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Dorsal/Ventral Hippocampus, Fornix, and Conditioned Place Preference

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ABSTRACT: Conditioned place preference (CPP) is a learning paradigm requiring formation of associations between reward and particular locations. White and McDonald (Behav Brain Res 1993;55:269–281) demonstrated that amygdala (AMG) lesions impair, while fornix (Fx) lesions enhance learning of this task. In the present experiments, we replicated the effects of AMG and Fx lesions, but we also found that complete hippocampal (HPC) lesions interfere with normal performance. Thus, the effects of Fx and HPC lesions on CPP are opposite. This is in contrast with spatial learning in the water maze. Because it has been demonstrated that damage of dorsal HPC interferes to a greater extent with spatial learning than damage of ventral HPC, we also tested animals with either dorsal or ventral HPC disruptions on CPP. Lesions limited to dorsal HPC were followed by impairment on this task. In contrast, lesions limited to ventral HPC resulted in enhanced learning. We argue that Fx and HPC lesions do not have interchangeable effects in all learning paradigms. To explain the complex pattern of results presently obtained, we propose a novel hypothesis regarding behavioral functions of HPC neural circuits. Implications regarding the interaction between memory systems are also considered. *Hippocampus 2001;11:187–200.* © 2001 Wiley-Liss, Inc.

KEY WORDS: amygdala; fornix; spatial; relational; configural; stimulus-reward association

INTRODUCTION

Since Scoville and Milner (1957) reported anterograde and retrograde amnesia following bilateral resection of medial temporal lobes, a multitude of studies have focused on the role of the hippocampus (HPC) in learning and memory. One of the animal models frequently used for investigating the role of this structure is created by producing lesions of either HPC proper or of one of its input/output pathways, the fornix (Fx). It is well known that lesions of either structure interfere with spatial learning (O'Keefe et al., 1975; Olton et al., 1978, 1979; Sutherland and Rudy, 1988; Sutherland and Rodriguez, 1989; Bouffard and Jarrard, 1988; Morris et al., 1982, 1990; Rawlins et al, 1993; Yee and Rawlins, 1994; Whishaw and Jarrard, 1996). Because of this, Fx transections are used as a means of disrupting HPC function. However, new data suggest that the two methodologies are not interchangeable in all situations (Whishaw and Jarrard, 1995; McDonald et al, 1997; Sziklas et al., 1998; Cassel et al., 1998).

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The reason behind differences in behavioral outcomes may be that the two lesions produce distinct types of disruptions of HPC function. These may have similar effects in some testing paradigms, but not others. The HPC proper, constituted of the dentate gyrus (DG) and CA3–CA1 fields, receives cortical input from the entorhinal cortex (EC) through the perforant path (PP). Its output back to EC is generated in CA1 and the subiculum (S) (Amaral and Witter, 1995). Subcortical HPC inputs/outputs are accomplished through the Fx, a collection of fibers which connects HPC with septum, nucleus accumbens (ACC), thalamus, hypothalamus/mammillary bodies, and brain stem. Fx lesions therefore leave intact the HPC proper and associated retrohippocampal connections. This creates the possibility for some sparing of HPC function. We investigated this hypothesis using a conditioned place preference (CPP) learning paradigm employed by White and McDonald (1993) and McDonald and White (1995a). The test is based on the general idea that normal animals spend more time at a location previously paired with food. Data previously published showed that AMG lesions abolish, while Fx lesions enhance this preference. We replicated these results in our first experiment, but we also found that complete (DG and CA3–CA1) HPC damage is associated with impaired performance. This pointed to two facts. First, lesions of Fx vs. HPC are not always followed by identical behavioral effects. This implies that careful considerations have to be applied in interpreting results based on usage of one vs. the other type of lesion. Second, as opposed to the conclusion previously drawn by McDonald and White (1995b), it seems that the AMG-based memory system by itself cannot form a functional representation in this learning paradigm, even when there is low cue ambiguity suggesting HPC function is essential for this task.

In agreement with physiological data (Jung et al., 1994) recent behavioral studies (Moser et al., 1993, 1995, 1998; Hock and Bunsey, 1998; Ferbinteanu and McDonald, 2000) indicate that the dorsal HPC pole is more efficient in processing spatial information than is its ventral counterpart. Because total HPC lesions impair normal CPP acquisition, our second experiment investigated whether conditioning to location can be accom-

TABLE 1.

*Lesion Coordinates**

Dorsal	Ventral
HPC lesion	
1. AP −3.1; L ±1.0; V −3.6 0.25 μl	6. AP −5.0; L ±5.2; V −5.0 0.25 μl
2. AP −3.1; L ±2.0; V −3.6 0.25 μl	7. AP −5.0; L ±5.2; V −7.3 0.25 μl
3. AP −4.1; L ±2.0; V −4.0 0.25 μl	8. AP −5.8; L ±4.4; V −4.4 0.25 μl
4. AP −4.1; L ±3.5; V −4.0 0.25 μl	9. AP −5.8; L ±5.1; V −6.2 0.40 μl
5. AP −5.0; L ±3.0; V −4.1 0.25 μl	10. AP −5.8; L ±5.1; V −7.5 0.40 μl
AMG lesion	
1. AP −2.3; L ±4.8; V −9.4 0.60 μl	2. AP −3.3; L ±4.6; V −9.4 0.60 μl
Fx lesion	
1. AP −1.5; L ±0.8; V −4.6 2 mA/20 s	2. AP −1.5; L ±2.2; V −4.6 2 mA/20 s

*AP, antero-posterior from bregma; L, lateral from bregma; V, ventral from bregma. All coordinates are given in mm.

plished based on the function of a fragmentary HPC network. We thus tested animals with dorsal or ventral HPC damage on the same CPP task. The data indicated that dorsal HPC lesions are followed by impaired acquisition. Ventral HPC lesions, on the other hand, resulted in enhanced learning.

EXPERIMENT 1: EFFECTS OF FX VS. HPC LESIONS ON CPP

In this experiment, sham animals and animals with AMG and HPC lesions underwent training in the CPP task (four training trials; for details, see below). To demonstrate the lack of effect on spatial learning following AMG lesions, we also tested these animals in a classic Morris water task. Sham animals and animals with Fx lesions were run in a similar CPP task which involved only three training trials.

Subjects

CPP: four training trials

(CPP-4) Thirty-six male Long Evans rats (Charles River Colonies) were involved in this experiment. All animals were individually housed in clear plastic cages with water ad libitum and were maintained on a 10 AM–10 PM dark/light cycle. Testing occurred during the dark period. All animals were food-restricted during behavioral testing. The subjects were randomly assigned to one of three groups: sham (n = 12), HPC lesion (n = 12), and AMG lesions (n = 12). Due to incomplete damage, data from two animals from each lesion group were discarded from the final analysis.

CPP: three training trials

(CPP-3) Twenty-one male Long Evans rats (Charles River Colonies) were involved in this experiment. Housing, testing, and feeding conditions were identical to those described above. The subjects were randomly assigned to one of two groups: sham (n = 11) and Fx lesions (n = 10). Following histological assessment, data from seven animals with Fx lesions were included in the final analysis.

Surgical Procedures

CPP-4 training trials

All animals weighed 275–300 g at time of surgery. The rats were anesthetized using sodium pentobarbital (65 mg/kg body weight) administered i.p. Atropine (5 mg/kg body weight) was also administered in order to avoid fluid accumulation in the respiratory tract. Stereotaxic lesions were produced by using a 5 mg/ml solution of NMDA in phosphate buffer (pH 7.4) injected through a 30-gauge cannula attached to a Harvard minipump. HPC lesion rats received 20 injections (10 per side), while AMG lesion rats received 4 injections (2 each side). The coordinates of each injection and the volumes injected are presented in Table 1. In order to prevent seizure development, valium was administered i.p.(10 mg/kg) and animals were monitored until completely awake and active in their home cages. Rats in the sham group were anesthetized and the scalp cut on the midline, but no penetration of the brain tissue was performed.

CPP-3 training trials

All rats weighed 275–300 g at time of the surgery. The anesthesia procedure was similar to the one described above. The Fx was

damaged by passing 2.0 mA of direct current for 20 ms through the tip of a stainless steel electrode insulated except for 1.0 mm at the tip. Each rat received four lesions, two for each side. coordinates are shown in Table 1. The electrode was left in place an additional 60 s in order to minimize damage during withdrawal from tissue.

At the end of the behavioral procedures, each animal was deeply anesthetized with sodium pentobarbital and perfused intracardially with 0.9% saline solution, followed by 10% formalin solution. The brains were frozen and sectioned (40 μm/section). The tissue was stained with acid thionin stain.

Apparatus

An eight-arm radial maze elevated 60 cm from the ground and painted white was used for the CPP task. The maze had an octagonal central platform (18 cm side). Each arm was 11 cm wide and 55 cm long. There was no separation between the central platform and the arms, but six wooden blocks were used to obstruct as many arms during preexposure and testing sessions (Fig. 1). Two similar blocks with panels attached to the end facing the animal were used in order to successfully confine the rat in the arm during training trials (see Procedure, below). The maze was situated in the middle of a windowless, well-lit room containing various visual cues: a chair, a filing cabinet, a garbage box, a pail, and various posters.

For the Morris water task, a white plastic pool 180 cm in diameter was employed. The pool was filled with water mixed with nontoxic paint covering (2–3 cm) a platform made of transparent plastic with a surface of 12 × 12 cm. The room contained various visual cues: posters, computer and computer rack, door, animal cages rack, and the experimenter.

Procedure

CPP paradigm

The CPP procedure (Fig. 1) was identical to the one described by McDonald and White (1993, 1995a). Animals were maintained at 85% of their ad libitum body weight. Each animal was assigned one of four pairs of opposite arms (i.e., 1-5, 2-6, 3-7, or 4-8). Of the pair, where food was presented the arm was designated "paired"; the other, where food was never found, was designated "unpaired."

During the first day (preexposure), the rat was placed on the central platform and allowed to freely explore the assigned pair of arms for 10 min. Access to the rest of the apparatus was blocked using the six wooden blocks. Next, four training sessions for AMG and HPC groups, and three training sessions for the Fx group, took place. Each training session required 2 days. During day 1, the rat was confined for 30 min at the end of the paired arm, where 50 Fruit Loops (Kellogg's, Battle Creek, MI) were placed. During the other day the rat was confined for the same interval but with no food at the end of the unpaired arm. Thus, the animal was exposed to distinct sets of visual cues in the paired vs. unpaired arms. Paired/unpaired identity of the arms and order of reinforcement (day 1 vs. day 2) were counterbalanced within each group.

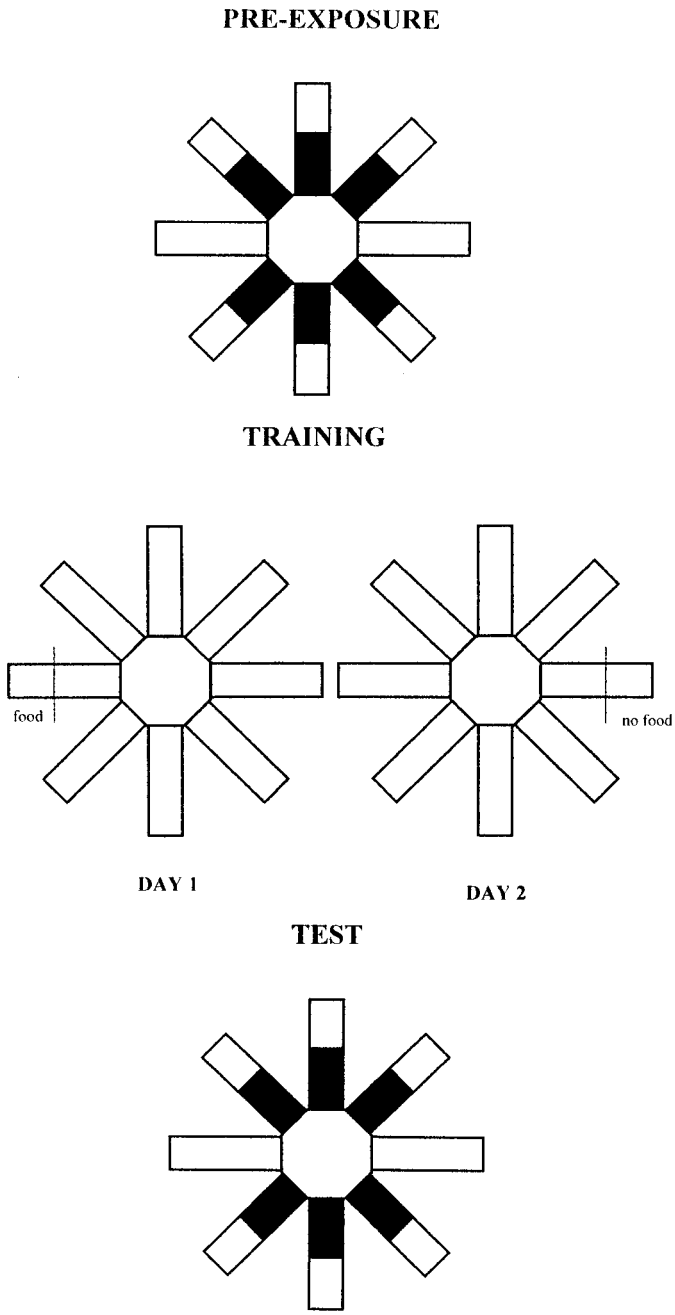

FIGURE 1. CPP paradigm. Animals are preexposed to the apparatus, after which a specific location is rewarded during a series of training trials. During the test session, normal animals spend more time at the location previously paired with food. For details, see text.

For testing, the arms were detached from the central platform, their position was shifted one slot, and then they were reattached. Thus information provided by local cues became irrelevant. No food was presented on the maze on this day, and each rat was allowed to move freely between the designated paired/unpaired locations as during preexposure, but for an interval of 20 min. Records were kept of times of entry and exit for each arm. A rat was considered in or out of the arm if both of his front feet had crossed the threshold of the arm.

Water task

Only animals with whole HPC and AMG lesions and the corresponding sham group were run in this task.

Testing lasted 6 days. All recordings were performed using a tracking system (VP118, HVS Image). Latency to find the platform, path length, time spent in the platform quadrant, and heading angle were computed for each trial by dedicated software. During the first 5 days, each animal was placed in water facing the pool wall and allowed to swim until either finding the platform at the end of a 60 s interval, whichever came first. At the end of the trial the rat was allowed to stand on the platform for 10 s. Each rat performed eight running trials per day. The sequence of starting positions was the same for all animals and varied from day to day. At the end of the training session, the results of the eight trials were averaged for each animal and considered one data point. During the last day, the platform was removed and the rats swam freely for 30 s.

Results and Discussion

Figure 2a shows the extent of AMG and HPC lesions. There was no damage to the Fx in either lesion group. Cortical damage, although present at the cannula insertion points, was minimal. HPC lesions encompassed both dorsal and ventral components of the structure. Damage to the S was minimal and restricted only to its most anterior part, immediately adjacent to CA1. Partial sparing of CA3's most anterior tip, as well as minimal parts of dorsal HPC, occurred in two cases. None of the AMG lesions extended to the ventral HPC tip or EC.

Figure 2b shows the extent of Fx lesions. In three cases the damage extended to the posterior parts of the septum; one such case has been selected as the largest lesion. In two other rats the damage extended to the most anterior tip of dorsal HPC, but it disappeared at the level of 2.12 mm posterior to bregma (coordinates according to Paxinos and Watson, 1986). In all cases, fibers constituting the Fx were thoroughly disrupted.

Figure 3a shows the results of AMG, HPC, and sham groups in the CPP task. A two-way lesion × location ANOVA showed no main effects of either lesion or arm, but a significant lesion × arm interaction ($F_{2,29} = 3.42$, $P < 0.05$). Planned comparisons between time spent in paired vs. unpaired location for each group indicated that neither AMG- nor HPC-lesioned rats preferred one arm vs. the other. In contrast, the control group spent more time in the paired arm ($F_{1,11} = 8.78$, $P < 0.013$). Figure 3b shows the results of Fx and sham groups. To attain homogeneity of variance, a logarithmic transformation was applied to this data set, after which a similar statistical analysis similar to the one described above was performed. The two-way ANOVA indicated a main effect of arm ($F_{1,16} = 5.32$, $P < 0.05$) but no significant main effect of lesion or lesion × arm interaction. This lack of effect was not surprising, because both sham and Fx lesion groups spent on average more time in the paired arm. However, comparisons within groups demonstrated that only animals with Fx lesions significantly preferred the paired location ($F_{1,6} = 31.17$, $P < 0.01$).

Figure 4 shows latency, path length, platform quadrant preference, and deviation of heading angle during the first 5 days of water maze testing for AMG, HPC, and corresponding sham groups. Two-way ANOVA analyses for latency, path, and quadrant preference indicated main effects of day in all cases ($F_{4,116} = 116.65$, $P < 0.001$; $F_{4,116} = 112.19$, $P < 0.001$; $F_{4,116} = 30.83$, $P < 0.001$) and main effects of lesion group ($F_{2,29} = 10.81$, $P < 0.001$; $F_{2,29} = 12.90$, $P < 0.001$; $F_{2,29} = 5.85$, $P < 0.001$). Analysis on the heading angle data restricted to the last 2 days indicated a close-to-significant effect of lesion ($F_{2,29} = 3.31$, $P = 0.0507$). Multiple comparisons using the Student-Newman-Keuls test indicated that the HPC group was different from the other two on all parameters, while there were no differences between AMG and sham groups. During the sixth day, heading angle was measured for each group (data not shown). One-way ANOVA showed a main effect of lesion ($F_{2,29} = 3.99$, $P < 0.05$) which was due to poorer performance of the HPC group relative to the other two groups.

The main conclusion of this experiment is that complete HPC lesions (DG and fields CA3–CA1) impair, while Fx lesions enhance, performance in this version of the CPP task. Our results replicate the AMG and Fx lesion effects reported by White and McDonald (1993) and McDonald and White (1995a) using identical behavioral procedures. Taken together, these data demonstrate a clear dissociation between Fx and HPC lesion effects, indicating that there are important differences between the functional consequences of damaging these brain structures.

Second, the results of this experiment showed that CPP acquisition requires not only AMG but also HPC function. Because both AMG and HPC lesions interfered with normal behavior, it follows that in normal animals, performance in this task requires a synergistic interaction of the memory systems based on these anatomical structures. It is generally accepted that AMG is involved in conditioning paradigms, but does not influence spatial learning (e.g., Sutherland and McDonald, 1990; McDonald and White, 1993). In agreement with this idea, it is likely that in CPP, AMG participates in the formation of cue-reward associations. The spatial component of the task is most likely solved by HPC function.

Because dorsal HPC areas have been found to be more important for spatial navigation, a question that followed directly from these results was whether normal performance in CPP requires the integrity or not of the whole HPC network. This issue was investigated in experiment 2.

EXPERIMENT 2: EFFECTS OF DORSAL VS. VENTRAL HPC LESIONS ON CPP

Recently, a series of experiments (Moser et al., 1993, 1995, 1998; Hock and Bunsey, 1998; Ferbinteanu and McDonald, 2000) demonstrated that there are functional differences between dorsal and ventral HPC areas. Data show that although processing of spatial cues may take place along the whole septo-temporal axis

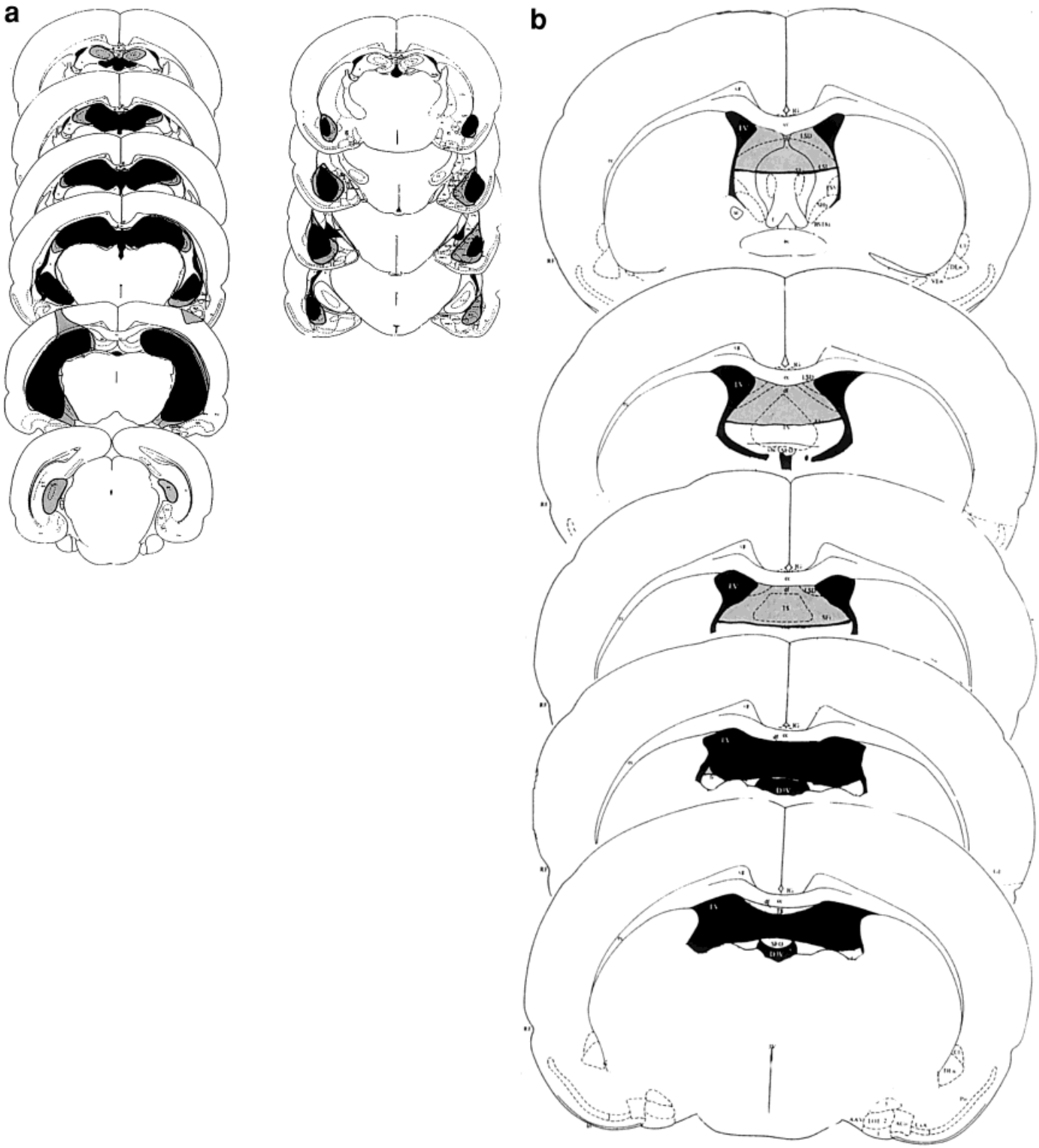

FIGURE 2. Reconstruction of histological damage for animals involved in experiment 1. Largest lesions are showed in gray, smallest lesions in black. a: HPC (left) and AMG (right) lesions. The Fx was not affected in either lesion group. b: Fx lesions.

of the structure, its septal pole acquires this type of information more efficiently (Ferbinteanu and McDonald, 2000). The results of experiment 1 demonstrated that performance in CPP requires HPC processing. It is therefore possible that dorsal HPC lesions could be more disruptive than their ventral counterparts for CPP because they would interfere more with spatial learning. However,

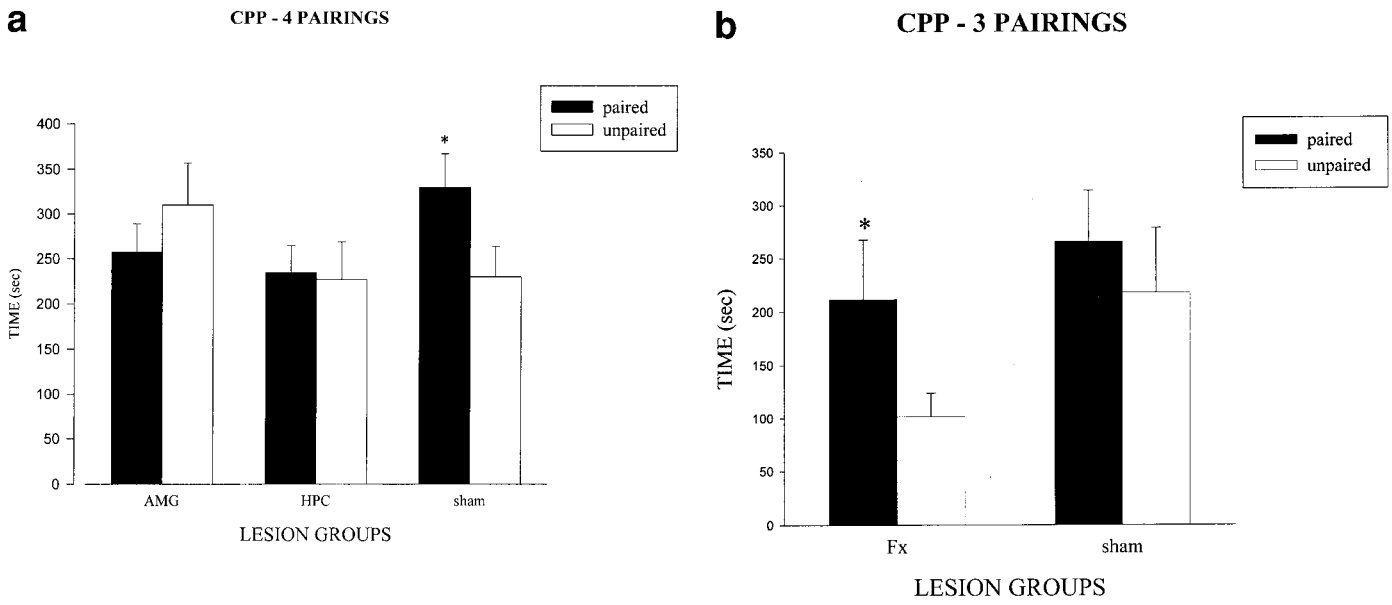

FIGURE 3. Results of experiment 1. a: Time spent in paired/unpaired arms by AMG, HPC, and sham groups following four training sessions. The sham group was the only one showing a significant preference for the paired arm. b: Time spent in paired/unpaired arms by Fx and sham groups following three training sessions. The Fx but not the sham group showed a significant preference for the paired location.

Fx lesions also produce impairment of spatial learning and are nonetheless followed by enhanced learning in this paradigm. Thus, a clear prediction of the effect of dorsal HPC lesions was difficult to formulate. The same was true for the effect of ventral HPC lesions. Presently there are no published data indicating a functional "specialization" for this area.

Subjects

CPP-3 pairings

Sixty male Long Evans rats (Charles River Colonies) were used for this experiment. Housing, feeding, and testing conditions were identical to those described in experiment 1. Animals were randomly assigned to one of three groups: dorsal HPC lesion, ventral HPC lesion, and sham. After histological evaluation, data from 11 rats with dorsal lesions, 14 rats with ventral lesions, and 16 shams were included in the final analysis.

CPP-4 pairings

Twenty-four male Long Evans rats (Charles River Colonies) were used for this experiment. Housing, feeding and testing conditions were as described above. Animals were randomly assigned to either a dorsal HPC lesion group or a sham group. After histological assessment of lesions, 8 rats with dorsal HPC lesions and 10 sham animals were considered for final analysis.

Surgical Procedures

All animals weighed 275–350 g at time of the surgery. Surgical procedures were identical to those for the neurotoxic lesions described in experiment 1. Dorsal HPC lesions were produced by performing injections 1–5 as described in Table 1, while ventral HPC lesions were produced by performing injections 6–10. We thus attempted to create lesions that would be in the middle range according to Moser et al. (1995).

A computerized lesion assessment was performed for dorsal and ventral HPC groups. The area of damaged tissue was marked on histological plates and measured in each case (Scion software). Evaluation of lesion size was performed by summing up volumes of successive tronconic "slices." The volume of each "slice" was calculated by multiplying the average of the two lesion areas delimiting the "slice" by the distance between them. Total HPC volume was calculated using the same method. The volume of each lesion was expressed as a percentage of total volume of the structure.

Apparatus

The same eight-arm radial maze was used as described in experiment 1.

Procedure

The CPP paradigm was the same as described for experiment 1. Animals with either dorsal or ventral HPC lesions, as well as shams, underwent three training trials. Animals with only dorsal HPC lesions and shams underwent four training trials.

Results and Discussion

Figure 5a shows a reconstruction of HPC damage in the dorsal and ventral lesion groups that underwent three training trials. Lesion size assessment indicated an average of 37.94 ± 3.46 % in the dorsal HPC group, and 42.89 +± 5.63 % in the ventral HPC

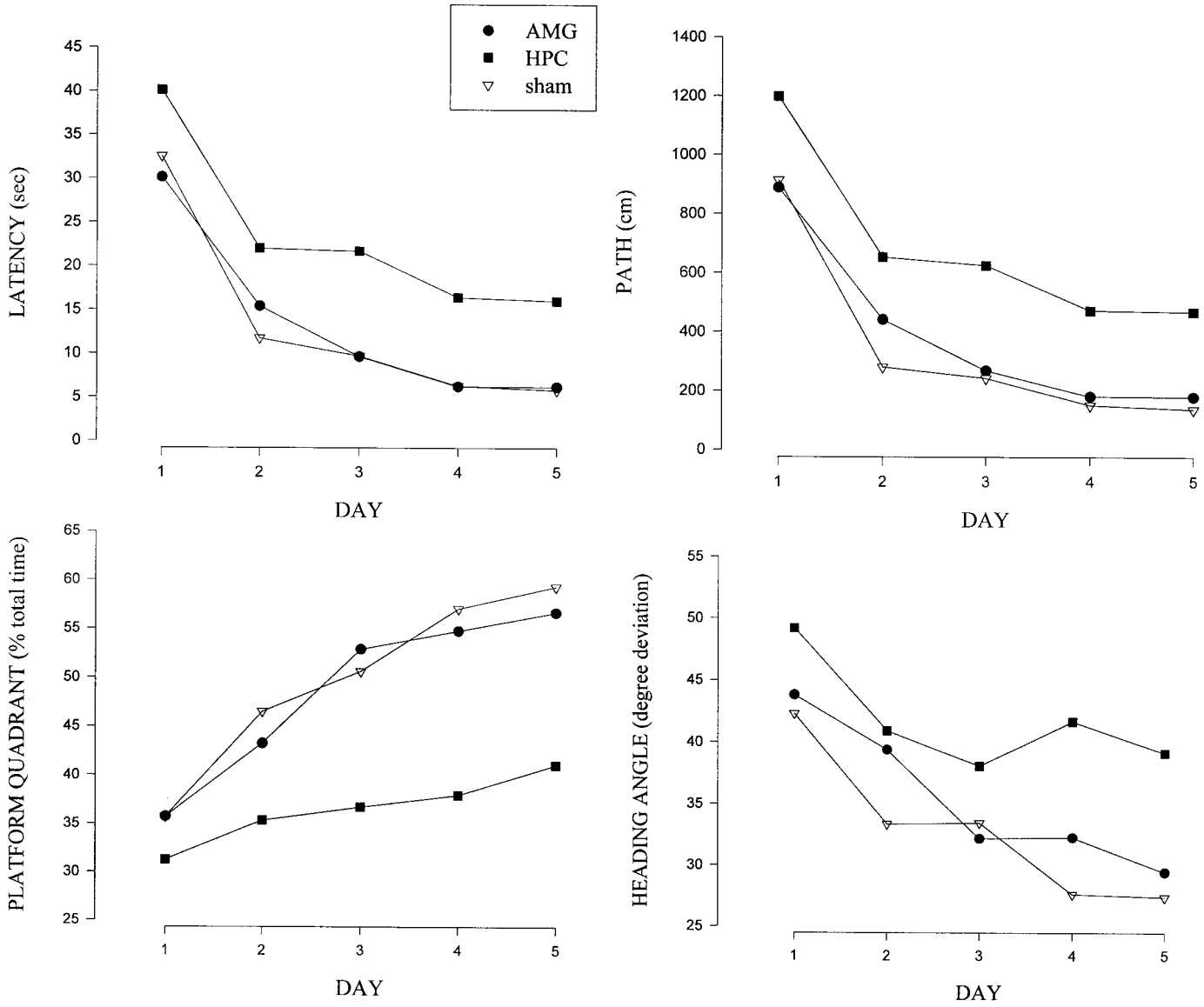

FIGURE 4. Results of Morris water task. Animals with HPC, but not AMG lesions showed impaired learning.

group. In the dorsal lesion group, 10 animals presented no cortical damage, and one of them showed unilateral damage at the site of cannula entrance. Five animals had damage of the inferior blade of the DG that extended to the splenial region, as shown in Figure 5a. One rat also had unilateral partial damage of the CA3 field in the splenial HPC. In the ventral HPC lesion group, sparing of the most anterior tip of the structure was found similar to that reported by Moser et al. (1995). The S was intact in all cases. Partial sparing of the most posterior CA1 was found in 8 animals unilaterally and in 3 animals bilaterally. Partial sparing of the most posterior DG was found in 4 animals unilaterally and in 2 animals bilaterally. Three rats had unilateral cortical damage at the cannula entrance point. Two rats had bilateral cortical damage, the larger of which is shown in Figure 5a as the largest ventral lesion.

Figure 5b shows reconstruction of damage to dorsal HPC in the lesion group that underwent four training trials. Lesion size assessment indicated an average of 36.25 $\pm$ 3.84% of total HPC volume. CA3 sparing was limited to posterior sections. The rat with the smallest damage had a 29.01% lesion volume, due mostly to unilateral sparing of fields CA3 and CA1. Unilateral cortical damage was present in two rats at the cannula entrance point. Bilateral damage was found in two animals; of these, the one with the larger damaged cortical area was also the one with the larger dorsal HPC lesion.

Figure 6a shows CPP learning after three training trials. The dependent variable was time spent in a particular arm. The two independent variables were lesion type and location (paired vs. unpaired). A logarithmic transformation was performed on the data to obtain homogeneity of variance. A two-way lesion $\times$ location ANOVA showed no main effect of either lesion or location, but a significant lesion $\times$ location interaction effect ($F_{2,38} = 4.76$, $P < 0.05$). Planned comparisons between time spent in the paired

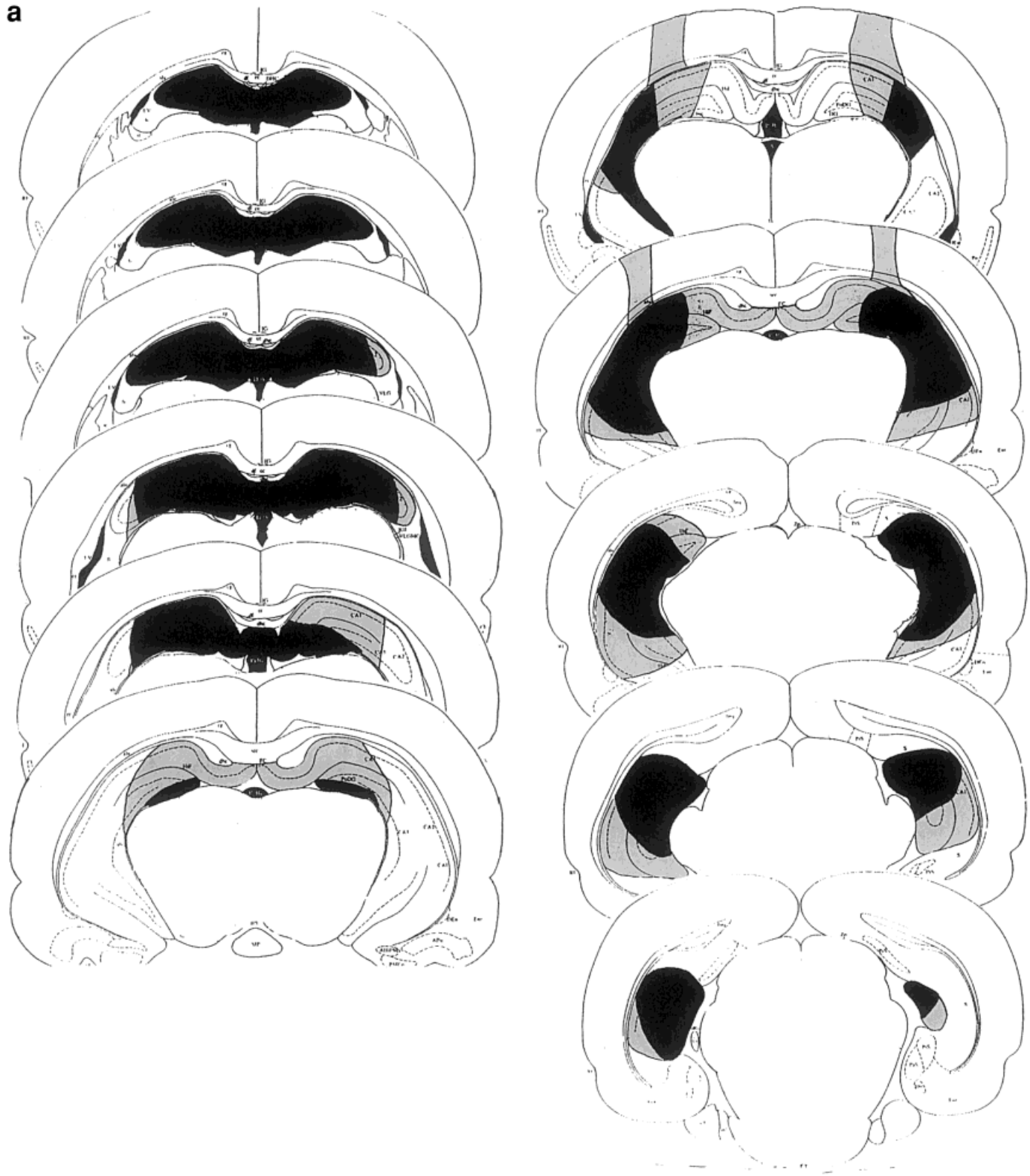

FIGURE 5. Reconstruction of histological damage for animals involved in experiment 2. Largest lesions are shown in gray, and smallest lesions in black. a: Left, dorsal HPC lesions; right, ventral HPC lesions. Animals in these groups underwent three training sessions in CPP. b: Dorsal HPC lesions. Animals in this group underwent four training sessions in CPP.

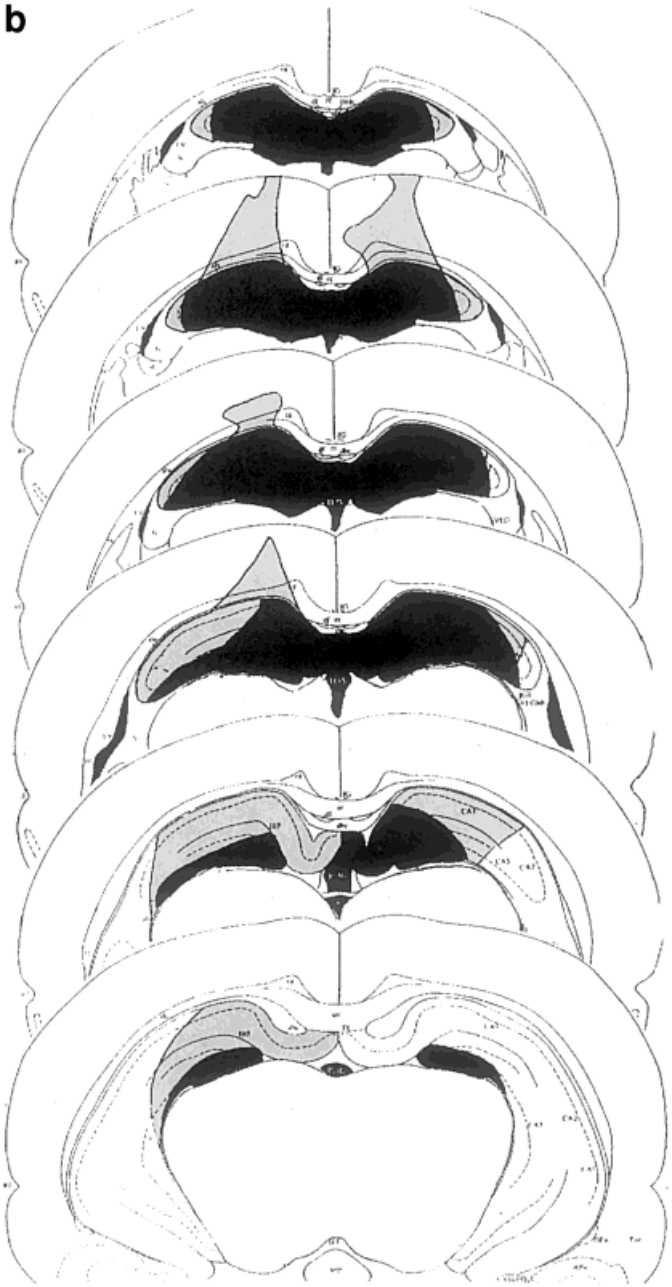

FIGURE 5. (Continued)

vs. unpaired arm showed that the ventral HPC lesion group preferred the paired arm ($F_{1,13} = 6.66$, $P < 0.05$). In contrast, the dorsal HPC lesion and sham groups showed no significant preference for either location. Taken together, these data indicated enhanced learning in CPP following ventral, but not dorsal HPC lesions.

Figure 6b shows CPP learning following four training trials. A similar two-way lesion × location ANOVA revealed a close to significance lesion effect ($F_{1,16} = 4.38$, $P = 0.0525$) and no significant location effect or lesion × location interaction. To increase power, the error term used for planned comparisons was pooled across the whole data set. Normally, such a pooled error term is not recommended for a repeated measures variable because of concerns regarding the sphericity assumption (Howell, p. 468). However, because in this case the location variable has only two levels, the sphericity assumption does not apply (SAS/STAT User's Guide, 1989). The sham group spent significantly more time in the paired arm ($F_{1,32} = 5.338$, $P < 0.05$), while the dorsal HPC lesion group did not show location preference. This indicated that dorsal HPC lesions are associated with impairment in acquisition of this version of CPP.

Results obtained in this experiment demonstrate that given an intact AMG, dorsal HPC is necessary and sufficient for CPP learning. Ventral HPC function seemed to have a suppressive effect on this process because its disruption resulted in enhanced conditioning. Experiment 1 demonstrated that normal performance in CPP requires acquisition of spatial information. This process is markedly affected by dorsal HPC lesions and only mildly impaired by ventral HPC damage. Considered separately, the results of dorsal HPC lesions in CPP can be explained as due to impairment in spatial learning. This interpretation, however, seems to be contradicted by the results of Fx lesions which, although known to produce severe spatial learning deficits, resulted nonetheless in enhanced CPP learning. Additionally, no explanation can be offered for the effect of ventral HPC lesions. Thus a different interpretation is necessary.

DISCUSSION

Which Structure is Doing What in CPP? A Hypothesis

The results raise two major problems. The first involves explaining how impairment of spatial navigation follows both dorsal HPC and Fx lesions, although performance in CPP, presumably requiring spatial learning, is impaired in the former but enhanced in the latter case. The second issue regards the enhancement effect found with Fx and ventral HPC lesions. Due to paucity of experimental data, formulating a conclusive statement regarding either of these topics is not possible. Some anatomical and physiological results suggest a hypothesis, but this should be taken as tentative and will have to be cross-validated by future research.

Figure 7 shows a diagram based on anatomical data (Amaral and Witter, 1995; Cassel et al., 1997; Van Groen and Wyss, 1990; Pennartz et al., 1994; Gloor, 1997; McDonald, 1991; McGeorge and Faull, 1989). Projections from the medial septum, nucleus of the diagonal band, and brain stem reach the dorsal HPC through the Fx. The Fx also contains fibers from dorsal HPC to lateral septum and lateral ACC, and from ventral HPC to lateral septum (not shown) and medial ACC. Input from the nucleus of the diagonal band and brain stem to the ventral HPC is conveyed through the ventral angular bundle. Bidirectional connections of AMG with ventral HPC and the medial strip of EC are also located outside of the Fx. Basolateral AMG projections are restricted to the medial ACC (McDonald, 1991). Also of importance are the topographically organized cortical-HPC projections. Dorsal HPC is

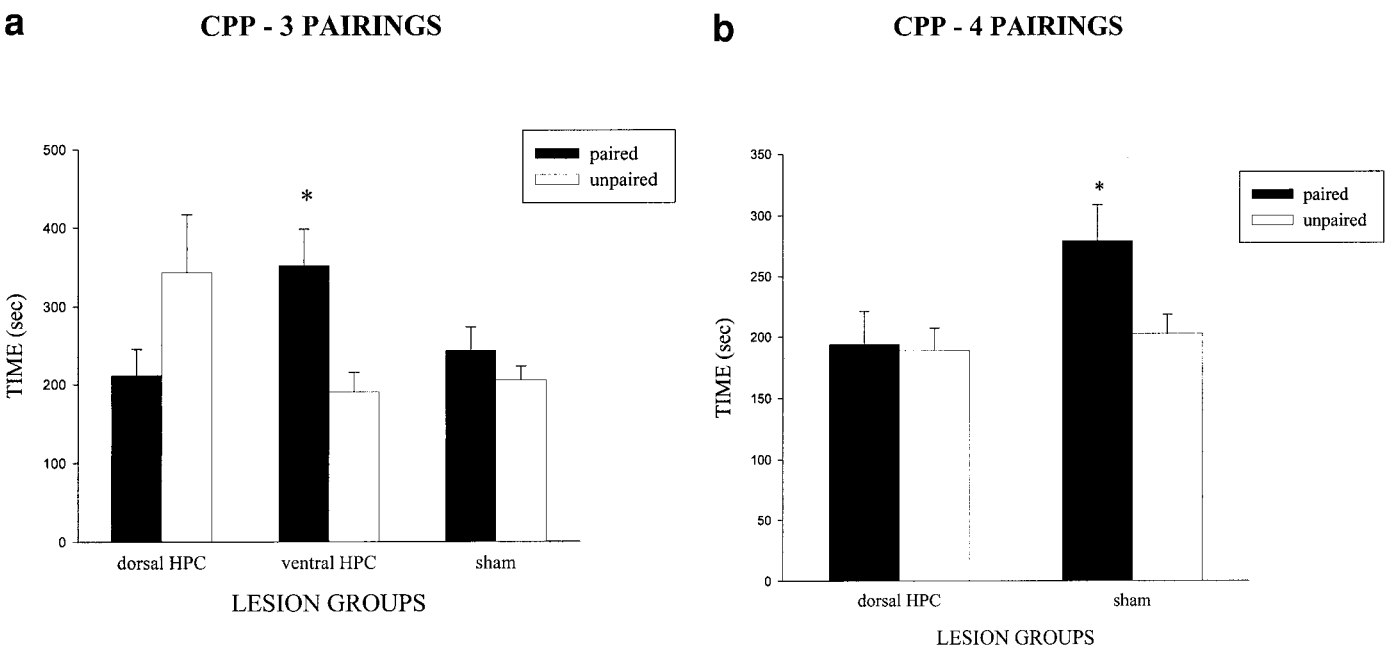

FIGURE 6. Results of experiment 2. a: Time spent in paired/unpaired arms by dorsal/ventral HPC lesion groups and shams after three pairings. The ventral HPC group, but not the other two, showed a significant preference for the paired location. b: Results of dorsal HPC and corresponding sham groups. Only the animals in the sham group showed significant preference for the paired arm.

connected to the lateral longitudinal EC strip and ventral HPC to the medial longitudinal EC strip.

The diagram in Figure 7 also shows the particular anatomical projections affected by dorsal HPC lesions (top), ventral HPC lesions (middle), and Fx transections (bottom). Dorsal HPC damage compromises communication with the lateral EC strip, input from the medial septum, the nucleus of the diagonal band and brain stem, and output to lateral ACC. Lesions of ventral HPC compromise functionality of circuits related to the medial EC strip and AMG and abolish output to medial ACC. Fx transections destroy subcortical input and output to dorsal HPC, while leaving input to ventral HPC and retrohippocampal connections intact. Notably, the output of ventral HPC to medial ACC is also affected in this case.

The results presently reported can be explained if different functions are attributed to the circuits described above. Comparison between effects of dorsal HPC and Fx lesions indicates that in both cases, the subcortical input and output of dorsal HPC is compromised. Thus, the septum-dorsal HPC-lateral ACC circuit may be essential for spatial navigation as required in water maze tasks. Lesions of this network produce spatial learning deficits, regardless of whether or not other circuits process spatial information.

Second, comparison between effects of dorsal and ventral HPC lesions indicates that input to the medial ACC is affected only by the second type of damage. That AMG and ventral HPC outputs to ACC are restricted to medial ACC may be of particular significance. Mulder et al. (1998) showed an interesting effect in medial ACC neurons that received dual AMG and Fx input. Stimulation of Fx fibers prior to AMG activation resulted in inhibition of the AMG effect on ACC neurons. In contrast, Fx-ACC transmission was facilitated if the AMG was stimulated first. This finding suggests that the AMG and ventral HPC compete for behavioral output at the level of the medial ACC. Activating projections from ventral HPC to medial ACC could inhibit AMG control on behavior. Consequently, ventral HPC lesions would translate at the behavioral level as enhanced CPP learning. In this case, the spatial component of CPP can easily be solved within dorsal HPC-lateral septum network. In contrast, dorsal HPC lesions render spatial learning slow and maintain inhibition on the AMG. This results in impaired performance on the CPP test.

Comparison of Fx and ventral HPC lesion effects supports this explanation. In both cases, AMG inhibition is abolished, creating the premise for enhanced CPP learning. In the case of Fx lesions, the spatial component of CPP may be solved by ventral HPC network activity, which has been shown to support some spatial learning (De Hoz and Morris, 1999; Ferbinteanu and McDonald, 2000). It is likely that spatial learning in this version of CPP is not as demanding on HPC function as spatial navigation in the water task. Previous data (McDonald and White, 1995b) demonstrated that an opposite-arm version of CPP, which lowers cue ambiguity, creates less demand on HPC processing. This may conceivably be within the functional abilities of ventral HPC network.

The view of medial ACC as the site of AMG-ventral HPC interaction should be qualified. Mulder et al. (1998) found that the medial ACC also contained cells that responded preferentially to either AMG or Fx stimulation, but not both. Thus, single and dual input cells were interspersed in the medial shell and medial core. In contrast, dorsal shell and ventromedial caudate contained only Fx-driven units. Ventrolateral core and shell contained only AMG-driven units. It seems, therefore, that the functional organization of ACC is complex and may or may not overlap with conventional anatomical divisions. Additionally, there is some empirical evi-

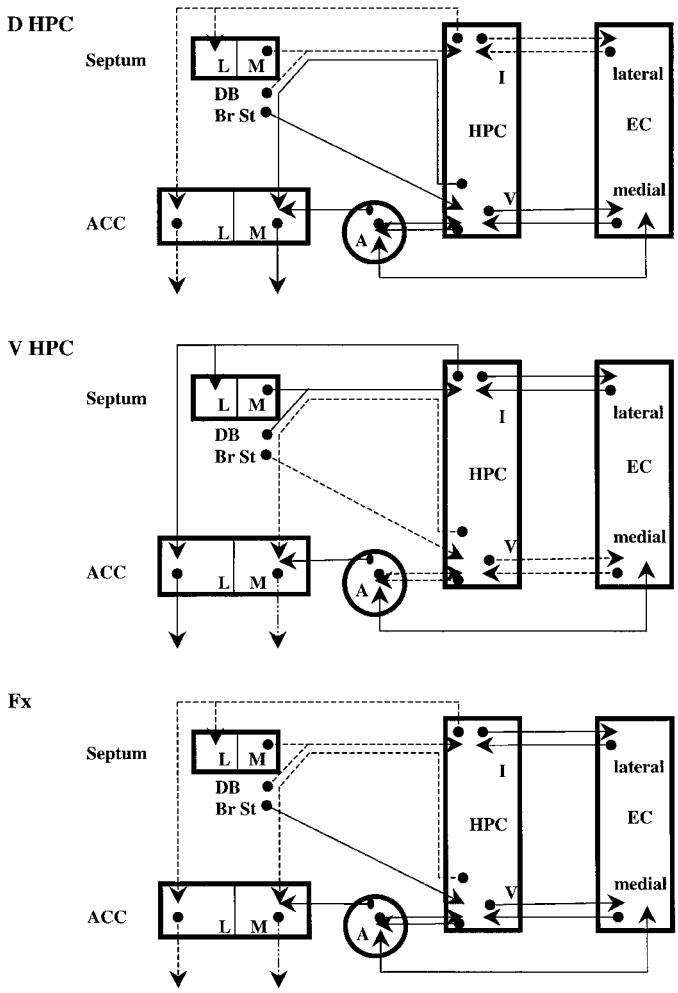

FIGURE 7. Diagram indicating connections between HPC, AMG, and other neural structures likely to be related to CPP performance. Connections whose functionality is compromised following dorsal HPC lesions (top), ventral HPC lesions (middle), and Fx sections (bottom) are marked by dashed lines. A, amygdala; ACC, nucleus accumbens; Br St, brain stem; DB, nucleus of diagonal band; HPC, hippocampus; EC, entorhinal cortex; L, lateral; M, medial; D, dorsal; V, ventral. EC division is not the classic histological one, but refers to EC organization in longitudinal strips as described by Amaral and Witter (1995).

dence (Parkinson et al., 1999) that the shell/core division in ACC may have behavioral relevance as well. Lesions of the core, but not the shell, impaired Pavlovian conditioning. Lesions of the shell, but not the core, abolished the stimulant effects of D-amphetamine.

The existence of ACC circuits with distinct behavioral roles is compatible with available empirical data. Sutherland and Rodriguez (1989) found deficits in spatial navigation associated with lesions of the medial ACC. At first sight this contradicts the view that the lateral ACC is essential for spatial navigation. However, a number of factors should be considered in qualifying this effect. First, the lesion reconstruction (Fig. 1D) is not very detailed, and thus it is not clear how much of the lateral ACC was actually affected. Second, direct comparison with the anatomical data presented by Mulder et al. (1998) (see Fig. 2) is difficult because of the differences in localization of sections. Third, these lesions were produced electrolytically rather than neurotoxically. Thus this evidence does not conclusively falsify the present hypothesis. Somewhat supportive are the results reported by Annett et al. (1989). These experimenters obtained impairment, but not abolishment of spatial learning following ACC lesions that spared the medial and lateral extremes of the structure. The one study that found impaired CPP retention following complete ACC lesions (Everitt et al., 1991) is unfortunately irrelevant for the present hypothesis because both medial and lateral ACC were damaged.

Fx vs. HPC Lesion Effects in the Literature

It is well-known that Fx lesions disrupt spatial learning (O'Keefe et al., 1975; Olton et al., 1978; Sutherland and Rodriguez, 1989), a behavior dependent on the HPC-centered memory system (O'Keefe and Nadel, 1978). The possibility of differences in behavioral modifications following Fx vs. HPC damage was briefly discussed by Olton et al. (1979), but extensive and systematic comparisons between the effects of the two procedures are missing from the literature. Rawlins et al. (1993) reported transient differences between rats with Fx lesions and rats with HPC lesions on a nonspatial matching-to-sample task, but it is worth noting that these investigators used aspiration as a lesion method. Additionally extended areas of ventral HPC were spared. It is true that aspiration destroys fibers of passage as well as cell bodies, and thus it is likely that the ventral HPC was not fully functional in this case. Nevertheless, the effects of aspiration vs. neurotoxic lesions are not well documented and introduce additional difficulties in interpreting these data.

Whishaw and Jarrard (1995) found larger spatial learning impairment and disruption in circadian activity with Fx transections than with HPC lesions induced by ibotenic acid. The authors attributed differences between groups to damage of projection fibers possibly originating in the subicular complex, EC, or other subcortical structures and coursing through the Fx. It remains a puzzle why Fx lesions would cause more marked spatial learning deficits, because in this case HPC cells are not destroyed, HPC-EC connections are not disrupted, and subcortical input to the ventral HPC network is spared. Data from a different experiment (Sziklas et al., 1998) showed that acquisition of associations between visual stimuli and their location was impaired in animals with dorsal HPC damage, while animals with Fx lesions eventually learned the task, presumably by using the ventral HPC network. Not surprisingly, both lesion groups were impaired on a spatial working memory task. Cassel et al. (1998) compared the effects of Fx lesions and ibotenic acid HPC lesions on locomotor activity and spatial learning. They found that HPC lesions resulted in higher hyperactivity and greater disruption in spatial radial maze paradigms where the rats had to remember the position of one arm across a number of days (reference memory task), or to retrieve food placed in each maze arm (working memory task). Differences may be explained by activity in the ventral HPC circuit in the Fx lesion group. Most evidence thus seems to tip the balance in favor of greater spatial

learning deficits following whole HPC lesions, but more empirical data are needed before formulating definitive conclusions.

McDonald et al. (1997) used negative patterning, conditional contextual, and biconditional discriminations as three different instances of nonspatial configural-realtional learning to compare the effects of Fx and HPC lesions. Fx lesions were found to have no effect in all three cases. HPC lesions impaired acquisition of the first task, had no effect on the second, and retarded learning on the third. According to the hypothesis formulated above, learning in the Fx-lesioned animals would have to take place based on ventral HPC activity. This is entirely possible, especially as this is the HPC area best connected to the AMG. Effects of whole HPC lesions seem to indicate that the only task requiring integrity of the HPC network is negative patterning. Conditional contextual discrimination and biconditional discrimination may be accomplished based on a combination of EC and AMG activity, especially as connections between these areas are left intact. Additionally, damaging the HPC implies that AMG control of behavior is facilitated.

To summarize, evidence provided by comparisons of Fx and HPC lesion effects seems to be compatible with the hypothesis formulated above, according to which the dorsal HPC network is particularly important for spatial navigation, and the ventral HPC network is involved in competition with AMG for behavioral control. However, the paucity of empirical data renders any statement tentative. It is left to future research to validate or invalidate our hypothesis.

CPP: what is new?

The CPP task we used involves passive conditioning: animals are confined at the end of the arm, and no free movement is allowed during training. This paradigm is identical to the one previously used by White and McDonald (1993), who showed that after four training trials, control animals spent more time in the arm previously paired with food. AMG lesions, alone or in combination with Fx lesions, interfered with normal learning. Fx lesions resulted in preference for the paired arm after only one training trial. In a different experiment (McDonald and White, 1995a), control animals were presented with two training trials, but while one group underwent preexposure as described in this report, a second group was not preexposed to the apparatus at all, and a third was preexposed in a different room. As previously demonstrated, animals preexposed to the same room did not develop a significant preference at the end of training. However, the other two groups did, suggesting that the inhibitory effect on AMG-based conditioning to location is due to information acquisition during preexposure. Fx lesions performed before preexposure resulted in enhanced learning. Fx lesions performed after preexposure or after two training trials were not associated with enhancement. Thus, the authors hypothesized that a functional Fx is required for acquisition but not expression of the inhibitory effect on AMG function.

A third study (McDonald and White, 1995b) investigated the effects of varying ambiguity of spatial cues and of conditioning type (active vs. passive). Ambiguity of spatial cues was increased by training the rats in adjacent (45° angle) rather than separated (135° angle) arms. Active cue presentation was accomplished by allowing free choice between designated arms (one reinforced and one not) during training. With adjacent arms/passive presentation, control animals did not acquire CPP after 2, 4, or 8 training trials, unlike Fx lesioned animals, who did so after 8 pairings. With adjacent arms/active cue presentation, control, AMG-lesioned and DS-lesioned, but not Fx-lesioned animals learned the task. With separate arms/active cue presentation, neither AMG nor Fx or DS lesions were followed by a learning impairment. Finally, with separate arms/active cue presentation, combined DS + Fx lesions resulted in impairment, AMG + DS lesions resulted in enhancement, and AMG + Fx lesions did not have any effect. The authors concluded that in the passive condition, AMG function is necessary for normal learning, regardless of ambiguity level. In active CPP, high cue ambiguity requires HPC function, while low cue ambiguity can be solved by either HPC or DS.

White and Ouellet (1997) found that, unlike the passive presentation condition, normal animals discriminated among highly ambiguous cues if passively switched from one arm to the other during training. This is presumably because in the second case they had access to alternative views of spatial cues during a short interval of time. Fx but not AMG lesions impaired learning in this condition, demonstrating that cue discrimination requires HPC function. The same lesions did not interfere with learning in an opposite arms/passive switching condition.

The results of this complex series of experiments indicate that information necessary to normal performance in the radial maze version of CPP is acquired in parallel by three memory systems: HPC-based, AMG-based, and DS-based. The involvement of one vs. another memory system is contingent upon situation. Thus, passive presentation of widely separated, nonambiguous cues requires AMG function. HPC function seems to be necessary and sufficient for normal performance in the active version of the task. However, DS activity is involved in this condition as well, most likely because of its role in associating cues and motor responses (McDonald and White, 1993, 1994).

It thus seemed that normal performance in the low cue ambiguity/passive presentation condition is based exclusively on the AMG memory system. The present experiments indicate that this is not the case. Some HPC function, however limited, seems to be required. A second implication is that although different memory systems specialize in acquisition and processing of separate types of information, their synergistic activity may be necessary in solving some (but not all) learning tasks.

Interactions Among Memory Systems

The hypothesis formulated above implies that the ACC is divided into two functional parts. The medial ACC is seen as the site of competitive AMG-HPC interaction. HPC input to this area diminishes the AMG's ability to control behavior. In contrast, HPC output to the lateral ACC could be related exclusively to spatial learning. This circuit can be conceived of as permissive of cooperative AMG-HPC interaction. This type of relationship is necessary in solving tasks such as passive CPP. Active CPP performance seems to be dependent on both HPC and DS memory systems (McDonald and White, 1995b). AMG + DS lesions re-

sulted in enhanced conditioning, suggesting that in certain conditions HPC function can be suppressed by the other two memory systems in certain conditions.

Interestingly, Devan and White (1999) found that information processing in the DS occurs in two parallel circuits. These authors used the modified spatial learning paradigm, in which training to visible (DS-dependent task) and invisible (HPC-dependent task) platforms alternates. At the end of training, the visible platform is moved to a new place, providing a choice between responding to location vs. responding to visible cue. Lesions of the lateral DS did not prevent acquisition of either cue or spatial information, but caused increased preference for spatial response. Lesions of the medial DS retarded both spatial and cue response learning and produced preference for cue response. Fx lesions resulted in a spatial learning deficit, no impairment in cue learning, and a preference for cue response. Combined HPC-medial DS lesions on counterlateral sides resulted in slow spatial and cue learning and preference for cue response. The authors concluded that 1) medial and lateral DS areas have different functional relevance; 2) HPC may interact competitively with lateral DS and cooperatively with medial DS; and 3) the cooperative interaction may take place in a circuit including both HPC and medial DS. These conclusions were supportive of an earlier study (Devan et al., 1999) which found that lesions of the medial DS impaired cue and place acquisition in the water task, were followed by a preference for local rather than spatial cue response, and resulted in increased thigmotaxis. In contrast, lateral DS lesions were not associated with any of these effects. These results suggested that the medial, but not lateral, DS is involved in integration of cognitive information and stimulus-response type behavior.

Thus a medial-to-lateral topographical organization of striatum functionality may exist. Lateral DS seems to be important for formation of stimulus-motor response associations. In contrast, medial DS may act cooperatively with the HPC by modulating spatial behavior. Lateral ACC may be the preferential output gate for spatial navigation. Finally, medial ACC may be the site of AMG-HPC competitive interactions and may be particularly relevant to conditioning-type paradigms. That the medial DS-lateral ACC may constitute a functional unit is somewhat supported by the finding that both ACC and medial DS lesions impaired CPP retention (Everitt et al., 1991).

CONCLUSIONS

The implication of these data for research on HPC function is that multiple factors have to be weighed when interpreting experimental results. First, the structures lesioned and the size of the lesions themselves should be carefully considered. It becomes increasingly clear that Fx and HPC lesions are not interchangeable. The same is true for partial vs. complete lesions of the HPC itself. Second, requirements posed by behavioral paradigms should be differentiated. Some tasks may involve spatial learning only, while others may additionally involve formation of associations between stimuli and motor or affective response. More demand on HPC function seems to be generated by tasks involving discriminations among multiple cues presented simultaneously (McDonald et al., 1997). The third factor is the interaction between memory systems. Depending on the particular setup, memory systems may cooperate or compete for behavioral output. Thus, spatial learning in the water task may involve a different pattern of neural activity than spatial learning in the radial maze. Assessment of this factor may be particularly difficult because interaction among memory systems may occur at various levels, i.e., cortical and/or subcortical. Future systematic comparisons between different types of tasks and different types of lesions should bring more light on these issues.

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