic innervations in the hippocampus and frontal cortex. These brain regions receive innervation from cholinergic neurons located in the medial septum/diagonal band of Broca and the nucleus basalis magnocellularis, respectively. Moreover, the effect of microwaves on the hippocampal cholinergic innervation was blocked by pretreatment with opiate antagonists, whereas that on the frontal cortex was not [Lai et al., 1987a, 1989]. In the present experiment, we found that treatment with naltrexone completely blocked the maze learning deficit of the microwave-exposed rats. This would imply that reversal of cholinergic activity in the hippocampus alone is sufficient to reverse the behavioral deficit.

The cholinergic systems of the cerebral cortex and hippocampus may play different roles in learning and memory in the radial-arm maze. It is known that the septo-hippocampal and basalis-cortical cholinergic pathways respond differently to learning in the radial-arm maze. For example, Wenk et al. [1984] reported an increase in cholinergic activity in the hippocampus of rats performing in a radial-arm maze, whereas the cortex showed a slight decrease. In other cases, the two cholinergic pathways have been shown to respond at different time courses after radial-arm maze training [Jaffard et al., 1989; Toumane et al., 1988, 1989]. While the role of the hippocampal cholinergic system on radial-arm maze performance is well established, the specific role played by the basalis-cortical cholinergic system

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is not entirely clear. Several studies have implied that the cortical cholinergic pathway is not as critical in radial-arm maze performance as the hippocampal system. Becker et al. [1980] showed that lesions of the fimbria-fornix, the pathway of cholinergic innervations to the hippocampus, have a more severe and persistent effect on radial-arm maze "working" memory function than lesioning of the frontal cortex in the rat. Another study [Murray and Fibiger, 1985] has shown that the basalis-cortical cholinergic pathway is not involved in "working" memory in the radial-arm maze, the memory function studied in our experiments. Miyamoto et al. [1987] also reported that lesioning of the septo-hippocampal pathway caused a more severe effect on "working" memory function in the radial-arm maze than lesioning the basalis-cortical pathway in rats. Deyo et al. [1990] showed that decorticated rats can do spatial learning in the radial-arm maze. Oades [1981] also reported no change in "working" memory function after neocortical lesioning in the rat. These reports suggest that the cortical cholinergic systems are less involved in the "working" memory function necessary for radial-arm maze performance. However, it must be pointed out that in other studies, it has been shown that rats with frontal cortical lesions showed specific "working" memory deficit [e.g., Bartus et al., 1985; Poucet, 1990; Walsh et al., 1984].

In addition, in a previous experiment [Lai et al., 1987b], we have found that after ten daily sessions of low-level microwave exposure, the cholinergic response in the hippocampus adapted, i.e., no significant response was observed after further exposure, whereas no adaptation was observed in the cortical cholinergic system. This is also consistent with the interpretation that the hippocampal cholinergic system is mainly responsible for the radial-arm maze learning deficit seen after acute exposure to microwaves, whereas the cortical cholinergic system only plays a minor role or is even not involved, since the microwave-exposed rats also showed a significant gradual improvement in performance with increased training, even though not as fast as the sham-exposed animals [see Fig. 1; Lai et al., 1989].

## ACKNOWLEDGMENTS

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