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Hippocampal Lesions and Active Avoidance[1]

DAVID S. OLTON[2] AND ROBERT L. ISAACSON[2]

University of Michigan, Ann Arbor

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OLTON, D. S. AND R. L. ISAACSON. *Hippocampal lesions and active avoidance.* PHYSIOL. BEHAV. 3 (5) 719–724, 1968.—Rats with lesions of the hippocampus were impaired relative to normal rats in the acquisition and retention of a one-way active avoidance task, but were superior to normal and partially neodecorticate rats in the acquisition of a two-way active avoidance task. The deficit of rats with hippocampal damage in the one-way task was accentuated when "no shock trials" (CS only) preceded acquisition or reacquisition training. Neocortically lesioned animals showed a slight deficit on both response and latency measures of performance. It is suggested that hippocampectomized rats are deficient in the ability to associate noxious events with cues indicating spatial location.

Acquisition Active avoidance Hippocampal lesions Neocortical lesions Retention

A SIGNIFICANT advance in the experimental study of the relationship between brain lesions and avoidance conditioning was the distinction between active and passive avoidance tasks [15]. Subsequent experimentation has indicated that an equally important differentiation must be made between one-way and two-way active avoidance problems [20]. It is now clear that passive avoidance tasks, one-way and two-way active avoidance problems tap different behavioral capacities in brain damaged animals [18]. Consequently, for an adequate understanding of the functions of particular brain areas, and of the differences in functions among different brain regions, it is necessary to determine how lesioned animals perform in each of these three tasks.

Although there is a great deal of evidence to indicate that animals with lesions of the hippocampus are deficient in the performance of passive avoidance tasks, there has been little systematic work comparing the performance of these animals across the two types of active avoidance tasks. What evidence there is, indicates that in active avoidance tasks which can be classified as "one-way tasks," rats with hippocampal damage are impaired in both acquisition [1, 2, 3, 16] and retention [22], although one exception can be found in the literature [17]. In two-way active avoidance tasks, on the other hand, rats with hippocampal lesions show enhanced performance during acquisition [8, 10].

The following experiments were designed in order to give a complete description of the performance of hippocampectomized rats in both types of active avoidance tasks, using acquisition, retention and relearning procedures.

To distinguish true retention of previous learning from alterations in postoperative learning ability, animals were tested after surgery using conditions in which shock followed incorrect responses (reacquisition) and conditions in which it did not (extinction). This procedure has been used before in evaluating effects of other brain damage [18] but not with animals with hippocampal damage. Moreover, to better evaluate the causes of the behavioral changes observed, and because in other tasks hippocampectomized animals have shown a deficit in the ability to alter previously established behavioral sequences [12, 19, 21, 24], some groups were given experience with the CS (alone) before training or testing.

METHOD

Apparatus

The apparatus was a 6 in. × 18 in. box, 12 in. high with a grid floor. One end was white, the other was black. One wall was made of glass for observational purposes. The box was separated into two compartments by a guillotine door which slid down to the top of a 2 in. high barrier in the middle of the apparatus. Each compartment was illuminated by a 6 W light bulb on one side. The CS consisted of the off-set of light in the compartment which was not occupied by the animal, the sounding of a doorbell buzzer located in the center of the apparatus, and the raising of the guillotine door. The US consisted of 0.8 mA shock delivered in 0.5 sec pulses, 1/sec, produced by a Grason–Stadler shock generator. The CS–US interval was 10 sec.

Subjects

Male albino rats from the Sprague–Dawley strain which weighed between 275 and 325 g at the start of the experiment were used. All rats were sufficiently handled both before testing and after surgery so as to become docile.

PROCEDURE

General Training

During acquisition and reacquisition procedures ("shock conditions"), if the rat did not jump over the barrier into the

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[2]Present address: Department of Psychology, University of Florida, Gainesville, Florida, 32601.

unoccupied compartment within 10 sec of CS onset, the US was applied until the response was made. An intertrial interval of 30 sec followed, during which the rat remained in the compartment which it had just entered. During adaptation and extinction procedures ("no-shock conditions"), the maximum duration of the CS was lengthened to 20 sec. If the rat did not jump over the barrier within this time limit, the CS was terminated, the rat remained in the same compartment, and another trial was begun after 30 sec. In both shock and no-shock conditions, when a response was made, CS and US were terminated as the rat's hind legs cleared the barrier.

After the intertrial interval in the one-way task, the rat was removed by hand from the compartment and replaced in the original compartment to await another trial. In the two-way task the rat remained in the compartment which it had entered and another trial was begun after the appropriate interval. Consequently, in the one-way task, the rat always jumped into the same "safe" compartment, i.e., a compartment in which it was never shocked, while in the two-way task, the rat could receive shock in either compartment, unless, of course, an avoidance response occurred within the CS–US interval.

Twenty trials a day were given on each of 3 consecutive days for a total of 60 trials in all procedures.

Because of the relatively large number of experimental manipulations, groups of rats will be referred to by appropriate symbols. Table 1 sumarizes the several experimental conditions. The use of a "1" with a group indicates that it was in the one-way task, while the use of a "2" with a group indicates that it was in the two-way task.

Learning

Rats assigned to the training procedures were handled before their random assignment to surgical subgroups. After the postoperative recovery period of 10 days, rats in the acquisition group were given 60 training trials with shock ("Ac"), while rats in the adaptation-acquisition group were given 60 pseudotraining trials without shock ("Ad") followed by 60 trials of training with shock ("Ac–Ad").

Retention

Animals assigned to the retention procedures were handled and then given acquisition training to criterion performance using the technique described above. A strict criterion of 19 avoidance responses each day for 3 consecutive days was used. They were then assigned to a lesion subgroup on the basis of the number of trials required to reach criterion in order to equate sub-groups on this variable. Surgery was performed within 48 hr after criterion performance was reached.

After a post-operative recovery period of 10 days, animals in the reacquisition procedures were given 60 training trials with shock ("Re") while those in the extinction-reacquisition procedure were given 60 pseudotraining trials without shock ("Ex"), followed by 60 training trials with shock ("Re–Ex").

Thus the groups "Ac" and "Re", "Ad" and "Ex", "Ac–Ad" and "Re–Ex" are operationally equivalent, respectively, except that rats in Ad and Ac conditions were naive when placed in the apparatus, while rats in Re and Ex conditions were trained preoperatively to criterion performance levels.

Surgery

The surgical procedure was similar to that described before [10], except that rats were not held in a stereotaxic instrument. Briefly, rats in the control group were anesthetized, the scalp retracted, and holes trephined through the skull. Rats in the cortically lesioned group then had the neocortex overlying the hippocampus removed by aspiration. Rats in the hippocampally lesioned group had the hippocampus, as well as overlying neocortex, removed by aspiration.

Histology

Following the experiment, the rats were sacrificed with a lethal dose of sodium pentobarbital and intracardially perfused with 0.9 per cent saline and 10 per cent formalin solution. The brains were removed, infiltrated with, and embedded in, paraffin before being sectioned at 10μ. After being mounted on slides, the sections were stained with thionin. The lesion of each animal was then reconstructed on the appropriate diagram of the rat brain as given by DeGroot [4] at regularly spaced intervals throughout the lesioned area. Following procedures developed previously [24] a grid composed of 0.5 cm squares was superimposed on these diagrams. The number of squares covered by each lesion was counted to compute a numerical index of the total amount of brain damage, and the extent of damage to individual structures within the brain.

TABLE 1

	Group	Symbol	Preoperative Procedure	Postoperative procedure	
				No-shock conditions	Shock conditions
Learning	Acquisition	Ac	—	—	60 trials
	Adaptation	Ad	—	60 trials	—
	Acquisition after Adaptation	Ac–Ad	—	(60 trials)	60 trials
Retention	Reacquisition	Re	Training to criterion	—	60 trials
	Extinction	Ex	Training to criterion	60 trials	—
	Reacquisition after Extinction	Re-Ex	Training to criterion	(60 trials)	60 trials

Summary of experimental design. For further explanation see text. Parentheses indicate antecedent training. i.e., animals in Ad were next place in Ac–Ad, while rats in Ex were next place in Re–Ex.

RESULTS

Histology

Six rats were discarded from the study because of poor health. The lesions of the other animals were very similar, but about 10 per cent smaller than the cortical and hippocampal lesions which have been reported previously [24] (Exact calculation of number of units tissue damage, per cent brain areas destroyed, and photomicrographs of representative lesions are available upon request from the authors). The hippocampal lesions involved about 60 per cent of this structure.

Performance

No-shock conditions. During the adaptation procedures there were no significant differences among groups of animals within a task on the mean number of responses made after the CS during the 60 trials in either task.

During the first day of extinction testing which was the first measure of retention, normal rats in the one-way task made significantly more responses (M = 28.25) than combined cortical and hippocampectomized groups (M = 14.75) (t test, two-tailed, $p < 0.05$). This difference in the two-way task did not reach significance.

Shock conditions. The performances of animals during shock conditions in the one-way and two-way task are presented in Table 2. Performance was measured by (a) the mean number of trials prior to the attainment of a criterion of 9 avoidance responses in 10 consecutive trials, and (b) the mean number of avoidance responses made during the 60 trials of a given procedure.

normal and cortically lesioned rats these two groups have been combined for comparison with hippocampal rats, except, of course, for Ac-Ad in the two-way task, where the two groups were significantly different. A one-tailed t test was used to assess significance.

Hippocampally lesioned rats. Both measures of performance give remarkably similar estimates of behavioral change. In the one-way tasks, hippocampectomized rats were inferior to animals in the combined control groups on both performance measures in all procedures ($0.001 < p < 0.03$). In the two-way task, hippocampectomized animals were superior to combined control animals during acquisition on both measures ($p < 0.005$, and $p < 0.002$). For the Ac–Ad group trained in the two-way task (where animals with neocortical lesions were significantly inferior to normal rats), the differences between normal and hippocampectomized rats were all insignificant. Compared to animals with neocortical lesions in this procedure, those with hippocampal lesions performed significantly better on both performance measures ($p < 0.01$, and $p < 0.025$). In the two retention procedures of the two-way task, the differences among groups of normal, cortically damaged and hippocampectomized rats were all insignificant.

Because the effects of hippocampal and neocortical lesions were in the same direction in the one-way task, a Mann–Whitney U test was used to compare directly groups of cortically and hippocampally damaged animals on the two behavioral measures. In all procedures, except "acquisition," the values of U ranged from 0 to 3 ($i = 0.005$ to $p = 0.032$). For acquisition, U = 8, $p = 0.184$ for total number of avoidance responses, and U = 10, $p = 0.107$ for number of trials to criterion.

TABLE 2

Procedure	Group	N	One-way Task Behavioral Measure 9/10	One-way Task Behavioral Measure Total	N	Two-way Task Behavioral Measure 9/10	Two-way Task Behavioral Measure Total
Ac	N	8	8.50	51.10	8	49.20	21.40
	C	4	14.50	46.50	4	(50.00)	17.25
	H	8	20.25	42.63	7	17.14	45.56
Ac–Ad	N	6	2.33	54.33	6	17.33	45.50
	C	4	17.50	48.25	4	(37.50)	27.50
	H	5	(27.40)	33.20	4	12.25	45.75
Re	N	6	1.00	59.00	6	1.67	59.00
	C	4	2.00	56.00	5	7.60	52.80
	H	6	9.80	52.20	5	5.40	56.80
Re–Ex	N	6	2.17	56.50	6	9.33	56.17
	C	4	9.00	48.50	3	11.67	47.33
	H	5	(26.67)	19.50	6	8.33	56.80

Performance of normal (N), cortical (C), and hippocampal (H) rats in both tasks. The behavioral measures are: (a) mean number of trials necessary to attain a criterion of 9 avoidance responses in 10 consecutive trials ("9/10"); and (b) mean number of avoidance responses made during the block of 60 trials ("Total"). Parentheses around a number in the 9/10 column indicate that at least one animal did not attain criterion performance. In such cases, animals were given a score of 60.

Cortically lesioned rats. The deficits in performance of animals suffering neocortical destruction were small but appeared consistently in every comparison. In only one procedure, Ac–Ad with the two-way task, was this difference between normal and cortically damaged animals statistically significant (t test, two-tailed, $p < 0.05$ on both behavioral measures.)

Because of the small differences in performance between

The average latencies of avoidance and escape responses during the 60 trials of acquisition are presented in Table 3. In the one-way task, the average latency of escape and avoidance responses of both groups of brain damaged animals was significantly longer than that of normal subjects (t test, two-tailed, $p < 0.05$ for escape and $p < 0.01$ for avoidance responses). In the two-way task, the escape latencies, but not the avoidance latencies, were significantly

longer for all brain-damaged animals (t test, two-tailed, $p < 0.05$).

TABLE 3

	One-way Task		Two-way Task	
	Escape	Avoidance	Escape	Avoidance
N	1.67	1.99	1.77	3.76
C	2.15	3.26	2.58	5.28
H	2.56	3.64	4.29	2.91

Average latency in seconds of escape (shocked) and avoidance (unshocked) responses of normal (N), neocortically lesioned (C) and hippocampectomized (H) animals during acquisition procedures.

DISCUSSION

The present series of experiments represents an attempt to provide a complete examination of the effects of hippocampal destruction on active avoidance behavior. The present studies allow meaningful comparisons among the several avoidance paradigms and lesion groups because of the use of similar subjects, training conditions, and laboratory environment. Also, new information was obtained concerning the effects of various alterations in training procedures which may lead toward better understanding of the behavioral deficits produced by the destruction of the hippocampus.

Rats suffering from lesions of the hippocampus were found to be superior to control animals in the performance of a two-way active avoidance task, but were inferior to normal animals in the performance of a one-way active avoidance task. The performance increments found in the two-way task appeared only during acquisition training, while the decrements in the one-way task appeared during both acquisition and retention.

The deficit in performance on the one-way task exhibited by animals with hippocampal damage was found in all but one procedure when they were compared with either normal animals or cortically damaged animals or both groups combined. The only exception was in the acquisition procedure where hippocampally damaged animals were impaired relative to a combined control group of both normal and cortically damaged animals but were not significantly different from the animals with damage limited to neocortex which also exhibited an impairment in avoidance conditioning, as will be discussed below. The weight of the data in this report as well as data from other experiments makes it likely that the additional involvement of hippocampal damage accentuates the deficit observed after cortical lesions on the one-way task.

When a block of trials was given in which only the CS was presented (shock did not follow) differential effects were obtained during subsequent acquisition training. For normal animals this procedure produced faster acquisition in the two-way task, and a difference in this same direction just failing to reach significance in the one-way task. This failure to reach significance may be due to the relative ease with which the one-way problem is learned by normal animals under standard conditions. Even though the adaptation to the CS before training proved beneficial to the normal subjects, animals with destruction of the neocortex failed to profit from the experience. Animals with hippocampal damage, however, were strikingly impaired in the one-way task when the CS adaptation period preceded acquisition training.

When tested under extinction conditions for the retention of the preoperatively learned active avoidance response in both the one-way and two-way procedures, the animals with either neocortical or neocortical and hippocampal destruction showed similar retention deficits. The addition of hippocampal damage to the neocortical removal did not increase the retention deficit produced by damage to the neocortex.

The performance enhancement in the two-way task and the performance decrement in the one-way task following the destruction of the hippocampus are consistent with certain previous reports [1, 2, 3, 8, 10, 16, 22]. However, comparisons among performances on the various tasks were tenuous since there were major differences among the studies in terms of subjects, apparatus, procedures, and methods used to induce brain damage. In the present experiment as many of these variables as possible were held constant, assuring a better foundation for comparisons of performances not only between the two avoidance tasks, but also among the different training paradigms.

In the two-way task, animals must return to a location in which shock has been received in the past. Perhaps the superior performance of the hippocampally damaged animals is related to a reduced tendency to avoid places in which shock has formerly been received. It is well known that animals with hippocampal damage show deficiencies in passive avoidance tasks [see 6]. In a passive avoidance situation animals with hippocampal lesions return more readily to places in which they have received shock than do control animals. This passive avoidance impairment may represent deficiencies of several types, but one possibility is of special interest. The animals could be deficient in making an association between the noxious stimuli and the place in which the shock was delivered. If cues concerning "place" were unavailable to the animals with hippocampal damage then the difficulties exhibited in passive avoidance problems and the changes observed in the active avoidance tasks would be expected.

This hypothesis would predict the inferior learning of the one-way active avoidance problem since hippocampectomized animals would have difficulty in associating the punishment with the starting compartment, while normal animals would have the advantage of utilizing place cues in determining a unique place to be avoided. Similarly, in the two-way active avoidance task, hippocampectomized animals would not exhibit a tendency to avoid previously shocked locations, a tendency that is present in normal animals and interferes with the successful performance of this task.

A possible deficit in the utilization of place cues is indicated by the impaired tendency for spontaneous alternation which has been found in animals with hippocampal damage [7, 23]. Douglas [5] has shown that the behavior reflected in spontaneous alternation phenomena represents a tendency to avoid previously visited "places" and not a tendency to alternate responses *per se*.

Rats learn the two-way active avoidance task as if it were two separate one-way problems [20]. The hypothesis that hippocampally damaged animals are deficient in the use of place cues suggests that the two components of the two-way task should be less differentiated for these animals than for control animals. This hypothesis can be assessed by calculating a Pearson product moment correlation coefficient between the first avoidance response made on the left to right component of the two-way task and the first avoidance

response made on the right to left component during acquisition. This correlation should be greater for the rats with hippocampal damage than for the other groups of animals. For normal animals $R = +0.385$, for cortically lesioned animals, $R = -0.088$, for hippocampectomized animals $R = +0.988$. Hippocampectomized animals are significantly different by an r to z transformation [9] from both normal ($p < 0.01$) and cortically damaged animals ($p < 0.05$). This suggests that when hippocampectomized rats make an avoidance response in one direction they are much more likely to make a correct response in the opposite direction, a result which would be expected on the basis of a deficiency in utilizing the place cues.

Another important aspect of the present experiment is the effect of the blocks of CS (only) trials given before acquisition training and during the testing for retention under extinction conditions. Our results suggest that hippocampectomized animals have a deficit in the ability to shift their anticipations of environmental contingencies when the situation is so altered that formerly adaptive responses now bring different reinforcing consequences. Behavioral deficiencies based on the perpetuation of inappropriate responses which have been previously learned have been reported in other tasks [11, 12, 24]. Furthermore, a similar suggestion has been made by Klüver [14] based upon a different line of reasoning.

The results obtained with a CS adaptation period before training stand in sharp contrast with the results obtained when ten unescapable CS–US pairings were given animals before training. Olton and Isaacson [19] reported that when 10 trials of this type of "fear" conditioning were given prior to training in the one-way active avoidance task, hippocampectomized rats no longer showed the expected deficit in performance. This treatment would help the hippocampectomized rats establish an association between the noxious stimulation and the place in which it was received. This, in turn, should improve conditioning in this type of task.

Observation of our animals with hippocampal damage suggests that the shock was indeed anticipated. These animals often exhibited unusual mannerisms in the one-way active avoidance task. Upon presentation of the CS, the rats would crouch for several seconds, often orient toward the safe compartment, but then rise upon its hind legs looking toward the ceiling. Occasionally they would squeal just before the onset of the CS. Usually after the onset of the shock, the rat would promptly cross the barrier to the safe compartment.

To more carefully examine these mannerisms, we gave additional trials to the animals with hippocampal damage after their relearning experiences in the Re–Ex_1 procedure. The CS was presented in the usual manner but shock was not applied. All animals exhibited a similar pattern of behavior. At approximately 10 sec after CS onset (the usual CS–US interval), the animal rose, squealed and sometimes even fell over backwards onto the grid. The shock, of course, did not occur. After exhibiting some behaviors which appeared to indicate a surprise reaction to the absence of shock, they would right themselves and again explore the compartment. They anticipated the shock, but were unable to utilize this information effectively in the one-way task. These types of behaviors were never observed in normal animals or animals with only neocortical destruction in either task. They were not observed in animals with hippocampal damage in the two-way procedure.

There are several reasons for believing that an increase in general activity level is not responsible for the changes in avoidance performance found in our present experiments. First, no differences were found in the number of responses emitted during the (CS only) trials presented before the acquisition training among the several groups of animals. Second, the enhancement of two-way active avoidance performance has been shown to be independent of activity level changes in animals with small hippocampal lesions [8]. Third, if an increase in activity produced an enhancement of performance in the two-way task, it is not clear how it would also act to produce the deficit found in the one-way task.

Animals with destruction limited to the neocortex had a slight but consistent deficit in response latencies in both types of active avoidance tasks. Two other studies [8, 19] have also reported deficits in active avoidance tasks following neocortical damage. Our data show that extended latencies occurred during both avoidance and escape responses in the one-way task. Apparently, the neocortical destruction acts to reduce the speed of reaction in shock avoidance tasks. The data from the two-way problem also tend to support this view.

The possibility of the CS producing differential effects upon the several groups of animals should be considered. For normal rats, it has been shown that a localized CS has little effect on the difference between performance or one-way and two-way active avoidance problems [20]. This may not be true of animals with limbic damage. However, if such differential effects occur, they should be found in the procedures in which the CS was presented by itself, i.e., the adaptation periods. No significant differences were found between the animals with hippocampal damage and either of the other two groups of subjects.

From all of the above, we believe that our data indicate that animals with hippocampal damage are able to adequately anticipate the occurrence of noxious events but have difficulty in using this information when it must be coupled with information about a specific place and the consequences of moving to or from it.

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