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Both dorsal and ventral hippocampus contribute to spatial learning in Long–Evans rats

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Abstract

The hippocampus (HPC) may be functionally heterogeneous in supporting spatial learning in rats. Thus, dorsal but not ventral HPC lesions have been reported to impair acquisition in the Morris water task which consists of finding a submerged platform in a pool filled with opaque water. To further investigate the functional differences between dorsal and ventral HPC regions, we used a one-trial matching to position water task in which the submerged platform occupied a different position during each session. This task is very sensitive to HPC damage. The results show that either dorsal or ventral HPC NMDA lesions disrupt the rapid acquisition of new place information. The acquisition deficit diminishes with training in both lesion groups. The data thus suggest that the entire HPC axis is involved in acquisition of spatial information.

Keywords: Hippocampus; Lesions; Water maze; Spatial learning

It has recently been suggested that the hippocampus (HPC) may be composed of sub-circuits with different behavioral functions [1]. Spatial navigation in the rodent requires intact HPC activity [14]. We have previously found [7] that animals with dorsal HPC lesions perform more poorly when navigating to a submerged platform, but the impairment was parameter-contingent and diminished as training progressed. We also found that on a competition test that offered a choice between responding to cue vs. location, animals with either dorsal or ventral HPC lesions preferred the cue response. Usually, half of the control animals respond to the visible cue and the other half to location while animals with HPC damage respond predominantly to the visible cue [11]. The data thus suggested that while dorsal HPC lesions are more disruptive for spatial learning, their ventral counterparts have a similar type of effect on this ability.

To further assess spatial learning deficits associated with partial HPC lesions in the present study we used the one-trial matching to position paradigm. If ventral HPC lesions produce a similar but less profound spatial leaning deficit than dorsal HPC lesions, then a more sensitive behavioral assay of HPC function should better reveal the impairment. The one-trial matching to position paradigm has been shown to be particularly sensitive to hippocampal dysfunction [2,18,19]. Furthermore, to the extent that either dorsal or ventral HPC can support spatial learning, both lesion groups should ultimately learn the task.

Forty male Long–Evans rats were individually housed in clear plastic cages with food and water available ad libitum and maintained on a 10 a.m. to 10 p.m. dark/light cycle. Testing took place during the dark period. Subjects were randomly assigned to one of three groups: dorsal HPC lesion ($n = 14$), ventral HPC lesion ($n = 14$), and sham ($n = 12$); NMDA lesions were performed on the experimental groups by infusing the neurotoxin through a cannula connected to a microinfusion pump. Surgical procedures and the testing apparatus have been described elsewhere [7]. The one-trial matching to sample task requires navigation to an invisible platform that is kept in the same location during one training session, but is moved across days. The first trial is an exploratory search without information about the platform position. The ability to locate the platform reflects only procedural factors. Spatial information can be learned during this trial and the following 10 s interval the animal spends on top of the platform (see below). During

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subsequent trials, the rat can use its memory to search directly for the platform. The trial 1–trial 2 comparison would thus reflect spatial working memory as defined by Olton et al. [15], that is memory for information acquired in one trial. In contrast, the trial 1–trial 8 comparison indicates what an animal has learned over the testing session. Within Olton's conceptual framework, this reflects reference memory, that is memory for information useful across a number of trials.

Each subject performed eight swimming trials a day. The sequence of starting positions was randomized within each day and was the same for all animals, but differed across days. Each animal was in turn removed from the holding cage and placed in the water facing the pool wall. The trial began when the rat was released in the water and stopped either when the animal reached the platform or after 60 s elapsed, whichever came first. The animal spent 10 s on the top of the platform at the end of each trial and then it was returned to its holding cage. Testing lasted a total of 15 days after which the rats were anesthetized with sodium pentobarbital and perfused intracardially. The histological procedures were as previously described [7].

Data from seven animals were discarded from the analysis because the lesions were incomplete or imprecise. Final analysis included results of ten animals with dorsal lesions, 11 animals with ventral lesions, and 12 shams. Fig. 1 shows the maximum and minimum extent of dorsal (Fig. 1A) and ventral (Fig. 1B) HPC damage and photographs of one dorsal (Fig. 1C, top row) and one ventral (Fig. 1C, bottom row) lesion. Dorsal HPC lesions had an average of 35.99 ± 4.55% of total HPC volume, while ventral HPC lesions had an average of 46.02 ± 4.12%.

Working memory abilities, as reflected by modifications in performance on trial 1 vs. trial 2, were investigated separately after collapsing data for each animal across three successive days at the beginning (days 1–3), middle (days 7–9) and end (days 13–15) of training interval (Fig. 2). Multiple comparisons between lesion groups were performed using the Ryan–Einot–Gabriel–Welsh (REGWQ) procedure (a post-hoc test designed to control Type I error rate while simultaneously maximizing power) [9]. The three-way ANOVA lesion × trial × day performed on the latency and path length parameters (note that Fig. 3 shows only data collected during days 1–6 and 10–15) indicated that the pattern of results was identical. We present here only the results of the latency analysis. Multiple comparisons between lesion groups using the same REGWQ procedure were performed on trial 8 data. The quadrant preference and heading angle measurements did not indicate any differences between groups and no further analyses were pursued.

All groups performed at similar levels during the first trial throughout training (Fig. 2, trial 1). Initially, animals tended to swim close to the pool wall, but they soon switched to a strategy of search across the pool area. Consequently, latencies and distances covered before

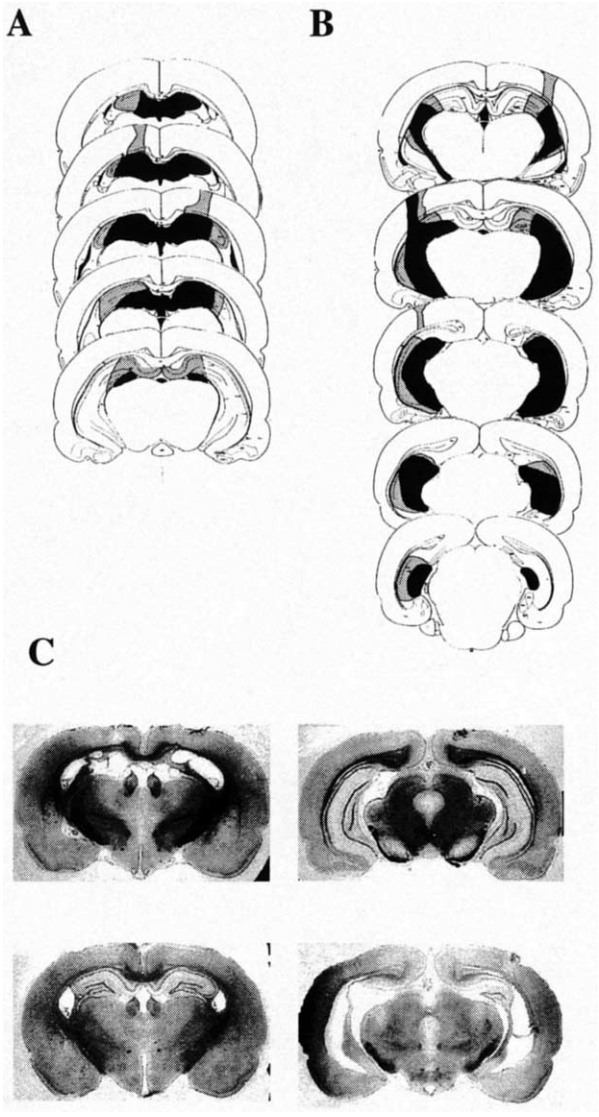

Fig. 1. Reconstruction of dorsal (A) and ventral (B) HPC lesions. Smallest lesions are shown in black, largest lesions are in gray. (C) Examples of HPC dorsal (top row) and ventral (bottom row) lesions.

locating the platform decreased across testing for all groups. In contrast, quadrant preference was consistently close to chance levels (25%). Deviation in heading angle also maintained a relatively consistent level (around 40°). Thus, it appears that neither lesion group was different from controls on procedural aspects.

Comparison between performance during first and second trials (Fig. 2) reflected lesion effects on spatial working memory. Comparisons between groups indicated that both lesion groups performed similarly showing some level of acquisition deficit, as in the later stages of training they needed more time and swam longer distances than the sham group. However, there were no differences between groups on the quadrant preference and heading angle measurements. These data indicate that both dorsal and ventral HPC lesions had an effect on spatial working memory.

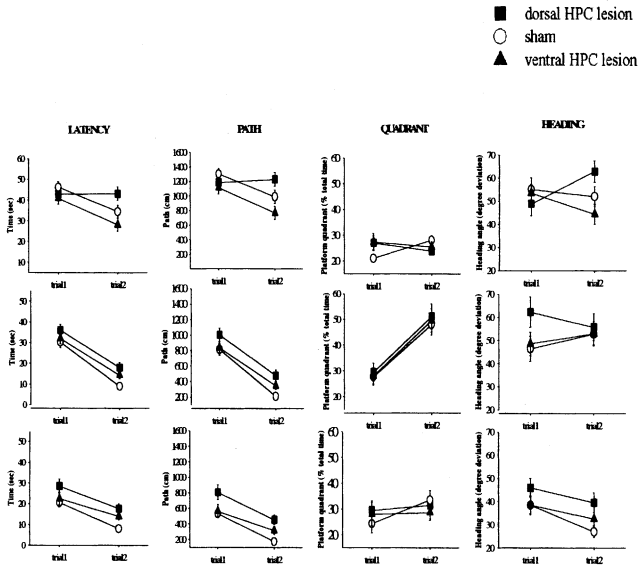

Fig. 2. Performance on the working memory component of the task at the beginning (upper row), middle (second row) and end (third row) of training. Statistical differences were found only on the latency and path length measurements. Error bars represent one standard error.

Although the spatial learning deficit was apparent both lesion groups improved significantly with training (Fig. 3). Despite the differences in performance during the second trial, all three groups found the platform considerably faster on the last three of the eight training trials that comprised one daily session. The overall performance of both lesion groups improved so that while during days 1–3 the average latency was well over 10 s, at the end of the training the values dropped to around this value. All three groups spent similar amounts of time in the platform quadrant and oriented themselves equally well towards the platform (data not shown). The overall ANOVA on the latency parameter indicated significant main effects of lesion ($F_{(2,30)} = 18.39$, $P < 0.0001$), day ($F_{(14,4200)} = 51.47$, $P < 0.0001$), and trial ($F_{(7,210)} = 166.26$, $P < 0.0001$) and significant lesion × trial ($F_{(14,210)} = 2.50$, $P = 0.026$), lesion × day ($F_{(28,420)} = 1.60$, $P = 0.029$), and trial × day ($F_{(98,2884)} = 2.78$, $P < 0.0001$) interactions. Multiple comparisons on trial 8 data indicated no differences between lesion groups and no differences between shams and the ventral HPC group (i.e. the ventral HPC group was in an 'intermediate' position between dorsal HPC rats and shams). Thus, lesioned rats acquired a relatively good representation of platform position regardless of whether the damage affected the dorsal or the ventral HPC areas. This would explain the lack of differences on heading angle and quadrant preference measurements. The lesioned rats would be able to orient themselves sufficiently well to navigate towards the appropriate location, but they would take somewhat longer to get to the precise position of the platform.

The central finding is that spatial memory was impaired in animals with either dorsal or ventral HPC lesions although the dorsal lesions were somewhat more disruptive. The lesion groups showed improved performance with increased amounts of training indicating that both dorsal and ventral HPC remnant areas can support acquisition of spatial information to a considerable extent. Neither type of lesion had procedural effects. These data suggest that spatial learning can be supported by either the dorsal or ventral HPC network, albeit with different degrees of efficiency.

One alternative interpretation of these results is that the impairment obtained following ventral HPC lesions is in fact caused by encroachment of the damage onto dorsal HPC areas. However, in this case it is impossible to explain how animals with dorsal HPC lesions, which have only the ventral HPC functional, learned the task to the extent that they were performing very close to control level. Second, comparison of dorsal and ventral lesion areas (Fig. 1) reveals that the overlap between lesions, when present, is small and restricted to the splenial HPC area. Third, prior findings seem to corroborate our observation that ventral

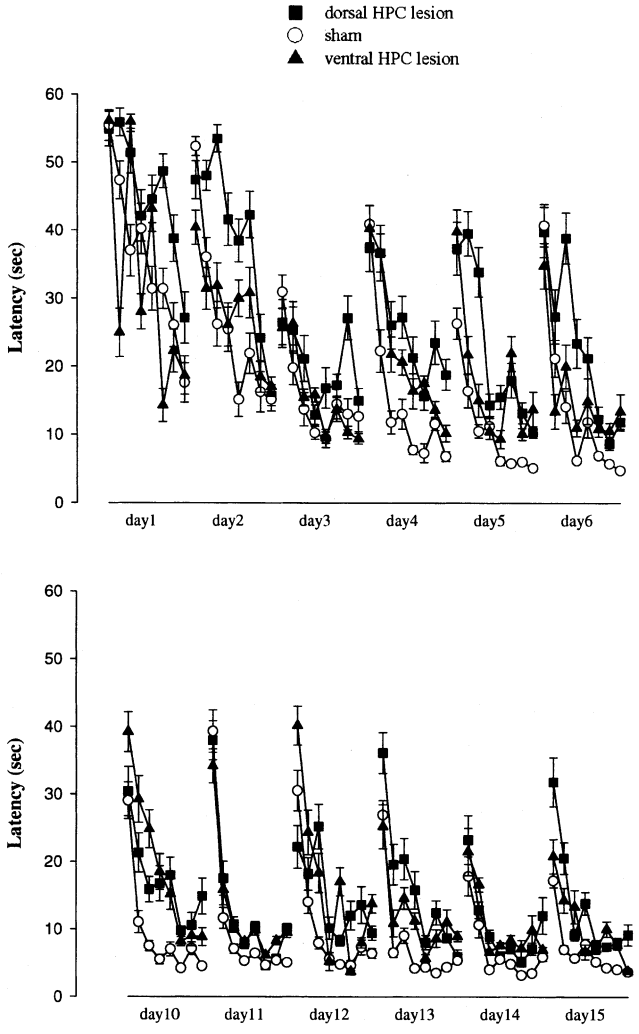

Fig. 3. Performance on the one trial matching to position water task during all eight trials. The first trial occurs in the absence of information about platform position. The second trial data reflect spatial working memory and the rest of the trials within the session reflect spatial reference memory. Error bars represent one standard error.

HPC lesions introduce a spatial learning deficit. Histological reconstructions of ventral HPC lesions previously reported to have been associated with spatial learning deficits (Ref. [12], Fig. 1; Ref. [13], Fig. 1) indicate that the crucial variable for predicting the spatial impairment appears to be extension of the damage progressively *from splenial HPC to the temporal pole* (and *not* extension from the temporal pole towards the dorsal HPC). Thus, it seems that the impairment obtained with larger ventral HPC lesions was associated with progressive extension of the lesion to *more ventral* (rather than more dorsal) HPC areas. Finally, we have previously reported a clear dissociation between the effects of similar dorsal and ventral HPC lesions on conditioned place preference [8] demonstrating that the effects of these lesions can be quite distinct depending on task requirements. Taken together, these factors make it unlikely that the acquisition deficit in the ventral HPC lesion group is due to inadvertently disrupting the dorsal HPC network.

The overall patterns of latency and path length data in the present study were very similar. Latency, swim speed and path length are directly related (path length = latency × swim speed) and thus, our results do not suggest any differences between lesion groups with respect to swim speed. In contrast, Bannerman et al. [3,4] recently reported that lesions of ventral but not dorsal HPC were associated with faster swimming. Because of the direct relationship between latency, path length and swim speed, we did not perform a separate analysis for the latter parameter. However, two factors argue against faster swimming in the ventral HPC group. The first is the absence of differences between groups on trial 1. If animals with ventral HPC damage swam faster, given that they do not exhibit thigmotaxis, it would be expected that they would have 'checked out' the pool area and found the platform sooner. Second, we performed an informal analysis by averaging swim speed for the last 6 days. The results did not suggest major differences between groups (26.26 cm/s for the dorsal HPC group, 25.99 cm/s for the shams and 22.77 cm/s for the ventral HPC group) and if anything, the ventral HPC lesion group had the lowest average.

Presently, the issue of partial HPC lesion size necessary to produce acquisition deficits remains unsolved. The only systematic studies available indicate discrepancies between the results of electrolytic [12] and neurotoxic [13] procedures. Electrolytic lesions of ventral HPC encompassing 39–52% of total HPC volume resulted in impairment while neurotoxic lesions encompassing 40–60% of total HPC did not. Similarly, electrolytic dorsal HPC lesions of 20–30% resulted in impairment, but neurotoxic lesions of 20–40% did not. Using neurotoxic lesions, Bannerman et al. [3,4] reported deficits with dorsal HPC lesions only (25–45% for dorsal and 45–50% for ventral HPC lesion size), but a parallel study using identical lesions and procedures [17] did not obtain impairment with either dorsal (average 55% of total HPC volume) or ventral HPC lesions (average 45–50% of total HPC volume). We found [7] a small deficit with ventral lesions (average 46.02% of total HPC volume) and a more pronounced one with dorsal damage (average 35.99% of total HPC volume). One reason for the differences between the effects of electrolytic vs. neurotoxic lesions may be damage in the former case of fibers of passage connecting HPC with other brain areas involved in spatial learning, such as the septum. A different factor in determining the magnitude of behavioral impairment is the testing paradigm (compare present results with previous ones [7]). The water temperature in our experiment was 21 °C and the control animals showed very robust learning. In other cases [3] the temperature was 25 °C and the control groups swam much longer distances before reaching the platform. de Hoz and Morris [6] showed that training spaced in time attenuates differences found on the Morris water task between animals with dorsal vs. ventral HPC lesions. This suggests that in addition to lesion size, type and position along the septo-temporal HPC axis, there are other important factors influencing behavioral performance.

Our interpretation of the present data is consistent with other results. Animals with dorsal HPC lesions could not spontaneously retrieve information acquired with an intact HPC, but they performed normally as long as they were given one 'reminder' trial [5]. Both dorsal and ventral HPC were found to be involved in working memory for allocentric distance [10]. Lidocaine inactivation of ventral HPC impaired performance in a spatial hole-board task [16]. Taken together, these studies suggest that ventral HPC supports acquisition of spatial information on its own.

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References

[1] D.G. Amaral, M.P. Witter, Hippocampal formation, in: G. Paxinos (Ed.), The Rat Nervous System, 2nd Edition., Academic Press, New York, 1995.
[2] R.N. Auer, M.L. Jensen, I.Q. Whishaw, Neurobehavioral deficit due to ischemic brain damage limited to half of the CA1 sector of the hippocampus, J. Neurosci. 9 (1989) 1641–1647.
[3] D.M. Bannerman, R.M.J. Deacon, S. Offen, J. Friswell, M. Grubb, J.N.P. Rawlins, Double dissociation of function within the hippocampus: spatial memory and hyponeophagia, Behav. Neurosci. 116 (5) (2002) 884–901.
[4] D.M. Bannerman, M.A. Good, B.K. Yee, M.J. Heupel, S.D. Iversen, J.N.P. Rawlins, Double dissociation of function within hippocampus: a comparison of dorsal, ventral, and complete hippocampal cytotoxic lesions, Behav. Neurosci. 113 (6) (1999) 1170–1188.
[5] L. de Hoz, S.J. Martin, R.G.M. Morris, Retrograde amnesia and hippocampal damage: recovery of an apparently lost memory, Soc. Neurosci. Abstr. (2001) 315.8.

[6] L. de Hoz, R.G.M. Morris, Rats with a small percentage of hippocampus spared temporally can learn a reference memory task in the water maze, Soc. Neurosci. Abstr. 25 (1999) 1624.
[7] J. Ferbinteanu, R.J. McDonald, Dorsal and ventral hippocampus – same or different?, Psychobiology 28 (3) (2000) 314–324.
[8] J. Ferbinteanu, R.J. McDonald, Dorsal/ventral hippocampus, fornix, and conditioned place preference, Hippocampus 11 (2001) 187–200.
[9] D.C. Howell, Statistical Methods for Psychology, 4th Edition., Duxbury Press, Belmont, CA, 1997.
[10] J.M. Long, R.P. Kesner, The effects of dorsal versus ventral hippocampal, total hippocampal, and parietal cortex lesions on memory for allocentric distance in rats, Behav. Neurosci. 110 (5) (1996) 922–932.
[11] R.J. McDonald, N. White, Parallel information processing in the water maze: evidence for independent memory systems involving dorsal striatum and hippocampus, Behav. Neural Biol. 61 (1994) 260–270.
[12] E. Moser, M.B. Moser, P. Andersen, Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions, J. Neurosci. 13 (9) (1993) 3916–3925.
[13] M.B. Moser, E. Moser, E. Forrest, P. Andersen, R.G.M. Morris, Spatial learning with a minislab in the dorsal hippocampus, Proc. Natl. Acad. Sci. USA 92 (1995) 9607–9701.
[14] J. O'Keefe, L. Nadel, S. Keightely, D. Kill, Fornix lesions selectively abolish place learning in the rat, Exp. Neurol. 48 (1975) 152–166.
[15] D.S. Olton, J.T. Becker, G.E. Handelmann, Hippocampus, space and memory, Behav. Brain Sci. 2 (1979) 313–365.
[16] B. Poucet, T. Herrmann, M.C. Buhot, Effects of short-lasting inactivations of the ventral hippocampus and medial septum on long-term and short-term acquisition of spatial information in rats, Behav. Brain Res. 44 (1991) 53–65.
[17] M.A. Richmond, B. Pouzet, L. Veenman, J. Feldon, B.K. Yee, J.N.P. Rawlins, D.M. Bannerman, Dissociating context and space within the hippocampus: effects of complete, dorsal, and ventral excitotoxic hippocampal lesions on conditioned freezing and spatial learning, Behav. Neurosci. 113 (6) (1999) 1189–1203.
[18] R.J. Sutherland, L.S. Leung, M.P. Wiesend, J. Schlife, R.J. McDonald, An evaluation of the effect of partial hippocampal kindling on place navigation by rats in the Morris water task, Psychobiology 25 (2) (1997) 126–132.
[19] R.J. Sutherland, R.J. McDonald, D.D. Savage, Prenatal exposure to moderate levels of ethanol can have long-lasting effects on learning and memory in adult offspring, Psychobiology 28 (2000) 523–539.