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RESPONSE TO STIMULUS CHANGE FOLLOWING OBSERVATION OR EXPLORATION BY THE RAT: DIFFERENTIAL EFFECTS OF HIPPOCAMPAL DAMAGES

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Abstract. The tendency of the rat to approach the place that had been changed between two successive trials was studied in a total of 118 rats. The experiment was conducted in an enclosed T-maze under two different conditions of stimuli presentation on trial 1. In the "passive" test the rat was allowed to inspect the white-black maze arms but prevented from entering them by transparent partitions, in the "active" test the rat was permitted to explore the entire T-maze. On trial 2 of both tests, the color of one arm was changed, so that the arms were either both white or both black. Sham operated controls showed a preponderance of choosing the changed arms in 75–80% in both tests. Rats with lesions of the anterodorsal or the posteroventral hippocampal region showed no arm preference in the passive test, while in the active test, the same groups displayed significant preference for the changed arm. Since performance in both tests relies on memory required for detection of the place of change, the behavioral dissociation following the hippocampal damage cannot be explained by recent hypotheses postulating involvement of the hippocampus in recognition memory, working memory or construction and execution of cognitive spatial maps.

INTRODUCTION

The behavioral role of the hippocampus has long been the focus of intense research, however, there is little agreement as to the function of this structure. Recently, several theories have emerged (5, 18, 20) that renewed the classical notion that the hippocampal system is concerned with mnemonic processes, as suggested in early studies from the human clinical literature (23). The most elaborated theory, put forward by O'Keefe and Nadel (19) postulates that the hippocampus forms a neural substrate for spatial cognition. These researchers distinguished between two kinds of memory systems: the locale system which provides the animal with spatial maps, and the taxon systems enabling an animal to solve a problem by specific responses to cues. Since damage to the hippocampus has a devastating effect on cognitive maps, a hippocampal animal can perform successfuly only in those tasks that can be resolved by the use of the taxon systems.

The opponents of the O'Keefe–Nadel theory called attention to several weak points, among them the role of exploration in cognitive mapping (3, 4). Locomotion is considered to be a fundamental information processing mechanism, whereby the animal (especially the rat) acquires spatial information. However, in several experiments (see 4) the mere transporting of animals over paths allowed them to learn about the environment. This indicates that cognitive maps could be formed in the absence of locomotion. We should note that behavior might be vulnerable to the hippocampal damage, although it is based on informations acquired solely by observation. The study of Gaffan (5) is an example. He used the "response to stimulus change" test introduced by Dember (2). In this two-trial test, a rat is confined to the stem of an enclosed T-maze and allowed to inspect the maze arms differing in brightness through the transparent partitions. Then, the color of one of the arms is changed and the rat is allowed a free choice. Normal rats tend to explore the arm that had been changed between trials (2, 5, 11, 14). In doing so, the rats displayed memory of spatial pattern of the stimuli presented on the first trial. Gaffan (5) found that fornicotomized rats performed at chance level and attributed the result to the loss of recognition memory. It seems, however, more conceivable that normal rats construct simple maps of the small environment formed by the enclosed T-maze and perceive the spatial relationships between the different parts of the maze even in the absence of locomotion. From this point of view, the effect of fornicotomy would be consistent with the notion of spatial mapping as a function of the hippocampal system. However, assuming the importance of explora-

tion for spatial mapping, the failure to respond to stimulus change might be far more probable if the rats would be permitted to walk around the maze during the presentation of stimuli.

The aim of the present study was to determine whether hippocampal lesions would affect, to a similar extent, the response to stimulus change in rats tested under two different experimental procedures. One employed the procedure used by Gaffan (5) and the other allowed rats to explore the entire maze instead of looking through the transparent partitions at the maze arms. We have labelled the latter procedure the "active" test in distinction from the Gaffan's procedure that we have labelled the "passive" test. Since recent data (8, 17) indicate functional differentiation of the hippocampus, we intended also to compare the effects of lesions placed in the anterodorsal and the posteroventral part of the hippocampus.

METHOD

Subjects. The subjects were 118 male Wistar rats about 110–120 days old at the time of the experiment. They were housed in groups of 5–7 with food and water available ad lib. About 40 rats were assigned to each of three surgical treatments: anterodorsal hippocampal (DH) and two posteroventral hippocampal (VH_1 and VH_2). Within each treatment, the subjects were randomly divided into operated and the control groups. The experiment was performed successively, so that only one operated and one control group were tested at a given time period. Prior to the present study, emotional reactivity (15) and open-field behavior (16) were examined. The present experiment started 1 day after open-field testing.

Surgery and histology. The brain lesions were performed by stereotaxic coagulation according to König and Klippel coordinates (7) (for details, see 15). The control rats, received an incision of the skin and holes were drilled in their skulls, but no electrode was inserted. After completion of the experiment, deeply anesthetized rats were perfused with 10% formalin solution. Frozen sections were prepared at 50 μm and stained with the Klüver-Barrera method.

Apparatus. An enclosed T-maze, painted gray, with the stem 27 cm long × 13 cm wide and the arms 40 cm long × 13 cm wide was used. The walls were 30 cm high. Plastic inserts, painted white and black could be put into the arms. A mirror hung above the maze enabled the observation of the rat's behavior.

Testing procedure. The passive test consisted of two trials. During the first, the exposure trial, the rat was allowed to observe the maze arms, one with the white insert and the other with black insert, but it was prevented from entering the arms by clear plexiglass partitions. After 15 min exposure, the rat was removed from the maze and reintroduced 1 min later for the second trial, the choice trial. Between trials while the rat was out of the maze, one insert was altered so that both arms were of the same color, i.e., either white or black. The partitions were removed, so on the choice trial the rat was free to enter either arm. The choice trial was terminated as soon as the animal entered one of the arm or lasted 180 s maximally, when the rat did not choose either arm. Only the first entry, defined as four legs being in one arm was recorded. Additionally, the following records also were taken: (i) the observing time recorded whenever the animal had his head turned in the direction of one or the other arm during the exposure trial, (ii) the choice latency of the time elapsed between putting the rat in the maze stem and its entering the arm on the choice trial, and (iii) defecation and urination on both trials. The passive test was performed on the 18-th day after surgery.

The active test, similar to the passive test, consisted of the exposure trial and the choice trial separated by a 1 min break. However, in contrast to the passive test, in the exposure trial of the active test, the rat was allowed to explore white-black maze arms. At the end of the exposure trial, that lasted 3 min, the animal was taken out of the maze, and one insert was changed for the insert of the opposite color. The floor and walls of *both* inserts were carefuly wiped clean by the same sponge. This cleaning provided olfactory symmetry of the arms in the event that wiping did not eliminate scent-marks completely which could be left by the exploring rat in one arm. Further procedural steps were the same as in the passive test. The first entry was recorded as well as other behavioral measures: (i) the time of exploration of the white and the black arm, separately, (ii) the number of entrances to the arms during the exposure trial, (iii) the choice latency on the choice trial, and (iv) defecation and urination during both trials. The active test was performed 3 days after the passive test.

The DH and VH_1 treatment groups were subjected to both tests while the VH_2 lesioned group and its control group received only the active test. In each group, the rats were randomly assigned to four conditions resulting from the spatial arrangement of colors in the exposure trial (white — right, black — left, and vice versa) and the change of colors making both arms white or black.

Statistics. The data were evaluated by analyses of variance (for non correlated data and mixed design according to Lindquist (9)). For more detailed comparisons, Duncan tests were done, when appropriate.

RESULTS

Anatomy. The dorsohippocampal lesions (Fig. 1*A*) mostly affected the anterior part of this structure and the dorsal section of fascia dentata. In some cases there were small and mainly unilateral destructions of the fimbria. The ventrohippocampal lesions (Fig. 1*B*) damaged the posteroventral part of the hippocampus, the ventral section of fascia dentata and also the medial fragment of subiculum. More anatomical details have been presented elsewhere (15).

Choice reaction. The number of rats selecting the changed or the unchanged maze arm in the passive test and in the active test are presented in Table I*A*. The response-to-change frequencies were subjected to analysis of variance (Treatments × Groups × Tests) with raw scores transformed to arc sin $\sqrt{P}$, where P denotes the percentage of responses to the changed arm. This transformation corrects the distribution of percentages to better estimate homogeneity of the scores and allow use of analysis of variance techniques.

Table I

The number of rats choosing the changed and the unchanged maze arm. Part *A* refers to groups examined in the passive test and in the active test, successively; part *B*, to groups examined only in the active test.

Treatments		Tests / Groups	Passive test		Active test	
			Changed	Unchanged	Changed	Unchanged
A	DH	Operated	9	11	14	4
		Control	15	5	16	3
	VH_1	Operated	10	10	15	5
		Control	16	4	17	3
B	VH_2	Operated	–	–	13	5
		Control	–	–	17	3

Note: In the DH treatment, two operated rats and one control rat did not choose any arm during the 180 s duration of the choice trial of the active test.

As seen from Table I*A*, in the passive test the two groups with the hippocampal lesions chose the changed arm in lower proportions than did the control groups. This observation was confirmed statisti-

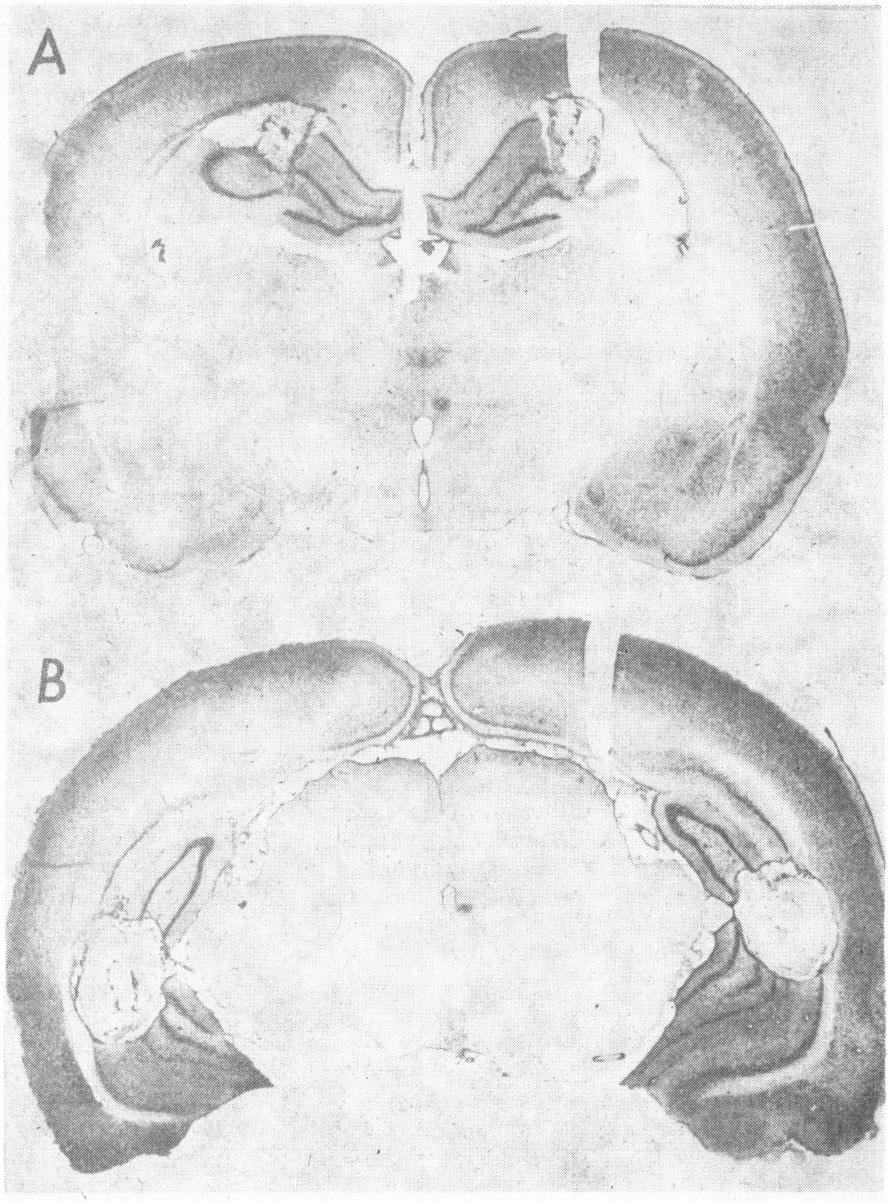

Fig. 1. Representative damages to the anterodorsal (*A*) and the posteroventral (*B*) hippocampal regions.

cally by a significant Group effect ($F = 610.86$, $df = 1/1$, $P < 0.05$). Duncan tests indicated that in the passive test each hippocampal group differed from its control group ($P < 0.05$). In the active test, the number of choices of the changed arm increased as shown by a Test effect

($F = 534.83$, $df = 1/1$, $P < 0.05$). Duncan test revealed that hippocampal groups selected the changed arm more frequently in the active test than in the passive test ($P < 0.05$), while in control groups the difference between the active test and the passive test was nonsignificant. In consequence the difference between hippocampal groups and their control groups, observed in the passive test, disappeared in the active test. The more pronounced effect of the active test procedure on response-to-change frequency in hippocampal groups than in control groups was also confirmed by the Groups $\times$ Tests interaction ($F = 156{,}60$, $df = 1/1$, $P \leqslant 0.05$). The nonsignificant Treatment effect indicated that the performance of groups with different placement of lesions was alike in the passive test as well as in the active test. The same was found for the control groups.

It might be supposed that increased preference to change displayed in the active test by hippocampal groups arose from their previous experience gained in the passive test. In order to exclude this possibility another hippocampal group (VH_2) was examined only in the active test. The scores of the VH_2 groups (Table I*B*) compared with those of the VH_1 groups in a separate ANOVA (Treatments $\times$ Groups) showed no differences, judging from nonsignificant effects of both factors.

In an attempt to statistically evaluate the proportions of choices of the changed and the unchanged arm of all examined groups in the passive test and in the active test, an ANOVA on type of response choice data (changed — unchanged arm. Table I*A*) was performed (Responses $\times$ Tests $\times$ Groups). The Treatment factor was omitted since its effect appeared nonsignificant from the previous analysis. As might be expected, the Response effect ($F = 641.23$, $df = 1/8$, $P < 0.001$) revealed the preponderance of choices of the changed arm. This finding was due to the more frequent choices of the changed than the unchanged arm, observed in the control groups during both tests as well as in the hippocampal groups in the active test. Although the main effects of Groups and Tests were nonsignificant, the significant interactions of Responses $\times$ Tests ($F = 137.29$, $df = 1/8$, $P < 0.001$), Responses $\times$ Groups ($F = 104.14$, $df = 1/8$, $P < 0.001$) and the triple interaction ($F = 41.29$, $df = 1/8$, $P < 0.001$) confirmed the above conclusions. Duncan comparisons indicated that the differences between the number of choices of the changed and the unchanged arm in the control groups were at the $P < 0.05$ level in both tests. In the hippocampal groups the significant difference between choices was found only in the active test ($P < 0.05$), while in the passive test this difference was nonsignificant. Thus, in the passive test the hippocampally lesioned groups responded at the chance level, showing no preference for the changed or

the unchanged arm, while in the active test they chose predominantly the changed arm, similar to their control groups.

Latency of choice. Large individual differences in this measure were observed in all groups tested. The group median latency ranged from 6.5 to 13 s. Comparison of the cumulative frequency distributions of choice latency of the hippocampal and the control groups revealed no differences among groups either in the passive test or in the active test. No relations were found between latency values and response type, and the latency distributions of rats choosing the changed arm did not differ significantly from those of rats choosing the unchanged arm (Smirnov two-tailed test).

Observing time. Since in the exposure trial the rats were placed into a novel environment, they explored the maze stem vigorously. They attempted also to force the partitions and get into the maze arms. Although it was impossible to tell whether the rat attended to visual stimuli when it sniffed the plexiglass partitions or climbed on them, the time spent in this behavior was considered as observing time. The situation was clearer if the rat stood in front of the partition looking directly into the arm. At any rate, attention to the maze arm and possibly to the colors presented there was a component of exploration of the whole area of confinement, therefore it cover only a small part of the exposure time. During the 15 min trial, observing time ranged in different groups from 153 s to 164 s (Table II). The observing time

Table II

Behavioral measures recorded in the passive and active tests.

Treatments	Tests / Means / Group	Passive		Active			
				Exploration time (s)			
		Observing time (s)	Defecation and urination scores	in white arm	in black arm	Number of entries	Defecation and urination scores
DH	Operated	153.1	1.3	35.3	70.3	11.5	0.5
	Control	156.9	1.0	35.0	63.5	11.8	0.5
VH_1	Operated	156.7	1.7	27.3	69.7	11.4	1.7
	Control	164.4	0.5	28.7	67.2	11.1	0.6
VH_2	Operated	—	—	24.7	53.3	12.3	2.0
	Control	—	—	32.1	52.2	13.6	0.8

decreased in three successive 5 min periods of exposure trial, which was already noted previously (11). An analysis of variance (Groups × Treatments × Periods) revealed that the effect of Periods only was

significant ($F = 85.22$, $df = 2/152$, $P < 0.001$). Nonsignificant effects of Treatments and Groups indicated no difference between hippocampal and control groups regarding observing times.

The relation between observing time and the type of response in the choice trial was analysed by an ANOVA (Groups $\times$ Treatments $\times$ Responses) which showed no significant effects of all three main factors, as well as their interactions. This result means that the amount of time spent in the observation of visual stimuli did not influence the choice between the changed and the unchanged arm.

Exploration time and number of entries. The data were collected from the exposure trial of the active test (Table II). Analyses of variance (Groups $\times$ Treatments) showed a nonsignificant effects of Groups while the effects of Treatments were significant ($F = 9.59$, $df = 2/110$, $P < 0.001$ — for exploration time and $F = 15.10$, $df = 2/110$, $P < 0.001$ — for number of entries). Duncan tests revealed that this effect was due to differences between VH_2 treatment groups and the other treatment groups. The lesioned and the control group from the VH_2 treatment showed a slightly shorter time of exploration ($P < 0.05$) but somewhat more frequent entries to the arms ($P < 0.05$), than did the remaining groups. These differences might be attributed to the fact that in the VH_2 groups, the active test was not preceded by the passive test. Other groups subjected to both tests did not differ among themselves. The rats from all tested groups explored the black arm longer than the white one as shown by a significant Color effect ($F = 143.79$, $df = 1/110$, $P < 0.001$). Nonsignificant Group and Treatment effects indicated that the hippocampal lesions did not affect preference to black over white color typical for rats. No relations were found between the time of exploration or the number of entries to the maze arm and the type of response on the choice trial ($F < 1$ for both measures).

Defecation and urination. Scores were low in all groups, nevertheless rats with the ventral hippocampal lesion defecated and urinated significantly more than their controls in the exposure as well as in the choice trial of both tests as shown by a significant Group effect ($F = 6.95$, $df = 1/149$, $P < 0.01$) and Duncan tests ($Ps < 0.05$). Rats with the dorsal hippocampal lesion did not differ from controls in this respect.

DISCUSSION

The results of the present study indicate that the hippocampal lesions affected the response-to-change examined in the passive test, in which rats could see the colors of the maze arms through the trans-

parent partitions. This finding is concordant with the finding of Gaffan (5) who used a similar procedure. However, when rats were allowed to walk and explore the maze, as in the active test procedure, the same hippocampal groups that responded at chance level in the passive test, showed a significant preponderance of choices of the changed arm. It should be noted that this difference in performance could not be attributed to experience gained in the passive test which preceded the active test, since the VH_2 group examined solely in the active test, also displayed preferences to the changed arm. Despite the procedural differences between tests, in both the rats could recognize the stimulus change only by comparison of the actual external information with their memory of past experience. Thus, the differential effect of the two testing procedures on responding to change by hippocampal rats is at variance with Gaffan's notion attributing recognition memory to the function of the hippocampal system. Normal performance of lesioned rats in the active test also provides an argument against the impairment of exploratory motivation postulated for hippocampal damage (1).

Although recent evidence has demonstrated that behavioral effects of hippocampal lesions vary as a function of their placement (24) and their magnitude (21), in our experiment small damages to the anterodorsal or to the posteroventral part of the hippocampus had an identical effect on responding to stimulus change. We cannot conclude if this effect is permanent, since only one passive test and one active test were performed, as rats preference to the changed arm disappears with test repetitions (12).

Our data are not compatible with the cognitive map theory (18) that assumes that the hippocampus forms the neural representation of space. It follows from the hypothesis that detection of any change in the environment will require the contribution of the hippocampus. Yet, in our study the hippocampal damage produced a clear deficit in one test and no difference in the other, although in both tests the rat's performance relied on exactly the same sort of events, i.e., detection of stimulus change and identification of the place in which this change occurred. O'Keefe and Nadel (19) postulated that the behavior of hippocampal animals depends on the taxon systems with different properties than the mapping system. They emphasized as the major distinction that active exploration is necessary for map formation in the rat, thus the opposite result could be expected than that obtained by us. The hippocampal rats should be defective in the active test involving maze exploration, rather than in the passive test, in which rats merely looked to the maze arms. However, if O'Keefe and Nadel consider that, in responding to stimulus change, rats rely on the taxon

system, then it is difficult to understand why the hippocampal lesions affected performance in the passive test. Obviously, cognitive map theory cannot account for the effect of hippocampal damage in the rat on the response-to-change test.

The reason why hippocampal rats responded to stimulus change, or not, depending on the type of stimuli exposure, is open to several interpretations. Some investigators concluded that hippocampal lesions decreased attention to visual cues (10). It was also shown that behavioral deficits following hippocampal lesions can be ameliorated by providing the animals additional cues (25) or enhancing the distinctiveness of relevant cues (22). One may argue that the exposure trial in the passive test was low in cue distinctiveness, so that information necessary for memory storage might not have been available, while in the active test the stimuli presented were more salient since free exploration enabled closer contact with them.

Another assumption is that contextual factors might account for the dissociation between the tests in our experiment. Hirsh (6) has suggested that the hippocampus is a part of a system mediating contextual retrieval. As shown by Winocur and Olds (26) hippocampal rats performed as well as controls when testing conditions were held constant, but were significantly impaired in the contextual shift condition. The partitions that prevented the entrance to the maze arms in the passive test exposure made this trial different from the choice trial in which partitions were removed. The absence of partitions might direct attention of the hippocampal rats to the free entrance to both maze arms, so that the animals did not discriminate between the changed and the unchanged arm. Alternatively, actual information of free entrance would affect retrieval, interfering with memory related to colors in the maze arms on the exposure trial. In the active test the exposure trial and choice trial were alike since partitions were not applied, thus the hippocampal rats were not subjected to the contextual shift and interference.

It seems, however, that if the hippocampal rats attended less to visual cues or were influenced by the contextual shift of the passive test, this should be reflected in other parameters of their performance like observing time or choice latency. Yet, there were no significant differences between lesioned and normal rats on these measures.

The finding of dissociation between performance of the hippocampal rats on the passive test procedure and that on the active test procedure is in line with concepts of different memory types with different characteristics. Recently Olton et al. (20) distinguished between working memory and reference memory. The former is involved in tasks

where the response to a stimulus varies from trial to trial, while the latter operates in tasks requiring the same response across trials. Citing references from the literature Olton et al. (20) included the response-to-change procedure used in Gaffan's study (5) to working memory procedures. Most procedures associated with working memory require subjects to remember not only the stimulus but also *when* it occurred, while response-to-change procedure requires subjects to remember not only stimuli but also *where* (instead of when) they occurred. However, the crucial point is the same: stimulus information is useful for one trial of an experiment (the exposure of stimuli and subsequent free choice may by viewed as a single trial). The passive test procedure does not differ in this respect from the active test procedure. Therefore both of them should be classified as working memory procedures. Thus, one may ask, why the hippocampal lesions influenced the passive, but not the active test procedure, and whether this result could be predicted by working memory theory. Presumably not, since the active test procedure did not convert the response-to-change into the reference memory procedure which is considered insensitive to hippocampal damage. Apparently the response-to-change test does not incorporate a working memory procedure, at least as formulated by Olton et al. (20) or the intact hippocampus is not critical for normal performance in every working memory procedure. However, it seems far more probable that the working memory procedure and reference memory procedure could not account for all various strategies used by the animals. Possibly, there are several different kinds of memory located in different places. Memory acquired in the procedure of the passive test required an intact hippocampal system, while that gained in the active test can be implemented by other structures. It would have been important to show that lesions placed elsewhere would affect responding to change in the active test but not in the passive test. Such experiments are now in progress.

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