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RAPID COMMUNICATION

Ventral Hippocampal Involvement in Temporal Order, but not Recognition, Memory for Spatial Information

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ABSTRACT: The hippocampus is critical for spatial memory. Recently, subregional differences in the function of hippocampus have been described in a number of behavioral tasks. The present experiments assessed the effects of reversibly lesioning either the dorsal (dHip) or ventral hippocampus (vHip) on spontaneous tests of spatial recognition and temporal order memory. We report that although the dHip is necessary for spatial recognition memory (RM) (distinguishing a novel from a familiar spatial location), the vHip is involved in temporal order memory (the capacity to distinguish between two spatial locations visited at different points in time), but not RM. These findings and others are consistent with the hypothesis that temporal order memory is supported by an integrated circuit of limbic areas including the vHip and the medial prefrontal cortex. © 2007 Wiley-Liss, Inc.

KEY WORDS: dorsal hippocampus; ventral hippocampus; radial arm maze; spontaneous behavior; medial prefrontal cortex

INTRODUCTION

Recent research suggests that discrete subregions of the rodent hippocampus, particularly along the septotemporal axis, have different functional roles in cognition (Bannerman et al., 2004). One perspective posits that the dorsal hippocampus (dHip) is preferentially involved in spatial learning and memory (Moser and Moser, 1998, but see de Hoz et al., 2003), whereas the ventral hippocampus (vHip) plays a more prominent role in the control of other aspects of behavior, particularly those related to fear and anxiety (Kjelstrup et al., 2002). However, lesions of the vHip disrupt spatial learning and memory in a variety of behavioral tasks (Floresco et al., 1996, 1997; Ferbinteanu et al., 2003; Broadbent et al., 2004; Rogers et al., 2006); thus, further examination of the roles of the dHip and vHip in various forms of spatial memory is warranted.

Recognition memory (RM) is a neural process by which a stimulus or environment is identified as one encountered on a previous occasion (Steckler et al., 1998) and is mediated by activity in the medial temporal lobe (Eichenbaum et al., 2007). Strong evidence suggests that the rodent hippocampus is critically involved in spatial RM (Jackson-Smith et al., 1993; Steckler et al., 1998; Gilbert et al., 2001; Mumby et al., 2002; Eacott and Norman, 2004), although most tasks have focused on the arrangement of objects within space as opposed to recognition of a unique spatial location. Temporal order memory (TM) refers to the ability to maintain a representation of the order in which events have been experienced over time (Fuster, 2001). TM is strongly dependent on the integrity of the prefrontal cortex (Chiba et al., 1994, 1997; Fuster, 2001; Hannesson et al., 2004a,b); however, the hippocampus has also been implicated, particularly in tasks in which specific spatial locations are encountered at different points in time (Chiba et al., 1994; Gilbert et al., 2001; Kesner et al., 2002).

To date, no studies have explicitly examined whether the dHip and vHip have distinct roles in spatial RM or TM. The present experiments address this question using two novel tests of spatial memory recently developed in our laboratory (Hannesson et al., 2004b). By recording patterns of unrewarded, spontaneous exploration in a modified radial arm maze (RAM), the tests provide reliable and sensitive measures of RM and TM for different spatial locations on the maze. The RM test requires rats to freely explore a novel arm of the RAM or one that has been previously explored. Given their innate preference for novelty, rats spend more time exploring the novel arm, thus exhibiting RM. In contrast, the TM test requires rats to explore two arms, both of which have been previously explored at different points in time. In this case, control rats exhibit TM by preferentially exploring the arm encountered earlier in time. In critical control experiments, we have confirmed that these two tests measure different forms of memory [see Hannesson et al. (2004b) for a detailed discussion].

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We assessed the roles of the dHip and vHip in the RM and TM tests by inactivating each structure using local intracranial microinfusions of the reversible sodium channel blocker lidocaine. Lidocaine infusions have been used successfully to inactivate discrete brain areas temporarily during behavioral testing (Seamans et al., 1995; Floresco et al., 1997) and have proved useful in identifying the neural circuitry critical for RM and TM in previous experiments (Hannesson et al., 2004a,b). The spontaneous nature of the spatial memory tests has a number of advantages over other tests as they do not depend on previously learned behaviors, or positive and negative reinforcement, and are not confounded by other procedural issues (Hannesson et al., 2004b). Additionally, identical components of behavior are measured during the two tests, thereby allowing for direct comparisons of performance between them.

MATERIALS AND METHODS

Subjects

Male Long–Evans rats (325–375 g; Charles River, Quebec, Canada) were used in all experiments. The rats were housed in pairs in plastic cages with food and water available ad libitum. Experimental procedures were carried out in the light portion of the 12:12 h light/dark cycle and were approved by the UBC Animal Care Committee. One week after arrival, rats were anesthetized with 100 mg/kg ketamine hydrochloride and 7 mg/kg xylazine. The rats' heads were shaved and placed in a stereotaxic apparatus prior to having the skin retracted and the skull leveled. Stainless steel guide cannulae (23 Ga) were implanted bilaterally above either the dHip (AP, −3.0 mm; ML, ±2.4 mm; DV −2.1 mm) or vHip (AP, −6.0 mm; ML, ±5.5 mm; DV −5.2 mm). Four jeweler's screws and dental acrylic were used to secure the cannulae in place. Stylets were also inserted into the cannulae. Rats were regularly handled beginning 1 week after surgery.

Behavioral Testing

Experimental procedures were similar to those described previously (Hannesson et al., 2004b). An experimenter blind to the treatment status of the animal performed behavioral testing and scoring. A within-subjects design was used for both the dHip and vHip experiments. Following procedures previously optimized (Hannesson et al., 2004b), rats were tested a maximum of twice in one of two rooms with numerous spatial cues and the effect of both treatments (sham or lidocaine) for a given test type (RM or TM) were assessed in the same room. The RAM was constructed from plywood covered with white corrugated plastic and elevated 50 cm off the floor. The center platform was 45 cm in diameter with 8 slots for removable arms 80 cm long and 10 cm wide. Four different arms were used during testing to ensure the behavior of the rats was not influenced by nonspatial cues. Between all trails, the maze was thoroughly cleaned with 50% ethanol and a damp sponge. Before testing, all rats were habituated to the infusion procedure and one of the rooms containing the maze four times over 8 days. For all habituation and test sessions, squads of rats (4–10 animals) were removed from the colony and held in a separate holding room for the duration of testing. During the habituation sessions, rats were individually removed from the holding room, dummy needles with short tips (3 mm) were inserted into their cannulae, and they were placed in one of the infusion boxes for 3 min. The infusion pump was turned on for the first 2 min, but no infusion was made. The rats were returned to the holding room and 10–15 min later, they were transported to one of the testing rooms on a cart. They were then placed on the central platform of the maze (without arms attached) for 5 min after which they were returned to the holding room. Before being tested in the second room, rats in the vHip group were given a single habituation trial in it.

Recognition memory was assessed by allowing the rats to freely explore the RAM during two 4-min trials separated by a 105-min delay. On the first trial, rats were allowed to explore two arms attached to the maze at novel locations. On the second (test) trial, rats were allowed to explore the RAM with an arm in one of the locations from the first trial (familiar arm) and one arm in a novel location (novel arm). Temporal order memory was assessed by exposing the rats to two training trials separated by 60 min. During each trial, the rats were exposed to two different arms (a total of four arms). After a delay of 45 min, the rats were allowed to explore two of the previous arms, one from the first trial, and the other from the second. The order of the behavioral tests was counterbalanced and successive tests were conducted 1 week apart. The choice of arm locations for all tests was random and counterbalanced provided two criteria were met: (i) two arms directly adjacent on the maze were never used on the same trial, and (ii) the same arm location was never used twice for a rat in the same testing room (except during the test trial of a given test).

Infusion Procedure

Given that lidocaine is estimated to effectively inactivate a given area for 15–25 min beginning 5 min after the infusion (Seamans et al., 1995; Tehovnik and Sommer, 1997), rats were removed from the holding room 15 min prior to the test trial and infusion needles were inserted 1 mm beyond the end of the guide cannulae. Rats were then placed in a Plexiglas infusion box (20 × 20 × 30 (h) cm). In the lidocaine condition, 0.8 μl of 4% lidocaine was delivered through each needle over 2 min with a Harvard microinfusion pump. Injection needles were left in the brain for an additional minute to allow for diffusion away from the needle tip. The infusion procedure in the sham condition was identical to the lidocaine condition, except that shorter needles flush with the end of the guide cannulae were inserted, and no infusion was made.

Histology

Following behavioral testing, rats were overdosed with sodium pentobarbital and perfused transcardially with 0.9% sa-

TABLE 1.

Total Arm Exploration Times (in seconds, Mean ± SEM) of Sham or Lidocaine-Treated Rats in the RM and TM Memory Tests

Test + infusion	Trial 1 (total)	Trial 2 (total)	Test trial (total)
RM + dHip sham	114.47 ± 7.5	N/A	133.73 ± 11.0
RM + dHip lido	121.43 ± 5.3	N/A	128.82 ± 8.1
RM + vHip sham	113.55 ± 7.1	N/A	130.81 ± 6.7
RM + vHip lido	131.08 ± 7.0	N/A	150.18 ± 6.1
TM + vHip sham	110.96 ± 7.4	136.47 ± 8.9	132.57 ± 8.8
TM + vHip lido	113.18 ± 6.9	128.94 ± 7.7	148.40 ± 8.4

Lido, lidocaine; dHip, dorsal hippocampus; vHip, ventral hippocampus.

line. Brains were stored in 10% sucrose/10% formalin until 60 μm coronal sections of the hippocampus were taken with a cryostat. Sections were mounted on slides, stained with cresyl violet, and the locations of the infusion sites were determined with the assistance of a rat brain atlas (Paxinos and Watson, 1997).

Data Analysis

The exploratory behavior of the rats was recorded by an overhead camera and analyzed after testing. A rat was judged to be in a given arm when all four of its feet crossed the boundary from the center of the maze into the arm. Two measures were calculated for each animal: the novel arm bias (D1) was calculated as the time spent in the novel arm (or older familiar arm in the TM test) minus the time spent in the familiar arm (or newer familiar arm in the TM test) and the weighted difference score (D2) was calculated as D1/time spent in both arms. Overall exploration times across trials were analyzed with repeated measures analysis of variance (ANOVA) with trial and infusion condition as factors and follow-up analyses were performed with *t*-tests. Test trial data were analyzed with a *t*-test (dHip) or a 2/2 repeated measure ANOVA (vHip) with test and infusion condition as factors. Additional comparisons were performed using within group *t*-tests and one sample *t*-tests (comparison value = 0 or no bias) as necessary.

RESULTS

Effects of Temporary Inactivation of the Dorsal Hippocampus

Total arm exploration times of rats in the dHip group (n = 15) during the RM test are shown in Table 1. The rats spent an average of approximately 2 min exploring the arms during the training and test trials. No significant differences were noted following analysis with a repeated measures ANOVA (main effect of condition: $F(1,14) = 0.02$, N.S.; trial by treatment interaction: $F(1,14) = 1.16$, N.S.), although the main effect of trial approached significance [$F(1,14) = 4.11$, $P = 0.062$]. As shown in Table 2, there was no significant difference in exploration times for the arms presented during the training trial in either the sham [$t(14) = -0.07$, N.S.] or lidocaine conditions [$t(14) = -0.80$, N.S.].

As expected, sham-infused animals explored the novel arm significantly more than the familiar arm during the test trial (Table 2, Figs. 1A,B; one sample *t*-test, D1: $t(14) = 2.82$; $P < 0.05$; D2: $t(14) = 2.94$; $P < 0.05$). In contrast, when rats were infused with lidocaine into the dHip before the test trial, they displayed a profound disruption in RM and spent a similar amount of time exploring both the novel and familiar arms (one sample *t*-test, D1: $t(14) = 0.14$; N.S.; D2: $t(14) = -0.13$; N.S.). Further analyses indicated that both the D1 [$t(14) = 2.36$, $P < 0.05$] and D2 [$t(14) = 2.84$, $P < 0.05$] measures were significantly greater following sham than lidocaine infusions. Locations of the infusion sites are depicted in Figure 1C.

Effects of Temporary Inactivation of the Ventral Hippocampus

Exploration times of rats in the vHip group (n = 15) during the RM and TM tests are summarized in Table 1. Similar to the dHip rats, rats in the vHip group explored the arms for an average of 2–2.5 min during each trial of either the RM or TM test. For the RM test, a repeated measures ANOVA revealed significant differences in exploration time for both trial [$F(1,14) = 13.97$, $P < 0.01$] and condition factors [$F(1,14) = 8.83$, $P < 0.05$], but a significant interaction between these fac-

TABLE 2.

Individual Arm Exploration Times (in seconds, Mean ± SEM) of Sham or Lidocaine-Treated Rats in the RM and TM Memory Tests

Test + infusion	Trial 1 (A)	Trial 1 (B)	Trial 2 (C)	Trial 2 (D)	Test trial (familiar)	Test trial (novel)
RM + dHip sham	53.82 ± 5.2	54.44 ± 6.8	N/A	N/A	54.47 ± 5.5	77.64 ± 8.4
RM + dHip lido	55.66 ± 4.8	61.04 ± 5.1	N/A	N/A	60.88 ± 5.5	61.88 ± 6.7
RM + vHip sham	59.91 ± 5.6	53.65 ± 5.2	N/A	N/A	55.38 ± 4.2	75.43 ± 6.8
RM + vHip lido	59.13 ± 6.3	66.10 ± 6.8	N/A	N/A	64.99 ± 6.7	85.16 ± 6.6
TM + vHip sham	50.79 ± 5.3	53.02 ± 5.4	72.43 ± 9.5	57.49 ± 7.9	46.30 ± 7.7	75.19 ± 9.2
TM + vHip lido	58.49 ± 4.8	54.76 ± 5.9	68.44 ± 4.8	58.50 ± 6.9	81.38 ± 6.1	67.01 ± 5.6

Note that in the TM version of the test, both arms the rat explores in test trial have been previously explored. Therefore, for the test trial of the TM test, the familiar arm refers to the arm explored more recently (i.e. during Trial 2) and the novel arm refers to the arm explored less recently (i.e. during Trial 1). Arms A and C were used in the test trial. Lido, lidocaine; dHip, dorsal hippocampus; vHip, ventral hippocampus.

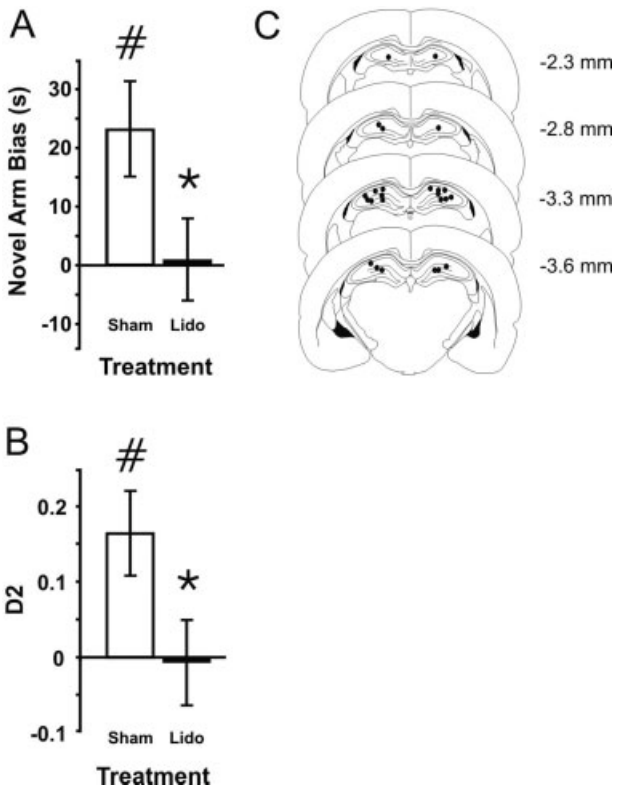

FIGURE 1. Effect of lidocaine inactivation of the dorsal hippocampus (dHip) on the recognition memory test. (A) Novel arm bias (D1) calculated as the time spent exploring the novel arm minus the time spent exploring the familiar arm for the rats in the sham and lidocaine (Lido) infusion tests. (B) Weighted difference score (D2) calculated as D1 divided by the total time spent exploring both arms. (C) Representative locations of the injection sites (filled circles) in the dHip of the rats included in the behavioral analyses. Locations of the plates (Paxinos and Watson, 1997) relative to bregma are indicated in millimeter. Error bars denote SEM, # denotes a significant difference from chance (0), * denotes a significant difference between groups ($P < 0.05$).

tors was not observed [$F(1,14) = 0.03$, N.S.]. Inspection of the data revealed that regardless of the treatment condition (sham or lidocaine) rats spent significantly more time exploring the arms during the test trial (140.5 s) than the training trial (122.3 s) and explored significantly more during the lidocaine condition (140.6 s) than the sham condition (122.2 s), over both trials. When the individual arm exploration times were analyzed for the training trial of the RM test were analyzed (Table 2), no significant differences were observed for either the sham [$t(14) = 0.76$, N.S.] or lidocaine [$t(14) = 0.73$, N.S.] conditions.

Analysis of the exploration times during the TM test revealed a significant main effect of trial [$F(2,28) = 8.93$, $P < 0.01$], but a nonsignificant main effect of condition [$F(1,14) = 0.25$, N.S.] and a nonsignificant trial by condition interaction [$F(2,28) = 3.30$, N.S.]. Post hoc analyses revealed that rats spent significantly more time exploring the arms during the test trial (140.5 s) than trial 1 (112.1 s; $P < 0.05$). Analysis of the individual arm exploration times for the training trials of the TM test (Table 2) did not reveal any significant differences in either the sham [$F(3,42) = 2.21$, N.S.] or lidocaine [$F(3,42) = 1.25$, N.S.] conditions.

When the data from the test trials were analyzed, an interesting pattern emerged (see Table 2, Figs. 2A,B). Rats in both the sham and lidocaine conditions showed a strong preference for the novel arm during the RM test. In contrast, vHip lidocaine infusions disrupted performance on the TM test. This pattern is confirmed by significant test by treatment condition interactions for both the D1 [$F(1,14) = 4.89$, $P < 0.05$] and D2 measures [$F(1,14) = 5.22$, $P < 0.05$] and a nonsignificant main effect of test [D1: $F(1,14) = 1.69$, N.S.; D2: $F(1,14) = 1.07$, N.S.]. Post hoc analyses revealed that the performance of

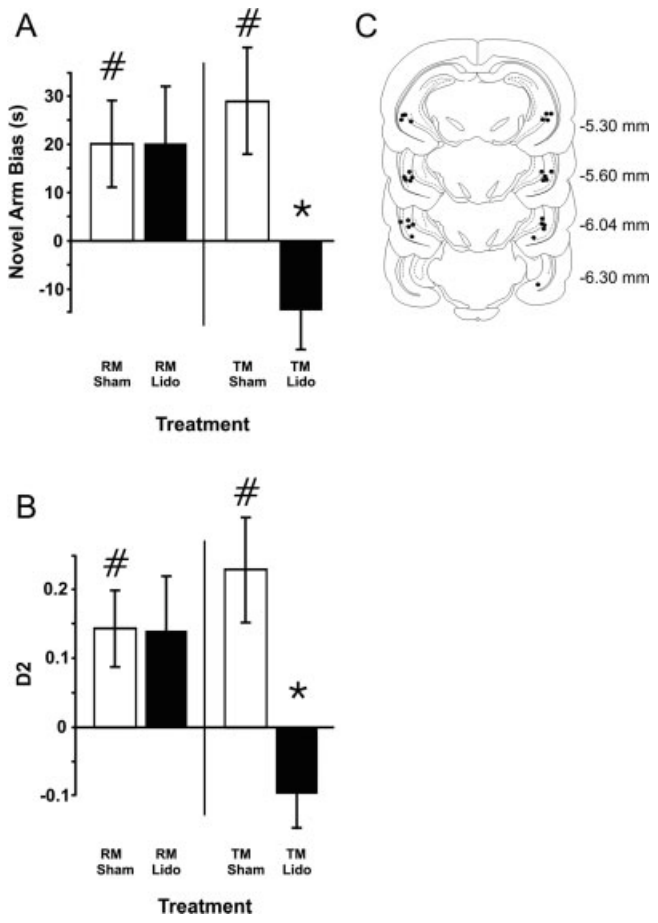

FIGURE 2. Summary of the bias in arm exploration after sham or lidocaine (Lido) infusions in the recognition (RM) and temporal order memory (TM) tests. (A) Novel arm bias (D1) calculated as the time spent exploring the novel arm (or initially visited arm in the TM test) minus the time spent exploring the familiar arm (or more recently visited arm in the TM test) for the rats following the sham and Lido infusions. (B) Weighted difference score (D2) calculated as D1 divided by the total time spent exploring both arms. (C) Representative locations of the injection sites (filled circles) in the dHip of the rats included in the behavioral analyses. Locations of the plates (Paxinos and Watson, 1997) relative to bregma are indicated in millimeter. Error bars denote SEM, # denotes a significant difference from chance (0), * denotes a significant difference between groups for the TM test ($P < 0.05$).

the lidocaine-infused rats in the TM test was significantly worse than following sham infusions [$t(14) = 2.85$, $P < 0.05$]. The main effect of treatment approached significance for the D1 measure [$F(1,14) = 4.24$, $P = 0.06$] and was significant for the D2 measure [$F(1,14) = 6.33$, $P < 0.05$]. As shown in Figures 2A,B, the main effect of treatment is primarily the result of the negative D1 and D2 scores when rats were tested in the TM lidocaine condition.

One-sample *t*-tests confirmed that the RM sham and TM sham groups' bias for the novel arm were significantly above chance [D1, RM sham: $t(14) = 2.22$, $P < 0.05$; TM sham $t(14) = 2.64$, $P < 0.05$; D2, RM sham: $t(14) = 2.58$, $P < 0.05$; TM sham $t(14) = 2.99$, $P < 0.05$] and that the bias following TM lidocaine treatment was not significantly different from chance [D1: $t(14) = -1.77$, N.S.; D2: $t(14) = -1.85$, N.S.]. However, the novel arm bias for rats in the RM lidocaine condition also failed to reach statistical significance when all rats were included in the analysis [D1: $t(14) = 1.71$, $P = 0.11$; D2: $t(14) = 1.76$, $P = 0.10$]. Inspection of the data revealed that one rat had a particularly strong bias for the familiar arm (its D1 score was −60.75 s which was 1.78 standard deviations from the mean). With this rat's value removed, the rats in the RM lidocaine condition also showed a statistically significant bias for the novel arm [D1: $t(13) = 2.34$, $P < 0.05$; D2: $t(13) = 2.42$, $P < 0.05$]. Locations of the infusion sites are depicted in Figure 2C.

DISCUSSION

The present experiments yielded a number of important results. First, we confirm that sham-infused rats spend significantly more time exploring spatial locations that are either novel (in the RM test) or were experienced earlier in time (in the TM test). These findings replicate our previous results with the spatial RM and TM tests and confirm their utility for studying memory for spatial information in the rodent (Hannesson et al., 2004b). We also demonstrated that temporary inactivation of the dHip is sufficient to disrupt performance of the RM test (Figs. 1A,B). Most importantly, results observed following temporary inactivation of the vHip indicate that the vHip is only involved in the TM test, and is not necessary for successful performance of the RM test (Figs. 2A,B).

Analyses of the total arm exploration times revealed some differences across trials in the present study. Rats in the dHip group tended ($P = 0.062$) to explore the arms more in the test trial than the training trial of the RM test whereas vHip group explored the arms more during the test trial in both the RM and TM tests (Table 1). Although we cannot provide a direct explanation for these effects, they are clearly not specifically related to the lidocaine infusions as they occurred during both the sham and lidocaine test sessions. It is also worth noting that in our previous study (Hannesson et al., 2004b), some variability was observed in total arm exploration times across trials in a given test, however, greater exploration during the test trials was not generally observed. Given that sham-infused rats in both studies performed similarly on both the RM and TM tests, it is unlikely that the increased exploration times during the test trials in the present study significantly confound the interpretation of the dHip or vHip inactivation effects.

Lidocaine infusions have been commonly used in our laboratory to assess the functional roles of cortical (Seamans et al., 1995; Floresco et al., 1997; Hannesson et al., 2004a,b) and subcortical areas (Floresco et al., 1996, 1997) in complex cognition with reliable results. Given the previous estimates of the spread of lidocaine using similar volumes (Seamans et al., 1995; Tehovnik and Sommer, 1997), the area functionally inactivated by the infusions likely spread between 0.8 and 1.3 mm from the tips of the injection needles. Therefore, substantial, nonoverlapping portions of the dHip and vHip would have been inactivated by the infusions. Although some spillover into adjacent areas such as perirhinal or entorhinal cortex is a potential concern for the infusions on the lateral border of the vHip, no behavioral differences were detected between rats with infusions in the lateral and medial aspects of the vHip. As a result, it is unlikely that inactivation of these cortical areas underlie the behavioral effects observed. However, it must be acknowledged that the main drawback of lidocaine lesions is that neuronal transmission in fibers of passage is also affected (Malpeli, 1999). Thus, some of the dHip infusions may have affected processing in the vHip by disrupting vHip afferents traveling through the alveus. It is also possible that the vHip lidocaine infusions disrupted TM by blocking activity in dHip afferents, although such an interpretation cannot explain the lack of effect of vHip infusions on the RM test. Further experiments examining the effects of axon-sparing lesions of the dHip and vHip in the present behavioral paradigms will help clarify these issues (see below).

Numerous studies have examined the role of the hippocampus in spatial RM and TM; however, several important differences exist between the design of the present study and others. For example, most previous studies have examined the effects of large, permanent lesions of the entire hippocampus (Jackson-Smith et al., 1993; Chiba et al., 1994; Mumby et al., 2002) or transection of the fornix (Eacott and Norman, 2004) on RM or TM tests. In the present study, we performed reversible lesions of either the dHip or vHip immediately before the test trial of the memory tests. Thus, the deficits in performance observed can be best attributed to impaired memory retrieval as animals in the lidocaine condition were trained with their hippocampi intact. Additionally, other studies of RM and TM have examined the role of the hippocampus in detecting changes in the spatial location of objects (Gilbert et al., 2001; Mumby et al., 2002; Eacott and Norman, 2004). As noted, the tests employed in the present study assessed memory for spatial location explicitly, thereby eliminating potentially confounding factors related to object exploration.

Substantial evidence suggests a role for the dHip in spatial learning and memory (Moser and Moser, 1998; Bannerman et al., 2004). The results of the first experiment support this conjecture as dHip lesions severely impaired spatial RM (Figs.

1A,B). Given this finding, it can be inferred that normal function of the dHip may also be critical for the TM test because the recognition of a specific spatial location is a prerequisite for spatial TM. Previous experiments have examined the role of different cellular regions within the dHip in tests with either RM or TM components. Interestingly, lesions restricted to the dorsal dentate gyrus (DG) disrupted spatial pattern separation (i.e., RM), whereas lesions of the dorsal CA1 region disrupted temporal pattern separation in a spatial task (Gilbert et al., 2001). Given the location of the infusion needle tips in the dHip (Fig. 1C) and the typical spread of lidocaine in the brain (Tehovnik and Sommer, 1997), portions of both the DG and CA1 were likely affected by the infusions performed in the present study. Future experiments specifically designed to assess the roles of the dorsal DG and CA1 in the present RM and TM tests may support the emerging hypothesis that different hippocampal cell populations have distinct roles in pattern separation (Rolls and Kesner, 2006).

In contrast to findings with the dHip, reversible lesions of the vHip failed to affect performance on the RM test but did impair performance on the TM test significantly (Figs. 2A,B). This result is best attributed to a deficit in temporal memory processing because animals with vHip lesions performed normally on the RM test thereby discounting confounds related to sensory/perceptual, motor, motivational or attentional factors. The specific memory impairment in the TM test may be related to the recruitment of the vHip due to greater processing demands of the TM test. It is interesting to note that the rats tended to show a preference for the familiar arm in the TM test following vHip lidocaine infusions, although this result failed to reach statistical significance. Further experiments are necessary to determine the reliability of this observation.

Previous results suggest that the integrity of the vHip may be necessary for processing spatial information in demanding tasks, such as a one-trial match to position task in the water maze (Ferbinteanu et al., 2003). The specific deficit in TM following vHip lesions is particularly interesting given the strong connections between the vHip and mPFC (Jay and Witter, 1991; Conde et al., 1995) and the dependence of the spatial TM test on the mPFC (Hannesson et al., 2004b). Thus, afferents from the vHip to the mPFC may be necessary for the mPFC to integrate spatial information and plan subsequent behavior based on the sequence of events in time when task demands are high (Floresco et al., 1997).

The neural circuitries involved in RM and TM are complex and depend on a number of factors including the specific temporal components of the task and the type of stimuli to be remembered. For example, under conditions of short delay and a relatively low memory load, the dHip and mPFC have redundant roles in a spatial nonmatching to sample task (Lee and Kesner, 2003). When the delay period increases (in this case from 10 s to 5 min), a specific role for the dHip becomes apparent (Lee and Kesner, 2003). However, when demands increase further, such as in the present TM test and other tasks where the delay is tens of minutes, processing in both the vHip and mPFC is necessary for normal performance (present data; Floresco et al., 1997). Numerous other studies have found dissociations in the neural structures involved in RM and TM for spatial stimuli versus objects. Interestingly, using a task that enables separate discrimination of object, place, and context RM, Mumby et al. (2002) found that hippocampal lesions produced selective effects on place and context RM without affecting RM for objects. In previous studies, our group (Hannesson et al., 2004a) and others (Winters and Bussey, 2005) have found that activity in the perirhinal cortex is necessary for RM for objects, whereas the transfer of information between the PRH and mPFC is necessary for object-based TM (Hannesson et al., 2004a). Thus, available evidence suggests that stimulus attributes sufficient for RM are stored in discrete posterior forebrain sites such as the hippocampus and perirhinal cortex. More complex mnemonic process such as TM are governed by the mPFC, which is anatomically well positioned to access and integrate information stored in other forebrain sites (Fuster, 2001; Mayes and Roberts, 2001; Hannesson et al., 2004a,b).

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