

## BRIEF COMMUNICATIONS

# Enhancement of Latent Inhibition in Rats With Electrolytic Lesions of the Hippocampus

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Two groups of rats—1 with electrolytic lesions of the hippocampus and 1 consisting of sham-operated controls—received flavor-aversion conditioning with 2 flavors. All subjects had received prior nonreinforced exposure to Flavor A. Latent inhibition was apparent in slower acquisition of the aversion to Flavor A than to Flavor B. Hippocampal lesions had no effect on acquisition to the nonpreexposed Flavor B but produced a marked enhancement of the latent inhibition effect. The contrast between this result and previous findings of an attenuation of latent inhibition in subjects with hippocampal lesions is discussed.

The term *latent inhibition* refers to the retardation of classical conditioning produced by prior nonreinforced exposure to the event that is later to be used as the conditioned stimulus (CS) in a conditioning procedure. A variety of explanations have been offered for this phenomenon (see Hall, 1991; Lubow, 1989, for reviews), but a notion central to several of them is that the effect reflects the operation of a mechanism that allows animals to reduce the extent to which they pay attention to events that lack importance (e.g., Lubow, Weiner, & Schnur, 1981; Mackintosh, 1975; Pearce & Hall, 1980). As a consequence, latent inhibition has been of interest to those wanting to investigate the hypothesis (proposed originally by Douglas & Pribram, 1966; see also Douglas, 1972; Solomon, 1979) that one of the functions of the hippocampus is to modulate sensory input, tuning out stimuli that lack motivational significance.

Experiments on the effects of hippocampal lesions on latent inhibition have used a wide range of procedures. Thus, McFarland, Kostas, and Drew (1978) used the flavor-aversion learning paradigm and Kaye and Pearce (1987) used appetitive classical conditioning; in both cases the subjects were rats with electrolytic lesions of the dorsal hippocampus. Rats with aspiration lesions were studied by Ackil, Mellgren, Halgren, and Frommer (1969) in a shuttle-avoidance procedure and by Schmajuk, Lam, and Christiansen (1994), who used the conditioned eyeblink response. Solomon and Moore (1975) used rabbits with aspiration lesions and conditioning of the nictitating membrane response. In all these studies, latent inhibition was attenuated or abolished in the subjects that suffered hippocampal damage. In only one report (by Honey & Good,

1993, who studied appetitive conditioning in rats with ibotenate lesions) did lesioned subjects show the same retardation of acquisition as was seen in controls; and in this case there is reason to believe that the source of the latent inhibition effect was different in the two groups in that the effect seen in lesioned subjects failed to show the context dependence that is normally a feature of the phenomenon.

The near unanimity of these experiments makes the results reported by Reilly, Harley, and Revusky (1993) particularly surprising. Their study (Reilly et al., 1993, Experiment 1) of flavor-aversion learning in rats with ibotenate hippocampal lesions found not an abolition but an enhancement of latent inhibition. Acquisition of the aversion occurred normally in preexposed subjects, but the retardation of conditioning produced by prior exposure to the CS was especially marked in subjects that had sustained hippocampal damage. The experiment we now report attempted to confirm the reliability of this striking finding.

The procedures used were closely similar to those of Reilly et al. (1993), differing in only three major respects. First, we used a within-subject design for the assessment of latent inhibition. All subjects were given initial nonreinforced exposure to a given flavor (A). They then received conditioning trials with Flavor A as the CS intermixed with conditioning trials with a novel flavor, B. More rapid conditioning to Flavor B than to Flavor A would constitute a latent inhibition effect. An advantage of this procedure over the between-subjects comparison used by Reilly et al. (1993) is that it demonstrates that the effect of preexposure is indeed specific to the particular stimulus used.

Second, on each trial, the subjects were offered a fixed amount of the flavored fluid and allowed to consume all of it. As a result, hippocampal and control subjects necessarily experienced the same amount of the flavor during preexposure, and there were no differences in the amounts consumed of Flavor A and Flavor B on the first conditioning trial. (Differences of this sort could potentially have played a role in the procedure used by Reilly et al., 1993.)

Third, we made the hippocampal lesions electrolytically.

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This allowed us to evaluate the speculation offered by Reilly et al. (1993) that the discrepancy between their own results and those reported previously by others depended on their use of the neurotoxic lesioning technique.

## Method

### Subjects

The subjects were 16 male hooded Lister rats with a mean weight, at the start of the experiment, of 355 g (range = 325–375 g). After undergoing surgery (see later discussion) they were allowed 2 weeks to recover before entering a program of behavioral testing. This consisted of a series of studies of classical conditioning using auditory and visual cues and food reinforcement. For these studies (which lasted for 4 months), the animals were maintained on a schedule of food deprivation. At the completion of these studies and before the start of flavor-aversion training, the animals, which hitherto had been housed in pairs, were transferred to individual cages and allowed free access to food.

### Surgery and Histology

Animals were assigned at random to one of two equal-sized groups: Group H (dorsal hippocampal electrolytic lesions) and Group S (sham-operated controls). For surgery, each rat was anesthetized with an intraperitoneal injection of avertin (made up as 1.25 ml of avertin concentrate added to 5 ml of absolute alcohol and 62.5 ml of physiological saline) at 10 ml/kg. (Avertin concentrate consists of 100 g of 2,2,2-tribromoethanol dissolved in 62 ml tertiary amyl alcohol.) Each animal was then placed in a stereotaxic frame, the scalp incised, a section of bone removed, and the dura parted. Bilateral dorsal hippocampal lesions were made by passing a 2.5-mA current from a constant-current lesion maker for 25 s through a wire electrode insulated to within 0.5 mm of its tip. The electrode coordinates were 3 mm anterior to bregma, 2.5 mm lateral to the midline, and 3.5 mm ventral to the brain surface. For sham-operated subjects, the procedure was the same except that the electrode was lowered only to the level of the corpus callosum and no current was passed.

At the end of the experiment, the animals were deeply anesthetized with pentobarbitone sodium and perfused intracardially with physiological saline followed by 10% formol-saline. The brains were removed and stored in formol-saline for 2 weeks before being embedded in paraffin wax and cut on a microtome in 10- $\mu$ m sections. Sections were retained at 150  $\mu$ m intervals throughout the lesioned area. They were mounted and stained with cresyl violet.

### Procedure

Before the start of the preexposure phase, the subjects became accustomed over 4 days to a schedule of water deprivation in which access to water was given daily for two 30-min periods at 11 a.m. and 5 p.m. In subsequent phases of the experiment, flavored solutions were presented during the first of these drinking periods; throughout the experiment, animals continued to receive access to water during the second drinking period. The flavors used were a 10% solution of sucrose and a 1% saline (sodium chloride) solution. Previous work in our laboratory has shown that rats can discriminate these flavors and will consume them with equal readiness.

Over the 8 days of the preexposure phase, all subjects were given 10 ml of Flavor A during the morning drinking session. The solution was administered at room temperature in an inverted 50-ml plastic centrifuge tube, with a rubber stopper holding a stainless steel

drinking spout. Fluid consumption was measured, by weight, to the nearest 0.5 ml. For half the subjects in each group (H and S), Flavor A was saline and for half it was sucrose.

There were four reinforced trials with each flavor. The first occurred on the day after the last preexposure session; subsequent trials were on alternate days thereafter. On reinforced trials, subjects were given 10 ml of a flavored solution, as before. At the end of the 30-min period of access, the tubes were removed and the subjects were given an intraperitoneal injection of 0.15 M lithium chloride at 10 ml/kg of body weight. Each conditioning day was followed by a recovery day in which the animals received free access to water for 30 min during both morning and afternoon drinking sessions. Trials with Flavors A and B occurred alternately. Half the animals in each group received Flavor A as the first trial in the sequence, and half received Flavor B.

Finally, there were three nonreinforced test trials with each flavor. For these, the sequence of alternating presentations of Flavors A and B, with intervening recovery days, was maintained. The procedure differed from that of the conditioning trials only in that the subjects were given free access to the solution for 30 min (rather than access to a fixed 10 ml) and in that no injections were administered.

## Results

### Histology

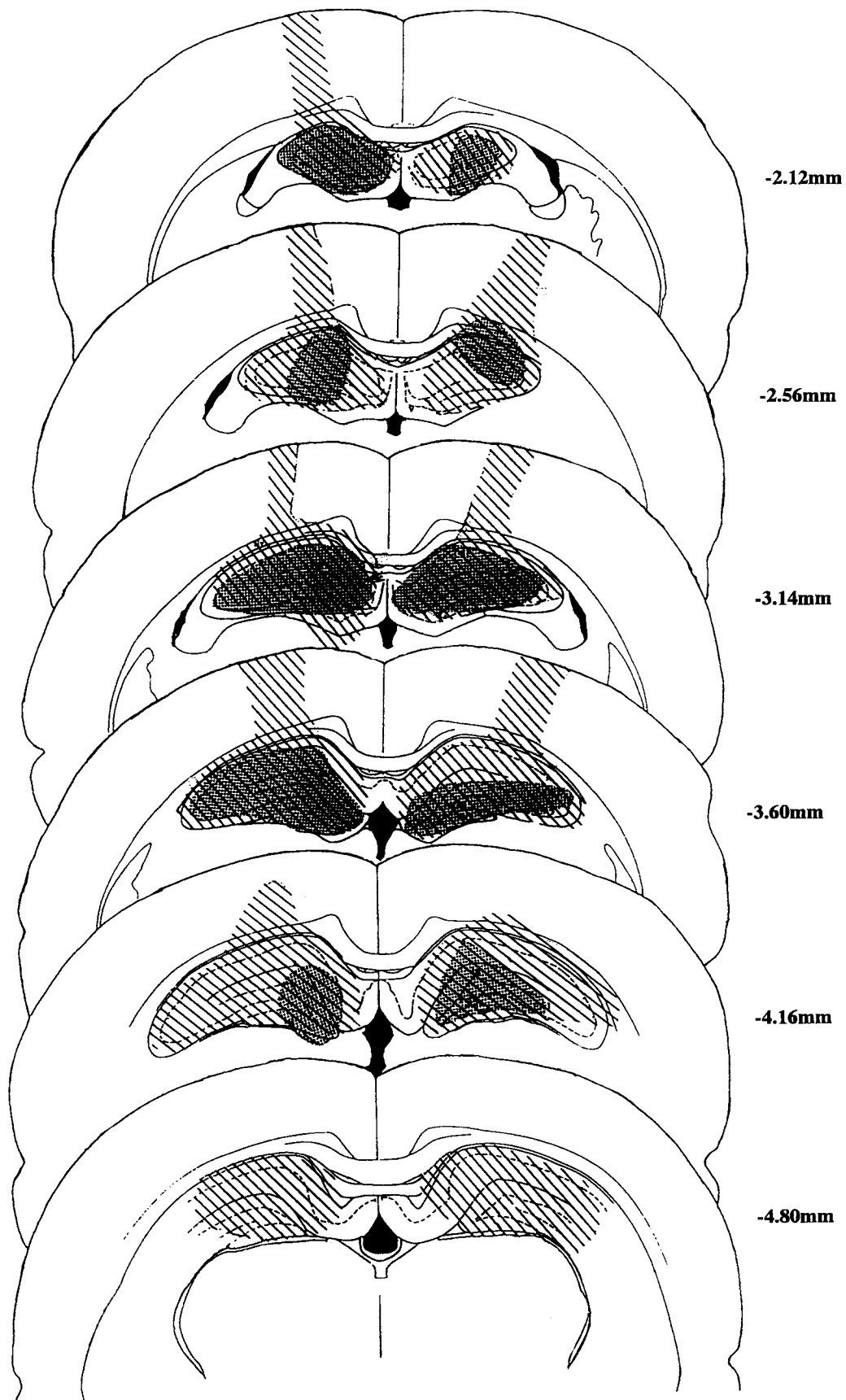
Figure 1 presents coronal sections through the rat brain on which are superimposed reconstructions of the lesion damage for all subjects in Group H. The striped area shows the maximum extent of the lesion, and the stippled area shows the minimum extent. It is evident that all animals sustained extensive dorsal hippocampal damage with minimal damage to underlying structures. A representative selection of brains from the sham-operated group was also sectioned; these exhibited no damage at all.

### Behavior

During the preexposure phase, the animals almost invariably drank all 10 ml of the fluid presented in the morning drinking sessions.

Figure 2 shows, separately for each group, the amount of fluid consumed on the conditioning and test trials with Stimulus A (the preexposed flavor) and Stimulus B (not preexposed). On the first conditioning trial with each flavor, all subjects drank the full 10 ml offered. Consumption was reduced over the course of the reinforced trials (1–4) and, except in Condition H-A, remained low over the test trials (5–7). The groups did not differ in their behavior toward the B stimulus. Both showed a latent inhibition effect, however, in that the aversion to Flavor A was acquired less readily than to Flavor B. Furthermore, the groups differed in this regard. Latent inhibition was more marked in Group H; these subjects acquired the aversion to Flavor A particularly slowly and readily lost it over the course of the nonreinforced test trials.

An analysis of variance was conducted on the data summarized in Figure 2, the factors being group (H or S), trial, and stimulus (A or B). The main effect of group was not significant,  $F(1, 14) = 2.94$ , but there was a significant effect of trial,  $F(6, 84) = 159.44, p < .01$ . The interaction of trial and stimulus fell short of significance,  $F(6, 84) = 2.16$ , as did the three-way interaction,  $F(6, 84) = 1.48$ . There were, however, significant



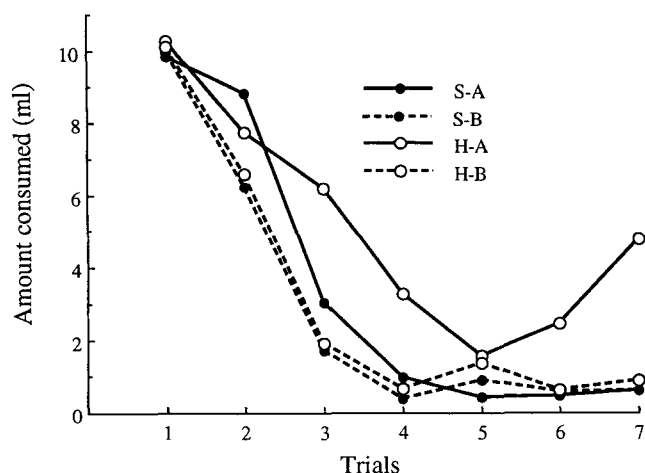


Figure 2. Amount of fluid consumed by subjects with hippocampal lesions (H) and sham-operated controls (S) on trials with a preexposed flavor (A) or a novel flavor (B). On Trials 1 to 4, consumption of the fluid was followed by an injection of lithium chloride; Trials 5 to 7 were nonreinforced test trials.

interactions between group and trial,  $F(6, 84) = 2.31, p < .05$ , and between group and stimulus,  $F(1, 14) = 4.69, p < .05$ . This last interaction is of central theoretical importance because it indicates that the effect of preexposure to the stimulus differed between the groups. An analysis of simple main effects revealed no significant difference between the stimuli in the S group,  $F(1, 14) = 1.35$ , but a significant difference in the H group,  $F(1, 14) = 17.88, p < .01$ . The groups did not differ with respect to the nonpreexposed, B, stimulus ( $F < 1$ ) but did so with respect to the preexposed, A, stimulus,  $F(1, 23) = 6.63, p < .05$ .

### Discussion

The results reported here demonstrate a selective effect of hippocampal lesions. The acquisition of a conditioned aversion to a novel flavor proceeded normally, but learning about a preexposed flavor was particularly slow; that is, the latent inhibition effect was enhanced. Our results thus confirm the finding reported by Reilly et al. (1993) and extend its generality by showing that the effect can be seen in a within-subject comparison as well as in the between-subjects comparison made by Reilly et al. (1993). The use of the within-subject design has certain advantages, noted early in this article, but it should also be acknowledged that it leaves open the possibility of an alternative interpretation of the effect. In particular, if hippocampal lesions were to enhance the discriminability of Flavors A and B, then our results might emerge independently of any effect of the lesion on latent inhibition. However, the assumption required by this account seems distinctly implau-

sible; and to introduce separate explanations for the results of the within-subject and between-subjects designs is lacking in parsimony.

The enhancement of latent inhibition observed in these experiments stands in marked contrast to the outcome generated by the majority of previous studies in which an attenuation or abolition of latent inhibition has been obtained with hippocampal lesions. Reilly et al. (1993) suggested that the discrepancy between their finding and the previous results might be a consequence of their use of a neurotoxic lesioning technique. The present experiment, in which the enhancement of latent inhibition was found in subjects with electrolytic hippocampal lesions, argues against this suggestion.

The most obvious distinction between experiments in which latent inhibition was attenuated and those in which it was enhanced is that the latter made use of the flavor-aversion learning paradigm. The one exception to this rule turns out to be more apparent than real. McFarland et al. (1978) reported an abolition of latent inhibition in flavor-aversion learning by rats with electrolytic hippocampal lesions. However, as Reilly et al. (1993) pointed out, the failure of this experiment to find a difference between preexposed and nonpreexposed groups in the hippocampal subjects reflects the fact that in neither group was there much evidence of the acquisition of an aversion. That is, the lesion appeared to prevent the formation of a conditioned aversion, making it impossible to draw conclusions about the effects of preexposure to the CS on such conditioning.

Although a retardation of flavor-aversion learning after hippocampal damage has been demonstrated in a number of previous studies (e.g., Best & Orr, 1973; Miller, Elkins, & Peacock, 1971), the present experiment found, as did several others (e.g., Murphy & Brown, 1974; Reilly et al., 1993), no sign of any effect when the CS flavor was novel. The source of this inconsistency is not clear, but the pattern of results generated in our experiment allows the conclusion that hippocampal lesions can have effects that are specific to those mechanisms involved in the latent inhibition procedure.

Theoretical interpretation of our result is not straightforward. It encourages the general view that the hippocampus is in some way involved in the processing whereby animals modulate the attention they pay to environmental stimuli (e.g., Moore, 1979; Schmajuk & Moore, 1988; Solomon, 1979). However, it gives no support to the more specific suggestion that damage to the hippocampus will render the animal unable to tune out irrelevant stimuli; rather, the loss of effectiveness suffered by a preexposed stimulus appears to be greater in hippocampal subjects than control subjects. A resolution of this issue will depend on the outcome of further experimental work aimed at identifying the critical differences that presumably must exist between the latent inhibition procedure as applied to flavor-aversion learning and that used in other conditioning procedures.

Figure 1 (opposite). Reconstructions of the maximum (striped) and minimum (stippled) extent of damage in the hippocampus-lesioned group superimposed on coronal sections derived from the Paxinos and Watson (1986) atlas.

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