Memory for spatial location: Functional dissociation of entorhinal cortex and hippocampus

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To test whether there is a functional dissociation between the hippocampus and entorhinal cortex, rats were trained on a variable spatial-location matching-to-sample (working memory) task with various delays. After training, rats with entorhinal cortex, entorhinal-cortex-plus-hippocampus/subiculum, hippocampus, control, or cortical control lesions were tested for performance within the task. Results indicated that in the variable spatial-location condition relative to the control and cortical controls, all lesioned groups showed a profound impairment in performance of the task across all delays. They were subsequently tested for acquisition of a constant spatial location task. In the constant spatial-location condition, the entorhinal cortex and entorhinal-cortex-plus-hippocampus/subiculum lesioned groups did not learn the task, whereas the hippocampal lesioned group did. It is suggested that there is a functional dissociation between the hippocampus and the entorhinal cortex. It is proposed that the hippocampus encodes new spatial information within a working-memory system, whereas the entorhinal cortex represents spatial information within a reference-memory system as part of a spatial cognitive map.

With respect to the encoding or representation of spatial information, two hypotheses have been proposed concerning the function of specific subdivisions of the hippocampal formation. One hypothesis emphasizes the interrelationships and shared functions among the entorhinal cortex, hippocampus, and subiculum (Barnes, 1988; Olton, Walker, & Gage, 1978; Rasmussen, Barnes, & McNaughton, 1989); the other hypothesis attempts to differentiate the functions of the hippocampus plus subiculum and entorhinal cortex (Eichenbaum, Otto, & Cohen, *in press*; Morris, Schenk, Tweedie, & Jarrard, 1990; Schenk & Morris, 1985).

There are two different views associated with the shared-function hypothesis. Olton et al. (1978) have suggested that the hippocampus, subiculum, and entorhinal cortex are primarily involved in representing spatial information in the form of working memory, which translates into memory for new incoming spatial information that needs to be remembered for a specific trial within a task. However, the above-mentioned neural regions do not represent spatial information in the form of rules and procedures (reference memory) which translates into memory for spatial aspects of events that occur on all trials of a task. Barnes (1988), on the other hand, has suggested that the hippocampus, subiculum, and entorhinal cortex

are involved in representing spatial information in both working- and reference-memory systems. The two views differ in that Olton emphasizes the importance of hippocampus, subiculum, and entorhinal cortex in mediating working but not reference memory, whereas Barnes assumes that these neural regions represent spatial information in both working and reference memory.

There are three views associated with the differential function hypothesis. Morris et al. (1990) have suggested that the hippocampus plus subiculum might be involved in the consolidation of new spatial information, whereas the entorhinal cortex is involved in retrieval of information for the selection of spatial rules and strategies. In a second view, it is proposed that the hippocampus represents relational information, whereas the parahippocampal region, including entorhinal cortex, represents nonrelational, individual-item information (Eichenbaum et al., *in press*). A somewhat different view is that the hippocampus plus subiculum is involved in representing new incoming spatial information that needs to be remembered within a working, or data-based, memory system, whereas the entorhinal cortex is involved in long-term representation of spatial information in the form of a spatial cognitive map within a reference, or knowledge-based, memory system (Kesner, 1990). The three views differ in that Morris emphasizes the operation of consolidation and retrieval of spatial information, Eichenbaum et al. emphasize differential relational as opposed to individual representations, and Kesner emphasizes the importance of spatial representations within working memory and reference memory. For a more detailed analysis of the role of the hippocampus in representing spatial in-

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formation within working or data-based memory, see Kesner (1990, 1991).

Support for the idea that the entorhinal cortex might mediate a spatial cognitive map within reference memory comes from a variety of sources. First, Jarrard, Okaichi, Steward, and Goldschmidt (1984) and Rasmussen et al. (1989) have shown that entorhinal cortex lesions in rats disrupt both working- and reference-memory components within eight-arm-maze spatial tasks. Also, Schenk and Morris (1985) have shown that entorhinal cortex lesions in rats disrupt both the acquisition and retention of a correct location within a water maze spatial-navigation task. It should be noted, however, that in all three of the above studies, the entorhinal cortex lesions extended into the subiculum and sometimes the ventral hippocampus.

Second, Miller and Best (1980) have shown that in addition to disrupting performance in an eight-arm radial maze, entorhinal cortex lesions also decrease the number of place cells in the hippocampus. Furthermore, those cells that had place fields responded more to intramaze than to extramaze cues.

Third, there are cells in the entorhinal cortex that have place field characteristics in both rats and monkeys (Quirk & Ranck, 1986; Rolls et al., 1989; Barnes, McNaughton, Mizumori, Leonard, & Lin, 1990; and Mizumori, unpublished observations). It should be noted, however, that the place fields found in the rat entorhinal cortex are somewhat larger than those found in the rat hippocampus, are more distributed, and have a lower signal-to-noise ratio.

To test the shared-function and differential-function hypotheses, an experiment was devised to measure memory for a single spatial location in an eight-arm maze, first using a variable-arm procedure, in which an animal had to remember a randomly selected arm that varied daily, and then using a constant-arm procedure, in which a rat had to remember the same arm (one of eight arms) each day. It was assumed that the variable-arm procedure engages working memory for spatial location information as well as a spatial cognitive map for generating spatial rules and strategies (Kesner, 1990). In contrast, it was assumed that after a few trials, the constant-arm procedure engages only reference memory to provide appropriate spatial rules and strategies based on a spatial cognitive map (Kesner, 1990; Olton, Becker, & Handlemann, 1979).

One form of the shared-function hypothesis (Olton et al., 1979) would predict a deficit for the hippocampus and entorhinal cortex using the variable task (working-memory procedure) but no deficits using the constant task (reference-memory procedure). A different form of the shared-function hypothesis (Barnes, 1988) would predict a deficit for both entorhinal cortex and hippocampus in both variable and constant tasks (working- and reference-memory procedures). The differential hypothesis would predict that both the hippocampus- and the entorhinal-cortex-lesioned rats would have a deficit on the variable task, but that, in contrast to the rats with hippocampus lesions, the entorhinal-cortex-lesioned an-

hippocampus lesions, the entorhinal-cortex-lesioned animals would not be able to learn the constant task.

METHOD

Subjects

Twenty-eight Long-Evans rats, approximately 90 days old and approximately 300 g in weight at the beginning of the study, were deprived to 80% of their ad-lib weights prior to preoperative training. Body weights were maintained at this deprivation level, plus an additional 5 g increase each week to compensate for normal development. The subjects were fed approximately 30 min after the completion of daily testing. They were housed individually and maintained on a 13-h-light:11-h-dark lighting schedule. All testing was carried out during the light phase of the dark-light cycle. Water was available ad lib.

Apparatus

The test apparatus was an eight-arm radial maze. The maze consisted of a central hexagonal wooden platform, 41 cm in diameter, with eight wooden arms, 61 cm long and 9 cm wide, projecting outward from the platform. A 3-cm-diam, 1.25-cm-deep food well was drilled 0.5 cm from the end of each arm. This food well placement prevented subjects from viewing the contents of the well from the center platform. All maze-floor surfaces were painted white. Clear 5-cm-high Plexiglas retaining walls were placed on both sides along the length of each arm. Clear 20-cm-high Plexiglas retaining walls were placed in the 5-cm gaps between arms at the point of attachment between the arms and the central platform.

Clear 20-cm-high Plexiglas doors were placed between each arm and the central platform. By means of a string-and-pulley system, these doors were attached to a control board adjacent to the maze room. This system allowed the experimenter to lower (open) and raise (close) each door, thus controlling access to each arm while remaining outside the maze room.

The maze was centered in a 2.5×1.75 m room. The surface of the maze was elevated 1 m above the floor of the maze room and 1.5 m below the overhead fluorescent lighting fixture. Several scenic posters of various sizes were placed on the walls of the maze room to facilitate the subjects' orientation in space.

Procedure

Shaping. Following initial deprivation, the subjects were allowed to individually explore the test apparatus for 15 min per day for a period of 1 week. Throughout this exploration period, four pieces of Froot Loop cereal (Kellogg's) were placed in each of four randomly selected food wells. The wells baited were changed daily. This procedure was halted when each rat retrieved all available rewards within 5 min of being placed on the maze. At this point, preoperative training was initiated.

Preoperative training. Subjects received one preoperative training trial each day for a total of five trials per week. Each trial consisted of a study phase and a test phase. During the study phase, one randomly selected arm was baited with one-half piece of Froot Loop cereal and the access door was opened. All other access doors remained closed. A rat was placed in the middle of the central platform oriented toward a randomly selected door, which could be the correct or the incorrect door, and allowed to retrieve the reward. Following a 10-sec interval in which to consume the reward, the subject was removed from the maze and not returned until the test phase.

Prior to the beginning of the test phase, the arm visited during the study phase was baited with one piece of Froot Loop cereal and the center platform was quickly wiped with a cloth saturated with dilute ammonia solution to remove olfactory cues. All access doors were then opened. The test phase was begun by placing the rat on the center platform, oriented toward a randomly selected

arm, which again could be the correct or incorrect door. The rat was then allowed to run freely until the reward was recovered. The rat was removed from the maze after the reward had been recovered and consumed. All arm visitations were recorded; however, for the primary analysis, only the first visitations to any of the seven unbaited arms within each trial were counted as errors. Repeated visits to unbaited arms were considered to be repetition errors and were analyzed separately.

The delay interval between the study phase and the test phase was manipulated on a random basis. Delay interval was defined as the time period between the removal of a subject from the maze during the study phase and the placement of the same subject on the maze to begin the test phase. Three delay intervals were used: 6 sec, 1 min, and 10 min.

Preoperative testing was terminated for an individual subject when that subject made fewer than an average of 1.2 errors per trial in 30 trials with 10 trials per delay. Surgery was performed on each subject following completion of its preoperative testing.

Surgery. The subject was anesthetized with sodium pentobarbital (Nembutal, 45 mg/kg i.p.) prior to surgery. The subject was placed in a stereotaxic instrument, and an incision was made in the skin above the skull. The margins of the incision were retracted, and the fascia clinging to the skull was scraped away with a scalpel blade to fully expose the dorsal portion of the skull. The position

of the incisor bar was then adjusted to level bregma to lambda on the horizontal plane. An epoxy-coated stainless steel insect pin with 1 mm of the tip scraped bare was used as the lesioning electrode.

The rats were assigned randomly to groups. Twelve rats received bilateral lesions of the entorhinal cortex. For entorhinal cortical lesions, the angle of the electrode carrier was adjusted to 10° away from the skull midline. Trephining points were measured and marked using the tip of the electrode as a marker at the following coordinates: 1.5 mm anterior to interpolated lambda point, at 3 and 5 mm lateral to midline (four trephining points). At each trephine, the electrode was lowered until the tip reached the bottom of the calvarium; then the electrode was raised 1 mm. A 1.2-mA current was applied for 30 sec using a Stoelting electrolytic lesion maker. Five control rats received surgical treatment identical to that of rats receiving electrolytic lesions, except current was not applied during control surgeries.

Six rats received bilateral hippocampal lesions with the following coordinates: (1) 3.5 mm caudal to bregma, 2.8 mm ventral from dura, and 1, 2.2, and 3.2 mm lateral to midline, and (2) 4.6 mm caudal to bregma, 5.2 mm lateral to midline, and 5.6 and 8.1 mm ventral from skull. A 1.2-mA current was applied for 10 sec to each of these 10 sites. Five rats served as cortical controls. They received lesions dorsal to the hippocampus, with the following coordinates: 3.5 mm medial to bregma, .5 mm ventral from dura, and

Figure 1. An example of the smallest and largest entorhinal cortex lesion (A) and the smallest and largest entorhinal cortex-plus-hippocampus/subiculum lesion (B).

Figure 2. An example of a large hippocampal lesion.

1, 2.2, and 3.2 mm lateral to midline. A 1.0-mA current was applied for 10 sec to each of these 6 sites.

Following application of current to all lesion coordinates, the incision was closed using 4.0 coated Vicryl suture. The subjects were returned to their home cages and allowed to recover for 10 days before postoperative testing was begun. During this recovery period, the subjects received oxytetracycline in their drinking water (1 mg/ml). Postoperative infections were treated with Bicillin (25 mg/day, i.m.).

Postoperative testing. The initial postoperative testing procedure was the same as that used during preoperative training. The subjects were tested until 10 trials had been conducted at each of the three delay periods. Delays were assigned randomly to trials. Errors were recorded as in the preoperative training trials. Following the initial 30 postoperative testing trials, the subjects were transferred to a constant-arm task in order to test for residual reference-memory capacity.

The constant-arm testing procedure was identical to the previous preoperative procedure, except that the rewarded arm remained the same throughout all subsequent trials. Additionally, all trials within a day were conducted with a 1-min delay between the study and test phase. Errors were recorded in the same manner as during preoperative training. Each subject received 5 trials per day with a 5-min intertrial interval on the constant-arm task until 20 trials had been completed. Rats with entorhinal cortex lesions received an additional 10 trials on the constant-arm task. Following these constant-arm trials, the subjects were prepared for histology.

Histology. Subjects were deeply anesthetized with an overdose of sodium pentobarbital (45 mg/kg i.p.). They were then decapitated, and their brains were removed and fresh-frozen in -70°C 2-methylbutane.

For brains with entorhinal cortex lesions, 20- μm horizontal sections of the lesion site, hippocampus, and subiculum were cut on a cryostat at -17°C . For brains with lesions of the hippocampus, 20- μm cross sections of the lesion site were taken. On the basis of the stained sections, rats were classified into the following experimental groups: (1) entorhinal cortex lesions, (2) entorhinal cortex lesions with additional damage to the subiculum or the hippocampus, (3) lesions of the hippocampus, (4) cortical control lesions, and (5) no damage other than electrode tracks (control rats).

RESULTS

Histology

Among the 12 rats that received entorhinal cortex lesions, 5 were classified as having large bilateral lesions of the entorhinal cortex. In addition, there was damage to presubiculum and parasubiculum. There was no damage to the perirhinal cortex. Five rats had complete entorhinal cortex lesions and additional damage to the hippocampus and subiculum. Among the latter group, the subiculum was damaged in 3 rats. The subiculum and the caudal margins of the hippocampus were damaged in the remaining 2 rats. Two rats had received unilateral entorhinal cortex lesions; these rats were excluded from the analysis. Control rats demonstrated no damage to the entorhinal cortex, hippocampus, or subiculum. A representative sample of a lesion of the entorhinal cortex and a lesion of entorhinal cortex plus hippocampus and subiculum is shown in Figure 1.

Among the 6 rats that received hippocampal lesions, 5 were classified as having complete bilateral dorsal and ventral hippocampal lesions. One rat exhibited no damage to several fields of the hippocampus; this rat was excluded from further analysis. A representative sample of a large dorsal and ventral hippocampal lesion is shown in Figure 2. These rats had retrosplenial and parietal cortical damage, but no observable damage of the entorhinal cortex. A representative sample of cortical control lesion is shown in Figure 3. These rats had damage to retrosplenial and parietal cortex.

Figure 3. An example of a cortical control lesion.

Figure 4. Mean errors per trial following entorhinal cortex, entorhinal cortex-plus-hippocampus, hippocampus, cortical control, or control lesions as a function of various retention delays in the variable-arm condition.

Figure 5. Mean errors per trial following entorhinal cortex, entorhinal cortex-plus-hippocampus, hippocampus, cortical control, or control lesions as a function of blocks of trials in the variable-arm condition.

Preoperative Behavior

All rats reached the preoperative criterion of 1.2 errors per trial based on 10 trials of each delay period. The mean number of errors per trial during the last preoperative block of 10 trials (ignoring delay) was 0.7, with a range of 0 to 1.2 errors per trial. The mean number of trials required to reach criterion performance was 100, with a range of 77 to 150. None of the rats made any repetition errors.

Postoperative Behavior

The results, shown in Figure 4, indicate that, for each delay, rats with entorhinal cortex lesions, lesions of both the entorhinal cortex plus subiculum structures, or hippocampal lesions performed more poorly on the postlesion variable-arm test than the control rats. A repeated measures analysis revealed that lesioned rats made more errors than control rats [$F(4,20) = 24.6, p < .0001$]. There was no significant effect for delay [$F(2,40) = 1.5, p < .3$], nor was there a significant interaction between type of lesion and delay [$F(8,40) = 0.45, p < .9$]. A Newman-Keuls comparison test revealed that each lesion group made more errors per trial than did the control or cortical control groups ($p < .01$). However, there were no differences between lesion groups (entorhinal, entorhinal plus hippocampus, and hippocampal) with respect to the number of errors made.

To analyze the data for possible recovery of function, error data were grouped into consecutive blocks of 10 trials, ignoring delay intervals. The results, shown in Figure 5, indicate that when considering consecutive blocks of 10 trials regardless of delay, lesioned rats performed poorly when compared with controls, suggesting no recovery of function. A repeated measures analysis revealed that lesioned rats made more errors than controls [$F(4,20) = 26.3, p < .0001$]. There was no significant effect for blocks of trials [$F(2,40) = 1.8, p < .2$]. There was no significant interaction between lesion group and blocks of trials [$F(8,40) = 1.2, p < .4$]. A Newman-Keuls comparison test revealed that the performance of lesion groups did not differ significantly with respect to errors made per trial. However, lesion groups did differ significantly from the cortical control and control groups with respect to the number of errors made per trial ($p < .01$).

With respect to repetition errors to unbaited arms, as can be seen in Table 1, only the entorhinal cortex and entorhinal-cortex-plus-hippocampus group made many errors. In contrast, rats with hippocampal lesions and the controls and cortical controls did not make any errors. The difference between the entorhinal cortex lesioned groups and the hippocampal and control groups is significant at the $p < .01$ level using the Mann-Whitney U test.

The results from the constant-arm test of reference memory, shown in Figure 6, indicate that rats with entorhinal cortex lesions and rats with lesions of both the

Table 1
Mean Number of Repetition Errors Per Trial

	Variable	Constant
Entorhinal cortex	1.5*	.8*
Entorhinal cortex and hippocampus	1.2*	.9*
Hippocampus	.0	.0
Control	.0	.0
Cortical control	.0	.0

*Mann-Whitney U test between entorhinal cortex or entorhinal cortex plus hippocampus vs. hippocampus, control, or cortical control ($p < .01$).

Figure 6. Mean errors per trial following entorhinal cortex, entorhinal cortex-plus-hippocampus, hippocampus, cortical control, or control lesions as a function of blocks of trials in the constant-arm condition.

entorhinal cortex plus hippocampus performed poorly on the postlesion constant-arm test of reference memory. However, rats with lesions of the hippocampus were able to acquire the reference-memory task and achieve a level of performance comparable to that of the two control groups.

A repeated measures analysis of variance revealed that when considering consecutive blocks of five trials on the constant-arm task, there was a significant effect for type of lesion [$F(4,20) = 5.6, p < .003$]. Rats with either category of entorhinal lesion performed poorly when compared with the two control groups. A Newman-Keuls multiple comparison test confirmed that these lesion groups made more errors per trial than the control group ($p < .01$). There was no difference between the entorhinal cortex lesion group and the entorhinal cortex and hippocampus lesion group with respect to the number of errors made per trial.

The analysis of variance indicated that there was a significant difference in the performance of groups across blocks of 5 trials [$F(3,60) = 11.9, p < .0001$]. However, the interaction between lesion and blocks of trials was not significant [$F(12,60) = 1.17, p < .35$]. Subsequent multiple comparison analysis revealed that the hippocampal lesion group exhibited a marked decrease in the number of errors made between the first and last blocks of 5 trials ($p < .01$). During the first block of trials, the performance of the hippocampal lesion group was significantly different from that of the control groups ($p < .05$) but indistinguishable from that of the entorhinal lesion groups. However, during the final block of 5 trials, the performance of the hippocampal lesion group was equivalent to that of the control group and significantly different from that of the entorhinal cortex lesioned groups ($p < .05$). The entorhinal lesion groups did not

exhibit this recovery of function. Even after an additional 10 trials, the entorhinal lesion groups continued to display impaired performance with a mean error per trial of 1.8 in the entorhinal cortex group and 2.2 in the entorhinal-cortex-plus-hippocampus group.

With respect to repetition errors to unbaited arms, it can be seen in Table 1 that only the entorhinal cortex and the entorhinal-cortex-plus-hippocampus groups made many errors. In contrast, rats with hippocampal lesions and the controls did not make any errors. The difference between the entorhinal cortex lesioned groups and the hippocampal or control groups is significant at the $p < .01$ level, using the Mann-Whitney U test.

DISCUSSION

The results of the present study indicate that animals with entorhinal cortex lesions with or without damage to the hippocampus or subiculum are impaired in terms of remembering a single spatial location across delays for both the variable- and constant-arm procedures. In contrast, animals with large lesions of the hippocampus are impaired only in the variable-arm procedure, but can acquire the constant-arm procedure. It should be noted that in the variable-arm procedure this deficit is observed even at the shortest delays and that there is no recovery of function. Similar deficits at extremely short delays have been reported for rats with large hippocampal lesions in a spatial continuous-recognition-memory task (Jackson-Smith & Kesner, 1990) and in monkeys with hippocampal lesions in a short-term-memory task for spatial locations (Parkinson, Murray, & Mishkin, 1988). It should be noted, however, that there is always a delay in these tasks, so it is possible that one might not detect deficits following hippocampal or entorhinal cortex lesions if one could employ a true 0-sec-delay condition. The results are consistent with previously reported findings of Hunt, Kesner, and DeSpain (1986), who showed that rats with large and even very small dorsal hippocampal lesions are impaired when using the same variable-arm procedure. Also, in the Hunt et al. (1986) study, different rats were pretrained using the constant-arm procedure and then, after reaching criteria, were subjected to large hippocampal lesions. The results indicated that there was only a transient impairment followed by total recovery of prelesion performance. These findings are consistent with the observation that hippocampal lesions do not affect the ability to learn not to enter four constantly baited arms or to learn to enter arms in which food is consistently paired with light (Olton & Papas, 1979; Packard, Hirsh, & White, 1989).

The data indicate that rats with hippocampal lesions can acquire new spatial information in a reference-memory type of situation. Additional support comes from a study by Walker and Olton (1984), who trained rats to enter a specific goalbox from each of three different starting positions. After a fimbria-fornix lesion, the rats were given transfer tests on a new starting position and tested for the selection of the same goalbox.

Successful selection of the goalbox on the transfer tests requires the utilization of a cognitive map. Animals with fimbria-fornix lesions as well as controls performed the transfer tests without any difficulty. In a somewhat different study, Kesner and Beers (1988) presented hippocampal or sham-lesioned rats with a constant sequence of five arms on an eight-arm radial maze followed by a test phase in which a recognition test was given between one arm that was always in the study-phase sequence and an arm that was never in the study-phase sequence. Reference memory was measured during the study phase of the trials as a pattern of correct or incorrect orienting responses in anticipation of the ensuing doors in the constant sequence. Since the sequence of spatial locations did not vary from trial to trial, it was assumed that the emitted orienting responses reflected the operation of the reference-memory component. Both groups of animals emitted the same pattern of correct orienting responses and made the same number and pattern of intralist and extralist intrusion errors.

It should be noted that in the present experiment as well as in the Walker and Olton (1984) and Kesner and Beers (1988) experiments, the rats had learned a substantial amount of information concerning the extra-maze cues in the room during the preoperative training conditions, which could have aided their performance in solving the reference-based spatial-location memory task. However, in other studies fimbria-fornix-lesioned rats that were not pretrained were impaired in the acquisition of baited arms (working-memory component) but were not impaired in the acquisition of nonbaited arms (reference-memory component) within an eight-arm maze (Olton, 1983). Similarly, Davis and Volpe (1989) showed that in a similar task ischemic rats with hippocampal damage failed to acquire the working-memory-task component, but acquired, albeit more slowly, the reference-memory-task component. Others, however, have found acquisition deficits on both working- and reference-memory components (Jarrard, 1986; Nadel & McDonald, 1980). In a different set of studies, Markowska, Olton, Murray, and Gaffan (1989) and Murray, Davidson, Gaffan, Olton, and Suomi (1989) showed that rats or monkeys with fornix lesions could acquire as easily as controls a conditional spatial-visual discrimination in which rats or monkeys had to select one of two objects when they were in one spatial location and select the other of the two when they were in a different spatial location. These same rats or monkeys were profoundly impaired in a spatial delayed-matching-to-sample task. The former task can be solved using reference memory, whereas the latter task requires the use of working memory.

In another study, Eichenbaum, Stewart, and Morris (1990) showed that relative to controls, rats with fornix lesions acquired, albeit more slowly, a place-learning task in a water maze using a fixed starting location procedure but were impaired in finding the correct spatial location using a variable starting-location procedure. In both the Eichenbaum et al. (1990) study and the present study, it is likely that the fixed starting position or the

constant-arm procedure resulted in the activation of reference memory proportionally more than working memory, whereas it is more likely that in the varied starting position or the variable-arm procedure there would be proportionally more activation of working memory than of reference memory.

It is possible that rats with hippocampal lesions can learn the constant-arm task using a single cue or an egocentric spatial strategy, since in this situation the rats need to attend only to a single cue or landmark or attend to an approach response based on proprioceptive feedback to solve the task in contrast to what might be expected in the variable task, which is likely to require the conjunction of both egocentric and allocentric spatial (relationships among two or more cues) strategies. Support for this possibility comes from the findings that memory for a single visual object, a motor response (right or left turn) or acquisition of a simple approach response is not impaired in rats with hippocampal lesions (Kesner, Dakis, & Bolland, 1993; McDonald & White, 1993; Packard et al., 1989). Thus, to the extent that rats used a proprioceptive feedback egocentric spatial strategy, they should be able to learn the task.

The spatial-memory deficits observed in this study following entorhinal cortex lesions are consistent with the observations of spatial deficits in complex mazes and water mazes in rats with electrolytically induced entorhinal cortex lesions (Jarrard et al., 1984; Rasmussen et al., 1989; Schenk & Morris, 1985). However, in a few studies, no observable deficits were found in a complex- or water-maze task following entorhinal cortex lesions made with ibotenic acid (Bouffard & Jarrard, 1988; Hagan, Verheijck, Spigt, & Ruigt, 1992). This suggests that electrolytic lesions could have produced impairments due to fibers of passage and adjacent fiber tracts. However, because rats with hippocampal lesions could learn the constant task, damage to perforant path input into the hippocampus cannot account for the observed deficits with entorhinal cortex lesions. Other possible fiber pathways connecting other cortical areas (e.g., parietal cortex) could, however, play a very important role.

There are also olfactory memory deficits following entorhinal cortex lesions (Staubli, Fraser, Kessler, & Lynch, 1986). However, these olfactory deficits cannot account for the spatial deficits observed following entorhinal cortex lesions, because, in the constant-arm condition, normal or hippocampal lesioned rats can solve the task without a study phase and rotation of the maze after the study phase does not interfere with the selection of the constant spatial location.

If one assumes that the variable-arm or starting-location procedure engages working memory for spatial-location information and that the constant-arm or fixed-location procedure engages reference memory (cognitive map) for spatial-location information, then the data support the Kesner and Morris forms of the differential but not the shared-function hypotheses. In other words, the data are consistent neither with the view that the hippocampus and entorhinal cortex mediate only spatial working but not

spatial reference memory nor with the view that the hippocampus and entorhinal cortex mediate both working and reference spatial memory.

The data are consistent with the view of a dissociation of function for the hippocampus and the entorhinal cortex, with the hippocampus primarily involved with spatial working memory and the entorhinal cortex primarily involved in reference memory in the form of a spatial cognitive map. The idea is not incompatible with the notion that the entorhinal cortex might be involved in the selection of spatial navigational strategies, since the navigational strategies are most likely dependent on a spatial cognitive map, and with the notion that the hippocampus might be involved in consolidation of new spatial information, since one aspect of spatial representations within working memory might be consolidation of spatial information when necessary. The present data are also consistent with Eichenbaum et al.'s (in press) view that the hippocampus mediates only spatial relationships and the entorhinal cortex mediates a single individual set of cues representing a single spatial location, if one assumes that in the variable-arm task animals must attend to specific spatial relationships to determine the correct spatial location, whereas in the constant-arm task animals need to attend to only one individual spatial relationship or a single set of visual cues. Further support for this dissociation of function for the hippocampus and entorhinal cortex comes from the repetition analysis of repeated visits to unbaited arms. If one assumes that repetition errors in this context represent reference-memory errors, then the data indicate that rats with hippocampal lesions do not make reference-memory errors even in the variable-arm condition and that rats with entorhinal cortex lesions make many reference-memory errors in both the variable- and constant-arm conditions. It should be noted that in this experiment neither the first nor a repeated visit to an incorrect arm resulted in reinforcement. It is, thus, not highly likely that repetition errors will occur for normal rats.

Additional support for the differential function hypothesis comes from the finding that lesions of the entorhinal cortex group in the present study did not damage the hippocampus or subiculum directly, whereas the lesions with the hippocampus-plus-subiculum group did not damage the entorhinal cortex directly. Thus, the entorhinal cortex, but not the hippocampus, might play a role in mediating a spatial cognitive map. Clearly, more experiments are needed, but thus far most of the extant data are consistent with the idea that the function of the entorhinal cortex might be distinctly different from that of the hippocampus proper.

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