Hippocampal lesions attenuate latent inhibition of a CS and of a neutral stimulus

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Rats with hippocampal or sham lesions were exposed extensively to a tone. Subgroups received either nonreinforced presentations of this stimulus or tone-mild footshock pairings. The subjects subsequently received pairings of the tone with a stronger footshock, and it was found that animals with hippocampal lesions learned this relationship more rapidly than did controls, regardless of whether they had received reinforced or nonreinforced prior experience with the tone. Comparisons with other control groups for which the tone was novel indicated that exposure reduced the associability of that stimulus for sham-operated rats. These results suggest that hippocampal lesions may disrupt a common mechanism underlying the loss of associability that occurs after exposure of a CS and of a neutral stimulus.

When animals receive a number of nonreinforced presentations of a stimulus, subsequent learning about the relationship between that stimulus and an unconditioned stimulus (US) is retarded. Lubow and Moore (1959) termed this phenomenon *latent inhibition*, and its generality in terms of both particular conditioning procedures and species is widespread (see Lubow, 1973). A number of authors have reported that damage to the hippocampus attenuates latent inhibition. Solomon and Moore (1975) found that upwards of 400 tone presentations retarded subsequent conditioning of the nictitating membrane response in intact rabbits, but this disruptive effect of stimulus exposure was not evident in animals with hippocampal lesions. Relevant control groups indicated that this difference was not due to any general superiority in rate of conditioning after hippocampal lesions. Similar effects of hippocampal lesions have been found by Ackil, Mellgren, Halgren, and Frommer (1969), using rats in a shuttlebox avoidance task; by McFarland, Kostas, and Drew (1978), using rats in a taste-aversion procedure; and by DeVietti, Emmerson, and Wittman (1982), using a conditioned emotional response (CER) procedure. Further evidence that the hippocampus is involved in latent inhibition is provided by Salafia and Allan's (1980, 1982) work on electrical stimulation of that structure. They found that this impeded or facilitated latent inhibition, depending upon the intensity of hippocampal stimulation; specifically, intense stimulation attenuated latent inhibition and lower levels augmented it.

Several theories of animal learning account for latent inhibition in terms of attentional mechanisms (e.g., Mackintosh, 1975; Pearce & Hall, 1980; Wagner, 1978, 1981), and at least two of these theories (Pearce & Hall, 1980; Wagner, 1978, 1981) predict that stimulus exposure will retard later learning whether a stimulus is repeatedly presented alone or in association with a US. Hall and Pearce (1979) demonstrated such an effect in a CER study with rats. A stimulus was repeatedly paired with a mild footshock until conditioning reached a stable asymptote. The conditioned stimulus (CS) was then paired with a much stronger shock, and it was found that conditioning was significantly retarded in preexposed rats compared to controls for whom the stimulus was novel. If it is the case that this phenomenon and latent inhibition are governed by a common mechanism, then it would be expected that hippocampal lesions would affect both similarly. The purpose of the present experiment was to test this prediction.

A method similar to that used by Hall and Pearce (1979) was adopted. Rats were trained in a CER procedure; two experimental groups (one composed of animals with hippocampal lesions, the other of sham-operated rats) received pairings of a tone with a mild electric footshock. In the test session, the same CS was paired with a strong electric shock. If hippocampal lesions attenuate latent inhibition of a CS, then the lesioned group would be expected to condition more rapidly than the sham-operated group. To test whether conditioning with the mild footshock was effective in reducing the associability of the tone during the first stage, a second sham-operated group received pairings of the tone and the strong shock in the test stage. This group received conditioning with a light and the mild shock during the first phase, and hence

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differed from the experimental group only in the novelty of the tone in the test session.

Three additional groups of rats were used to compare the loss of associability of a CS with that of a neutral stimulus. One lesioned and one sham-operated group received nonreinforced tone presentations during Stage 1, followed by pairings of that stimulus with the strong shock during the test session. It was expected on the basis of studies using a similar procedure (e.g., Solomon & Moore, 1975) that lesioned animals would learn more rapidly during this session. To test whether this procedure was sufficient to produce latent inhibition, a second sham-operated group received pairings of the novel tone and shock during the test session.

METHOD

Subjects

Forty-eight male Sprague-Dawley rats with a mean free-feeding weight of 427 g (range 365–490 g) were used. They were maintained on unrestricted food for about 3 weeks following surgery and then gradually reduced to 80% of their free-feeding weights. They were maintained under a 12 h light/12 h dark cycle from birth, and all testing occurred during the light period.

Surgery and Histology

Prior to surgery, 16 rats were randomly selected to receive bilateral lesions of the dorsal hippocampus. The subjects were anesthetized with sodium pentobarbital (50 mg/kg) and two burr holes were drilled in the skull, 3 mm posterior from bregma and 2.25 mm right and left of midline. The subjects were implanted with a concentric bipolar electrode 3.5 mm below the dura and an anodal current of 2 mA was passed for 45 sec at each site. The electrodes were made of 26-ga insulated stainless steel wire with a distance of 0.5 mm between the exposed poles. Following the experiment, subjects were deeply anesthetized and were perfused intracardially with a mixture of isotonic saline and 10% formalin. The brains were removed and 50- μ m coronal sections were cut through the extent of each lesion, stained, and examined microscopically. The remaining animals received sham lesions; the operations were identical to those of the subjects with dorsal hippocampal lesions, except that the electrodes were not lowered into the brain.

Apparatus

Eight operant chambers (Campden Instruments) housed in light- and sound-attenuated boxes were used for testing. Each was equipped with a lever and an adjacent recessed food magazine into which a 45-mg pellet could be delivered. The floor was composed of steel rods, 5 mm in diameter and spaced 1.5 mm center to center, running parallel to the wall containing the magazine. The floor could be electrified by a Campden Instruments shock generator, which provided scrambled shocks. A loudspeaker mounted on a side wall provided a 3-kHz tone of intensity 78 dB re 20 μ Nm². Background noise levels of 63 dB were provided by the continuous operation of an extractor fan. A 60-W striplight operated at 240 V, located above the translucent Perspex ceiling of the chamber, provided a diffuse light CS of luminous density 22.5 cd/m². The experiment was controlled by an Acorn microcomputer.

Procedure

For the first two sessions, the levers were removed from the experimental chambers and food pellets were delivered according to a variable-time 60-sec schedule. The levers were replaced on the

third session and a food pellet was delivered after every leverpress until a minimum of 100 responses had been made. During Session 4, responding was reinforced according to a variable-interval (VI) 30-sec schedule; thereafter a VI 60-sec schedule was employed. After six sessions of baseline training with the latter schedule, the subjects were assigned to six groups. Eight lesioned rats were assigned to Group HT+ and the other 8 were assigned to Group HT0. The 32 sham-operated subjects were divided into four equal groups. In each of the 10 sessions of Stage 1, Groups SL0 and SL+ received four 60-sec light presentations. The first was presented 15 min after the start of the session and the remainder at regular 10-min intervals. Subjects in Groups ST0, ST+, HT0, and HT+ received identical training except that a tone rather than a light was presented. For Groups SL+, ST+, and HT+, the offset of each stimulus was accompanied by a 0.5-sec footshock. During the first three sessions, the intensity of the shock was 0.1 mA. Because this resulted in little conditioning, particularly in Group HT+, the magnitude of the shock was increased to 0.2 mA for the remaining sessions. Groups SL0, ST0, and HT0 were not shocked during Stage 1 of the experiment. During the test session, all subjects received four tone presentations with the same temporal pattern as that of Stage 1, each terminating with a 0.5-sec 0.8-mA footshock.

RESULTS

Figure 1 illustrates the effects of the tone and light presentations on responding during Stage 1. Response suppression was expressed as a ratio having the form $A/(A+B)$, where A represents the rate of leverpressing during the CS and B represents that during the 60 sec immediately preceding CS onset (pre-CS). By the final session of this stage, suppression ratios were considerably lower in value for those groups receiving CS-US pairings than for those receiving nonreinforced light or tone presentations. There was an increase in conditioned suppression over sessions in Groups ST+, SL+, and HT+, but these groups did not appear to differ markedly from each other. Similarly, there were no obvious differences among Groups ST0, SL0, and HT0 in response suppression. An analysis of variance was performed on the individual suppression ratios for the six groups on the 10 sessions of Stage 1. This revealed significant effects of group [$F(5,42) = 6.60$] and session [$F(9,378) = 2.03$], and a reliable group $\times$ session interaction [$F(45,378) = 1.42$, $p < .05$]. The interaction was explored using tests of simple main effects (Kirk, 1967), and it was found that the groups differed on Sessions 2, 4–7, and 9–10 [$F(5,48) > 8.0$, $p < .05$]. The Newman-Keuls procedure (p set at .05) indicated that on Session 2 there was more conditioned suppression in Groups ST+ and SL+ than in any other, whereas on Sessions 4–7 and 9–10 conditioned suppression was greater in the three groups receiving shock than in the three receiving the nonreinforced stimuli. All other comparisons failed to reach significance.

Figure 2 shows the group mean suppression ratios for the four test trials with the tone. The sham-operated groups that had been exposed to the tone in Stage 1, Groups ST+ and ST0, showed less response suppression than shown by the lesioned groups, HT+ and HT0, and

Figure 1. Group mean suppression ratios during Stage 1.

the sham-operated groups, SL+ and SL0, for which the tone was novel. Whether the tone had been paired with shock or presented alone during the Stage 1 did not appear to influence learning during this session. Statistical analysis supported these observations. An analysis of variance comparing the individual mean suppression ratios for all four test trials revealed, for the four sham-operated groups, a significant effect of exposure to the tone during Stage 1 [$F(1,28) = 13.80, p < .01$], but no reliable effect of shock during Stage 1 or interaction between these factors ($F_s < 1$). A second analysis of variance compared individual suppression ratios for the four groups that had experienced the tone in Stage 1. This analysis supported the observation that learning was faster in the animals with dorsal hippocampal lesions, revealing a reliable effect of lesion [$F(1,28) = 4.20, p < .05$] but no effect of shock in Stage 1 [$F(1,28) = 1.38, p > .05$] or interaction between these factors ($F < 1$).

To ascertain that the differences between the groups were not simply due to overall differences in responding throughout the session, pre-CS rates of responding in the various groups were compared; these are presented in the lower panel of Figure 2. Subjects that had not previously received footshock had slightly depressed pre-CS rates of responding compared to subjects that had received CS-US pairings. An analysis of variance indicated that there were no reliable effects of shock in Stage 1 [$F(1,42) = 1.79$] or group ($F < 1$), and no reliable shock $\times$ group interaction [$F(2,42) = 1.16, p_s > .10$].

Figure 3 represents the largest and smallest dorsal hippocampal lesions, reproduced on diagrams of the rat brain (from Pellegrino & Cushman, 1967). Examination of the sections revealed damage to the dorsal hippocampus in all subjects; additionally, some animals were found to have lesions of the dentate gyrus and the fimbria. Visual inspection of the sections suggested that the distribution of the lesion sizes was approximately equal in the two groups. There was, however, a large amount of variability in the lesion size, and an attempt was made to correlate the amount of hippocampal damage with the amount of learning in the test session. Subjects in both groups were ranked according to lesion size, and then according to the magnitude of the difference between their suppression ratios on the final session of Stage 1 and the test session. Spearman rank correlation coefficients of -0.35 and -0.29 for Groups HT0 and HT+, respectively, indicated that there was a correlation between the measures, but it was not sufficient to reach statistical reliability ($p > .05$).

DISCUSSION

In this experiment, sham-operated rats given prior experience with a tone, either presented alone or paired with footshock, subsequently learned more slowly about that stimulus than did similar animals that did not receive prior exposure to the tone. Rats with dorsal hippocampal lesions that were exposed to the tone, on the other hand, subse-

Figure 2. Group mean suppression ratios during the test session (upper panel); responses per minute during the pre-CS period (lower panel).

quently learned about that stimulus at a rate similar to that of the nonexposed sham-operated animals. One possible explanation for this apparent lack of a preexposure effect following dorsal hippocampal damage is that these lesions increased sensitivity either to the shock or to the contingency between the tone and shock. The results of this experiment and other studies make this account unlikely, however. During Stage 1 of the experiment, there was no evidence that Group HT+ learned about the tone-weak shock relationship any more rapidly than did Group ST+. Indeed, the converse was true; during Session 2, responding in Group HT+ was significantly less suppressed during the tone than it was in Group ST+. Similarly, a number of authors have reported that hippocampal lesions have no influence on the reinforcing capacity of shock (e.g.,

Garrud et al., 1984; Rickert, Bennett, Lane, & French, 1978). A more likely explanation for the lack of a preexposure effect in Groups HT0 and HT+ is that this reflected a reduction in the loss of associability by the tone in these groups. The finding that latent inhibition of a neutral stimulus is disrupted by hippocampal ablation is well documented, and a number of investigators have explained this effect by proposing that the hippocampus is involved in attentional processes. Douglas (1967) proposed that intact animals learn to exclude or "gate out" irrelevant or redundant stimuli, and that this is a function of the hippocampus. Damage to this structure therefore disrupts the gating mechanism and results in irrelevant events' being readily learned about. Solomon (1980) also suggested that hippocampal lesions render an animal unable to ignore

Figure 3. Extent of largest (lined areas) and smallest (solid areas) lesions at 2.0, 2.6, and 3.0 mm posterior to bregma. (Sections taken from Pellegrino & Cushman, 1967.)

irrelevant stimuli. Moore and Stickney (1980) reported computer simulations that suggested that stimulus salience, as defined by Mackintosh (1975), remains high to a nonreinforced stimulus after hippocampal lesions, whereas it declines in intact animals.

Although this type of account can readily explain the results for the groups that received preexposure to the nonreinforced tone, it is not clear how it may be applied to the case in which preexposure involved reinforced presentations of this stimulus. For example, it is unreasonable to regard the tone for Group ST+ as irrelevant, since it signaled a US and therefore should not have been gated out or ignored. The significantly slower conditioning with the tone in this group than in Group SL+ during the test session suggests either that animals ignore stimuli according to principles other than relevance, or that attentional processes are not responsible for the effects of preexposure to a CS.

With regard to the second alternative, it is possible that for Group ST+, the loss of associability of the tone was due to subjects' learning a response to that stimulus in Stage 1 that lessened the effects of the shock in the test stage. It is further possible that the subjects in Group HT+ were unable to learn such an adaptive response and hence received a more effective shock in the test stage. Although this account could explain the retardation of conditioning in Group ST+ compared to controls and to Group HT+, it cannot explain the lack of any difference in conditioning to the tone by the final session of Stage 1. If subjects in Group ST+ had learned some US-diminishing response, then this ought to have resulted in a weaker asymptotic level of conditioning to the tone in this group than in Group HT+. That there was no difference limits the plausibility of this account. Furthermore, this account implies that the disruption of subsequent conditioning that is observed when an animal receives nonreinforced exposure to a stimulus occurs for different reasons than that seen when exposure is reinforced. This may be true, but since hippocampal lesions exert a similar influence on the outcome of both procedures, it seems more likely that the same process is responsible for the similar effects of these preexposure treatments. The theories of Wagner (1978, 1981) and Pearce and Hall (1980) propose the existence of such a process. According to Wagner, subjects acquire a context-stimulus association when a stimulus is presented in a particular experimental context. This association leads to decreased processing of the stimulus, and subsequently to slower conditioning when the stimulus is paired with a US. Context-stimulus associations are held to be formed regardless of whether the stimulus has previously been paired with a US; hence the model predicts retarded learning about any familiar event. The model formulated by Pearce and Hall (1980) proposes that novel stimuli will be attended to and learned about and that this attention will decline if the stimulus has regular, predictable consequences. In the case of CS-US pairings, the CS is reliably followed by the US. Thus, at asymptote, the amount of attention paid to a reinforced CS will decline. Simi-

larly, the model predicts that subjects will cease to attend to a nonreinforced stimulus. Insofar as the amount of attention paid to a stimulus is held to determine the rate of learning, it follows that any event that has in the past been a good predictor of its consequences will condition more slowly when it is paired with a US.

Both of these theories predict that the loss of associability of a CS and of a neutral stimulus should be similar after a large number of presentations, and it is encouraging to note that during the test session conditioning was retarded to a similar degree in Groups ST+ and ST0. Moreover, the finding that an independent variable (hippocampal lesions) affected the latent inhibition of both a CS and a neutral stimulus lends support to the idea that the two phenomena share a common mechanism.

These results are also consistent with the cognitive-map theory of O'Keefe and Nadel (1978; see also Nadel & Willner, 1980), which proposes that animals form a map of their environment. This map contains representations of both static features and phasic stimuli, such as intermittent tones. Any stimulus that is not already represented in the map elicits enhanced attention and readily enters into associations with other novel stimuli, whereas stimuli that *are* represented are "absorbed by the context" (Nadel & Willner, 1980, p. 224). This incorporation of a stimulus into the experimental context is reflected in latent inhibition. Hippocampal lesions are said to disrupt the formation of the mapping system, so that even if a stimulus is repeatedly presented in the same place, it will not be absorbed into the representation of the context, and latent inhibition will be disrupted. This theory also predicts that latent inhibition both of a neutral stimulus and of a CS will be similarly attenuated by hippocampal damage.

In conclusion, it should also be added that hippocampal lesions have been shown to interfere with other Pavlovian conditioning phenomena that may involve attentional mechanisms; thus, overshadowing has been shown to be attenuated (Schmajuk, Spear, & Isaacson, 1983) and blocking abolished (Rickert et al., 1978). The evidence for these effects is somewhat ambiguous, however, inasmuch as Garrud et al. (1984) demonstrated successful blocking and overshadowing after complete removal of the hippocampus. It is possible that differences in extra-hippocampal damage may account for this ambiguity; for example, Jarrard, Okaichi, Steward, and Goldschmidt (1984) found that maze learning deficits depended on hippocampal and extrahippocampal lesions. Alternatively, it may be the case that the occasional effects reported in compound conditioning are caused by factors other than those responsible for the disruption of latent inhibition reported in the present article.

REFERENCES

- ACKIL, J. E., MELLGREN, R. L., HALGREN, C., & FROMMER, G. P. (1969). Effects of CS preexposure on avoidance learning in rats with hippocampal lesions. *Journal of Comparative & Physiological Psychology*, **69**, 739-747.
- DEVIETTI, T. L., EMMERSON, R. Y., & WITTMAN, T. K. (1982). Dis-

- ruption of latent inhibition by placement of an electrode in the dorsal hippocampus. *Physiological Psychology*, **10**, 46-50.
- DOUGLAS, R. J. (1967). The hippocampus and behavior. *Psychological Bulletin*, **67**, 416-442.
- GARRUD, P., RAWLINS, J. N. P., MACKINTOSH, N. J., GOODALL, G., COTTON, M. M., & FELDON, J. (1984). Successful overshadowing and blocking in hippocampectomized rats. *Behavioral Brain Research*, **12**, 39-53.
- HALL, G., & PEARCE, J. M. (1979). Latent inhibition of a CS during CS-US pairings. *Journal of Experimental Psychology: Animal Behavior Processes*, **5**, 31-42.
- JARRARD, L. E., OKAICHI, H., STEWARD, O., & GOLDSCHMIDT, R. B. (1984). On the role of hippocampal connections in the performance of place and cue tasks: Comparisons with damage to hippocampus. *Behavioral Neuroscience*, **98**, 6, 946-955.
- LUBOW, R. E. (1973). Latent inhibition. *Psychological Bulletin*, **79**, 398-407.
- LUBOW, R. E., & MOORE, A. U. (1959). Latent inhibition: The effect of nonreinforced preexposure to the conditioned stimulus. *Journal of Comparative & Physiological Psychology*, **52**, 415-419.
- MACKINTOSH, N. J. (1975). A theory of attention: Variations in the associability of stimuli with reinforcement. *Psychological Review*, **82**, 276-298.
- McFARLAND, D. J., KOSTAS, J., & DREW, W. G. (1978). Dorsal hippocampal lesions: Effect of preconditioning CS exposure on flavor aversion. *Behavioral Biology*, **22**, 398-404.
- MOORE, J. W., & STICKNEY, K. J. (1980). Formation of attentional-associative networks in real time: Role of the hippocampus and implications for conditioning. *Physiological Psychology*, **8**, 207-217.
- NADEL, L., & WILLNER, J. (1980). Context and conditioning: A place for space. *Physiological Psychology*, **8**, 218-228.
- O'KEEFE, J., & NADEL, L. (1978). *The hippocampus as a cognitive map*. Oxford: Clarendon Press.
- PEARCE, J. M., & HALL, G. (1980). A model for Pavlovian learning: Variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psychological Review*, **87**, 532-552.
- PELLEGRINO, L. J., & CUSHMAN, A. J. (1967). *A stereotaxic atlas of the rat brain*. New York: Appleton-Century-Crofts.
- RICKERT, E. J., BENNETT, T. L., LANE, P. L., & FRENCH, J. (1978). Hippocampectomy and the attenuation of blocking. *Behavioral Biology*, **22**, 147-160.
- SALAFIA, W. R., & ALLAN, A. M. (1980). Conditioning and latent inhibition with electrical stimulation of hippocampus. *Physiological Psychology*, **8**, 247-253.
- SALAFIA, W. R., & ALLAN, A. M. (1982). Augmentation of latent inhibition by electrical stimulation of hippocampus. *Physiology & Behavior*, **29**, 1125-1130.
- SCHMAJUK, N. A., SPEAR, N. E., & ISAACSON, R. L. (1983). Absence of overshadowing in rats with hippocampal lesions. *Physiological Psychology*, **11**, 59-62.
- SOLOMON, P. R. (1980). A time and a place for everything? Temporal processing views of hippocampal function with special reference to attention. *Physiological Psychology*, **8**, 254-261.
- SOLOMON, P. R., & MOORE, J. W. (1975). Latent inhibition and stimulus generalization of the classically conditioned nictitating membrane response in rabbits (*Oryctolagus cuniculus*) following dorsal hippocampal ablation. *Journal of Comparative & Physiological Psychology*, **89**, 1192-1203.
- WAGNER, A. R. (1978). Expectancies and the priming of STM. In S. H. Hulse, H. Fowler, & W. K. Honig (Eds.), *Cognitive processes in animal behavior* (pp. 177-210). Hillsdale, NJ: Erlbaum.
- WAGNER, A. R. (1981). SOP: A model of automatic memory processing in animal behavior. In N. E. Spear & R. R. Miller (Eds.), *Information processing in animals: Memory mechanisms* (pp. 5-47). Hillsdale, NJ: Erlbaum.

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