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Research report

Movements of exploration intact in rats with hippocampal lesions

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Abstract

Prompted by the theoretical prediction that damage to the hippocampus should abolish exploratory behavior, the present study examined exploratory movements in control rats and rats with hippocampal lesions produced with the neurotoxin *N*-methyl D-aspartate (NMDA). In four daily 30-min sessions, control and hippocampal rats were exposed to an open circular table under room lighting. Both control and hippocampal rats spent a majority of time near, and organized trips away from, a portion of the table (home base) near a large cue placed proximal to the table. On Day 1, control and HPC rats made equal numbers of head orientations and a comparable number of trips, featuring equal travel distance and numbers of stops. By Day 4, dwell times near the home base increased and other movements decreased in the control rats but the activity profile of Day 1 persisted in the hippocampal rats. The high degree of similarity in behavior between hippocampal and control rats on Day 1 and the persistence of this behavior in hippocampal rats on Day 4 suggests that the hippocampus is not necessary for the display of normal exploratory movements per se. The absence of habituation of exploration in hippocampal rats is discussed in relation to contemporary theories of hippocampal function.

Keywords: Hippocampus; Exploration; Exploratory movements; Exploratory behavior and hippocampus; Hyperactivity and hippocampus; NMDA hippocampal lesions; Spatial behavior

1. Introduction

One of the most interesting aspects of O'Keefe and Nadel's [31] spatial mapping theory is the theoretical link between hippocampal circuitry and exploratory behavior. Their theory proposes that exploration is fundamental in building and updating the internal representation of the spatial layout of an environment. Consequently, they propose that if subject to hippocampal damage, "all forms of exploratory behavior should disappear from the animal's repertoire" [p. 242]. Following this proposal, studies have confirmed that there are alterations in the behavior displayed by hippocampal rats in open field tests [19,34,42,49], but other studies have reported that hippocampal rats still investigate novel objects and are sensitive to changes in their location [1,15,30,32,37,40]. Nevertheless, despite the reports of altered behavior of rats in open field "exploratory" tests, there has been no detailed analysis of the animals' ongoing movements and movement patterns.

What has hampered previous study of the role of the hippocampus in exploratory behavior is the absence of agreement of what constitutes exploratory behavior. Many studies have focused on measures of locomotor activity recorded within homogenous environments such as a home cage. Additionally, tests of open-field behavior are generally brief (circa 5–10 min) [20,31]. Indeed, detailed descriptions of animal exploration are often ignored because the structure of exploratory behavior is often assumed to be stochastic, and "very difficult to describe quantitatively" [27, p. 135]. Recently, however, a descriptive approach to the exploratory behavior of the laboratory rat has disclosed that the structure of a rats movement in an open field is far from random and is composed of specific movements that can be quantified [6,47,50]. For example, central to all exploratory behavior is the finding that rats adopt specific locations in their environment, even when that environment is relatively featureless, as home bases from which they organize exploratory trips [7,16].

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Movements displayed at the home base include grooming, rearing, and turning, while excursions are circuitous and consist of a number of progressions punctuated by stops, with an upper limit on the number of stops [11,41,50]. Typically, excursions are terminated by fast, direct returns to the home base [41,43,50].

In light of the finding that rodent exploration is organized, the purpose of the present study was to reexamine the issue of whether hippocampal lesions alter this organization. We used a test situation that is conducive for eliciting both home base behavior and excursions [2,16,17]. To produce selective lesions of the hippocampus, injections of the neurotoxin *N*-methyl D-aspartate (NMDA) were made into the cell fields of Ammon's horn and the dentate gyrus [22,44]. After a recovery period, control rats and rats with hippocampal lesions were placed on a circular table-top under lighted conditions on each of four daily sessions. A large cue was placed next to the table and remained in the same location throughout the experiment. Movement measures included measures of the quadrant and annulus dwell times, the number and duration of stops, total path length, number of trips, percent area traversed, and changes in head movements and direction.

2. Materials and methods

2.1. Subjects

Twelve female Long-Evans rats (University of Lethbridge vivarium) approximately 90 days old, weighing 250–300 g, were used in the experiment. Rats were housed in groups of three in Plexiglas cages in the colony room with the temperature maintained at 20–21 °C and a 12/12-h light/dark cycle (8:00–20:00). Food and water were provided ad libitum. Six rats received NMDA hippocampal lesions 2 weeks prior to testing, and six rats served as controls. All experimental procedures were approved by the University of Lethbridge Animal Care Committee, which follows the standards set by the Canadian Council on Animal Care.

2.2. Surgery

Rats were anesthetized with a mixture of isofluorane and oxygen during the surgery. Damage to the hippocampus was produced by stereotaxic microinjections (0.4 μl/site) of neurotoxin NMDA (7.5 mg/ml). There were six lesion sites per hemisphere, using coordinates measured from bregma [32] and the surface of the dura (in mm): anterior (A) = −3.1, lateral (L) = 2.0, and ventral (V) = −3.6; A = −4.1, L = 3.0, and V = −3.5; A = −5.0, L = 3.5, and V = −3.5; A = −5.3, L = 5.2, and V = −5.5; A = −5.3, L = 5.2, and V = −7.5; A = −6.0, L = 5.0, and V = −7.3. NMDA was infused via a 30 gauge cannula at a rate of 0.20 μL/min and the cannula was left in place for 2 min after each injection to permit diffusion. Following surgery, the rats were administered sodium pentobarbital (0.1 mL, 65 mg/mL, i.p.) to minimize epileptic seizures and Metacamp (0.06 mL, 5 mg/mL, s.c.) for analgesia. Rats were monitored for at least 90 min before being returned to the colony room. Rats were allowed to recover for 2 weeks before testing began.

2.3. Open field

The open field (Fig. 1) was a wooden circular table without walls measuring 255 cm in diameter [44]. The absence of walls reduced the probability that the rats would display thigmotaxic behavior to the edge of the open field. The table was painted white and mounted on ball bearings for rotation. The surface of the table was approximately 64 cm above the floor. The table was located in a large room that was illuminated. A number of visual cues were present in the testing room, including counters, posters and a large bookshelf. The table was rotated and wiped down with soap and water after testing each rat.

Fig. 1. The apparatus is a circular wooden table (255 cm in diameter) without walls. A prominent cue is positioned next to the table.

2.4. Visual cue

A black box (42 cm × 48 cm × 82 cm high) was placed 15 cm away from the edge of the table (Fig. 1), with its bottom level with the top of the table, and remained at that location for each daily session.

2.5. Procedure

At the start of an exploratory session, a rat was brought into the testing room and was placed in the center of the open-field. The experimenter left the room after placing the rat on the table. Each exploratory session lasted 30 min in which the animal was free to move around the circular table-top. At the end of the session, the rat was removed from the apparatus and returned to its home cage. This procedure was repeated on 4 successive days.

2.6. Movement tracking and manual coding

Each session was video taped by an overhead camera attached to a digital camcorder. AccuTrak software (AccuScan Instruments, Inc. Columbus, OH, 43228, USA) was used to determine the rat's position in a Cartesian coordinate system at a sampling rate of 30 Hz. The AccuTrak system automatically tracks the midline of a rat's back at the level of the forelimbs by selecting one pixel per frame of the digital computer file. The *x*- and *y*-coordinates were subjected to further analysis using a C++ computer program. This program was used to compute the cumulative distance, percent area, stops, and the quadrant and annulus preference scores. In addition, each video file was manually scored for the number of excursions made from the cue quadrant, and for head movements and direction. Behavioral measures were taken on the first and fourth days to alleviate the demand of manually scoring the animals excursions and head movements.

2.7. Behavioral measures

The following measures were used to describe the rats' exploratory movements with respect to the table and with respect to the visual cue:

(1) *Cumulative distance*. The exploratory paths of both control and hippocampal rats were reconstructed and measured for total length (cm).
(2) *Percent Area*. The surface of the table-top was divided into 900 individual squares. The percent area was derived using the following formula:

$$\text{Percent area} = \left[\frac{\#\text{ of squares transected}}{\text{total }\#\text{ of squares}}\right] \times 100.$$

(3) *Stops*. Stops were characterized by near zero speeds of <0.10 m/s. Stops were then grouped into a filter bin according to the amount of time they occupied. Bin times consisted of: 0–2, 2–10, 10–60, and 60+ s.
(4) *Quadrant and annulus preference*. The open-field was divided into four quadrants. The quadrant adjacent to the visual cue was designated as the target quadrant (T). The total time spent in quadrants A, B, and C was subtracted from the total time spent in the target quadrant. The resultant scores were added and their average derived according to the following formula: target preference score = [(T − A) + (T − B) + (T − C)]/3. In addition, the table was divided into three annuli: the inner (I), middle (M), and outer (O) annuli. In order to determine the preference score for the outer annulus, the total time spent in the inner (I) and middle (M) annuli were subtracted from the total time in the outer (O) annulus. The following formula was used to determine the average of the resultant scores: Outer annulus preference score = [(O − I) + (O − M)]/2.
(5) *Number of excursions from the cue quadrant*. An excursion, or exploratory trip, was defined as a round trip starting and ending within the outer annulus of the quadrant marked by the visual cue.
(6) *Head movements and direction*. The number of head turns that an animal made relative to the cue (90° from the cue, 180° from the cue, and 270° from the cue) was manually scored from the Days 1 and 4 video records. From this record the transitions of the head from one to another orientation and the duration of time in which an animals head was oriented toward or away from the cue quadrant was documented. Only head turns made while an animal was not walking were counted, but head turn measures reflect whole body turns as well.

2.8. Histological analysis

At the completion of the behavioral studies, animals were deeply anaesthetized and perfused intracardially with 0.9% saline, followed by 4% formalin solution. Each brain was removed from the skull and stored in 30% sucrose–formalin solution. The brains were frozen and cut coronally at 40 μm sections with a cryostat. Every fifth section was taken and stained with Cresyl violet. Measures of the amount of remaining hippocampus, compared to the hippocampus of control animals, were obtained by photographing sections ($A = -2.8$, $A = -4.3$, and $A = -5.8$) [33] and capturing the photos on a computer and then measuring the area of intact hippocampus using a graphics program (Scion Image). The area of intact hippocampus was measured from three sections.

3. Results

3.1. Histology

Representative sections from a control and a hippocampal animal are shown in Fig. 2. The NMDA lesions resulted in an extensive loss of cells in Ammon's horn and the dentate gyrus, while fibers of the fimbria-fornix appeared largely spared. Approximately 77% of the dorsal hippocampus at −2.8 mm from bregma was removed with slight sparing of the most rostral section of the hippocampus. In addition, approximately 89 and 72% of the ventral hippocampus was removed at −4.3 and −5.8 mm, respectively. Minimal sparing was observed at the most caudal sections of the hippocampus. There was only slight damage to the overlying corpus callosum and cortex at the sites of cannula penetration. The lesion extent is consistent with previous studies involving selective hippocampal damage [22,44].

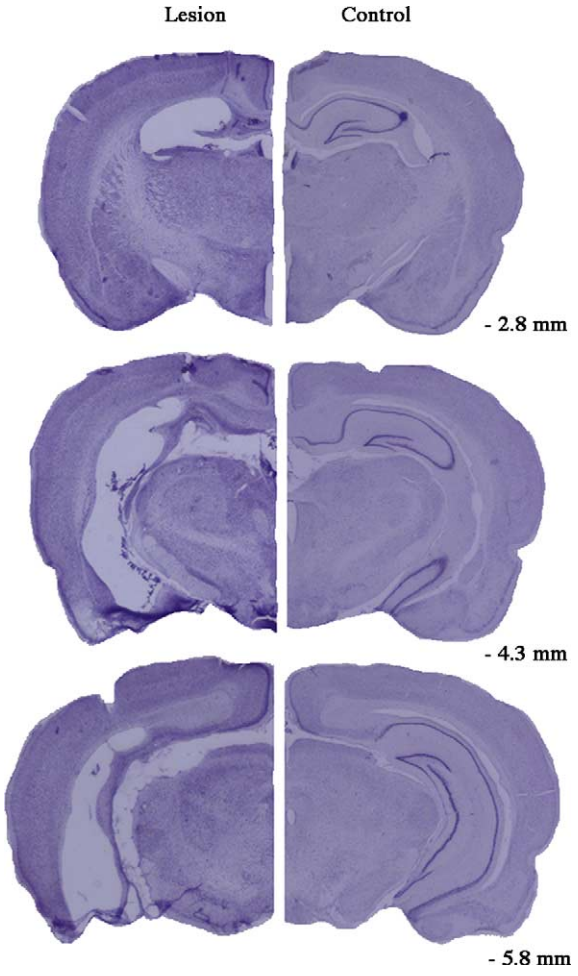

Fig. 2. Photomicrographs from three rostral-caudal levels from a rat with a NMDA (*N*-methyl D-aspartate) injection into the hippocampus (left) and from a control rat (right). All sections are defined in relation to bregma [33].

3.2. Behavioral results

Both the control and the hippocampal group were active in that they traversed wide regions of the table during the 30 min test sessions on Day 1 (Fig. 3). Activity levels of control rats decreased by Day 4. Behavior consisted of mainly locomotor progressions interrupted with periodic stops. Locomotion was mainly directed to the periphery of the table, especially the portion of the table adjacent to the cue, but also included occasional trips across the middle portions of the table. During stops the rats made many head movements that were directed to different portions of the room. Comparisons of the control group and the hippocampal group on an exhaustive array of behavioral measures showed that the two groups did not differ in their behavioral profile on the first exploratory session but by the fourth session, the control group was less active than the hippocampal group on all measures except the dwell time adjacent to the proximal cue. In contrast, the behavior of the hippocampal group did not differ between the first and the fourth test.

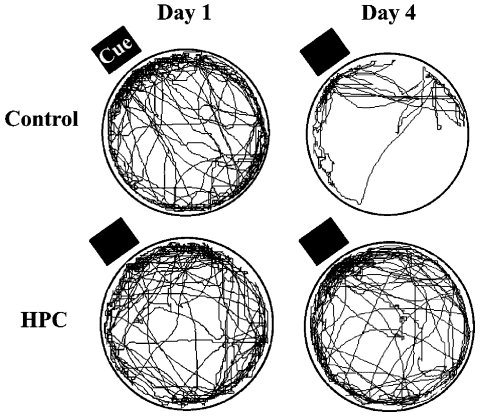

Fig. 3. Composite paths of control and hippocampal (HPC) rats on Day 1 (left) and Day 4 (right). The black square represents the location of the cue.

3.2.1. Cumulative distance

There was no difference in the distance traveled by the control group and the hippocampal group on Day 1, but by Day 4 the control group decreased their travel distance whereas the hippocampal group did not (Fig. 4A). An ANOVA on the total distance did not give a significant difference for group or day, but the group by day interaction was significant, $F(1, 10) = 5.178$, $P = 0.05$.

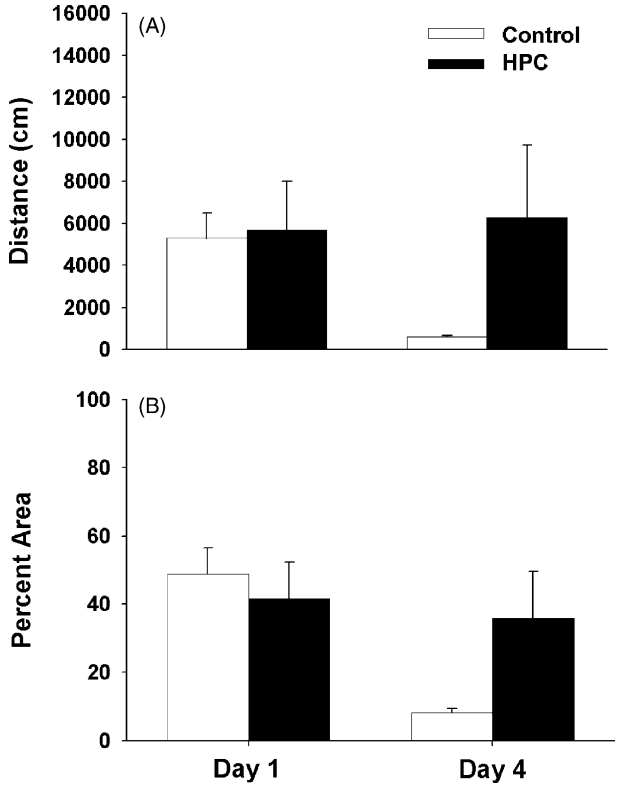

Fig. 4. (A) Distance (mean ± S.E.M.) traveled and (B) percent area (mean ± S.E.M.) of table traversed on Days 1 and 4 by control and hippocampal (HPC) rats.

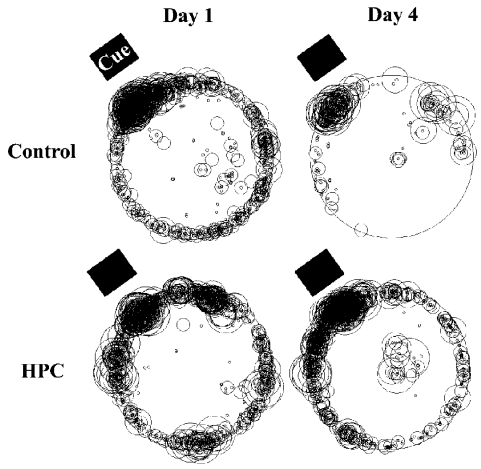

Fig. 5. Composite stops made by control and hippocampal (HPC) rats on Day 1 (left) and Day 4 (right). Stop duration is represented by the diameter of the circles: 0–2, 2–10, 10–60, and 60+ s (black square = cue location).

3.2.2. Percent area

There was no difference in the percent area of the table traversed by the control group and the hippocampal group on Day 1, but by Day 4 the control group decreased the area of the table that they visited while there was no change in the hippocampal group (Fig. 4B). An ANOVA did not give a significant group difference in percent area of the table traversed, but there was a significant effect of day, $F(1, 10) = 8.478$, $P < 0.05$, and there was a significant group by day interaction, $F(1, 10) = 4.807$, $P = 0.05$.

3.2.3. Stops

Fig. 5 illustrates the location and duration of stops performed by control and hippocampal groups during the Days 1 and 4 exploratory sessions. Note that longer duration stops were centered in the quadrant adjacent to the proximal cue for both groups of rats. One control rat, however, made long stops (set up a home base) to the right of the proximal cue rather than adjacent to the proximal cue. There was no difference in the number of stops made by the control group and the hippocampal group on Day 1, but by Day 4 the control group decreased their number of stops (Fig. 6). This was confirmed by a significant group-by-day interaction showing that the number of stops by control rats was less than that of the hippocampal group on Day 4, $F(1, 10) = 15.879$, $P < 0.005$.

3.2.4. Quadrant and annulus preference

Quadrant preference was determined in terms of the quadrant and annulus in which the most time was spent. Measurements showed that both the control and hippocampal groups preferred the quadrant containing the proximal cue (Fig. 7A) and the outer annulus (Fig. 7B) of the circular table-top. There

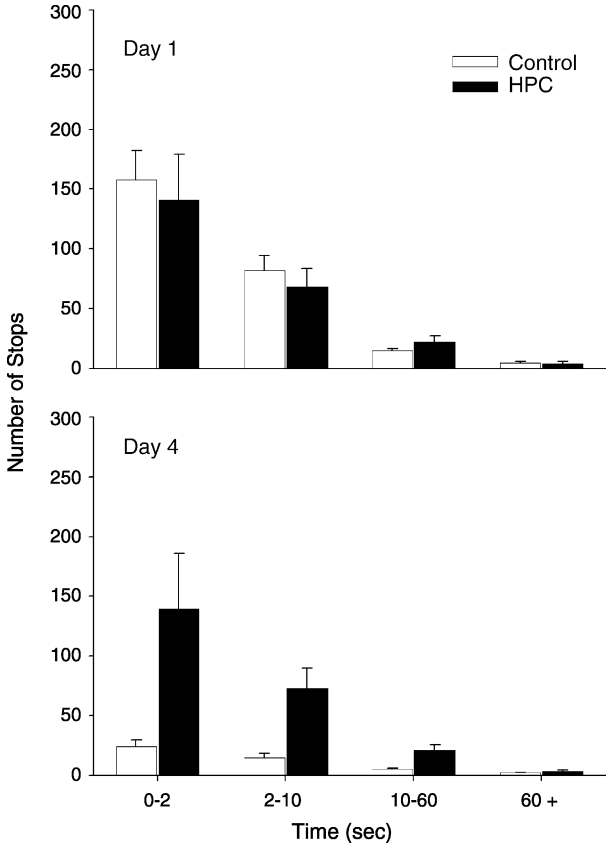

Fig. 6. The number of stops (mean ± S.E.M.) as a function of duration (0–2, 2–10, 10–60, and 60+ s) by control and hippocampal (HPC) rats on Days 1 and 4.

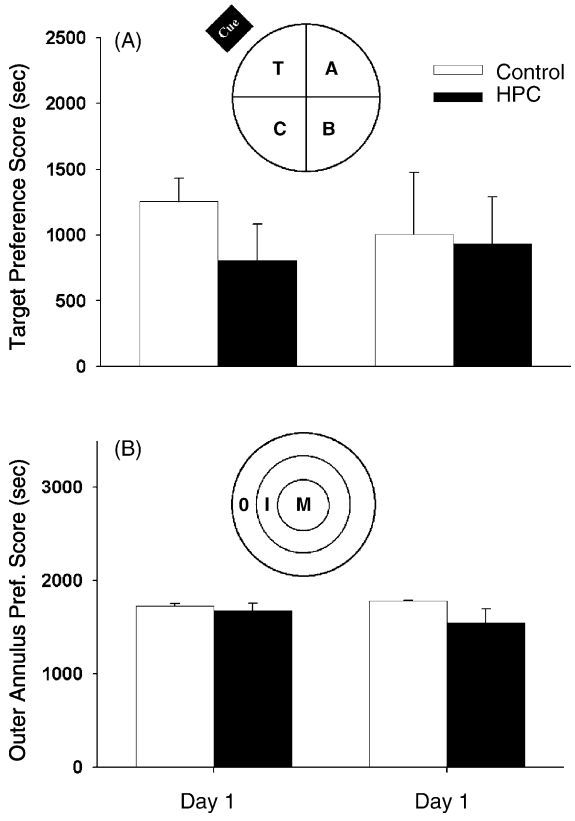

Fig. 7. (A) Target quadrant preference (mean ± S.E.M.) score and (B) outer annulus preference (mean ± S.E.M.) score on Days 1 and 4 by control and hippocampal (HPC) rats.

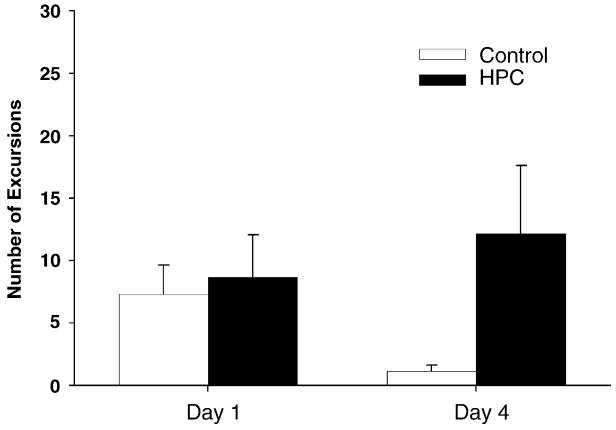

Fig. 8. The number of exploratory excursions (mean ± S.E.M.) made by control and HPC rats on Days 1 and 4.

were neither significant main effects nor an interaction on the preference measures. As noted above, however, one control rat made its long duration stops to the right of the proximal cue quadrant.

3.2.5. Number of excursions

Counts of the number of exploratory excursions made away from the outer annulus of the cue quadrant showed a similar number of excursions by both groups on Day 1, and a reduction in the number of excursion by the control group on Day 4 (Fig. 8). An ANOVA on the number of excursions gave a significant group day interaction, $F(1, 10) = 5.178$, $P < 0.05$, but no significant main effects.

3.2.6. Head movements and direction

Fig. 9 graphically illustrates the direction and transitions between head movements in the modal control and hippocampal rat on Day 1 and on Day 4. Note that directional selection is similar in the two animals but transitional movements remain high in the hippocampal animal but not the control animal on Day 4. Stimulus-sampling, estimated by counting the number of head turns made in the direction of the cue,

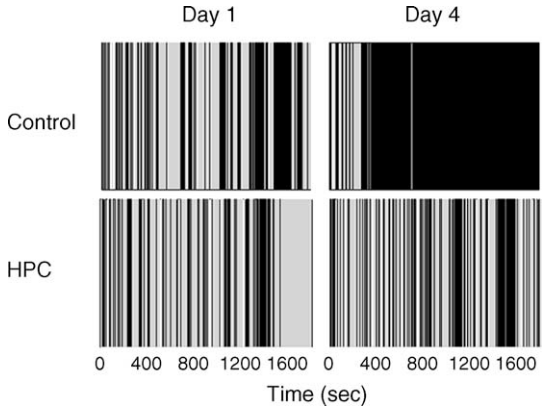

Fig. 9. Time spent oriented toward the cue (black vertical bars) or toward the rest of the open-field (gray vertical bars) by a representative control rat and hippocampal (HPC) rat on Day 1 (left) and Day 4 (right).

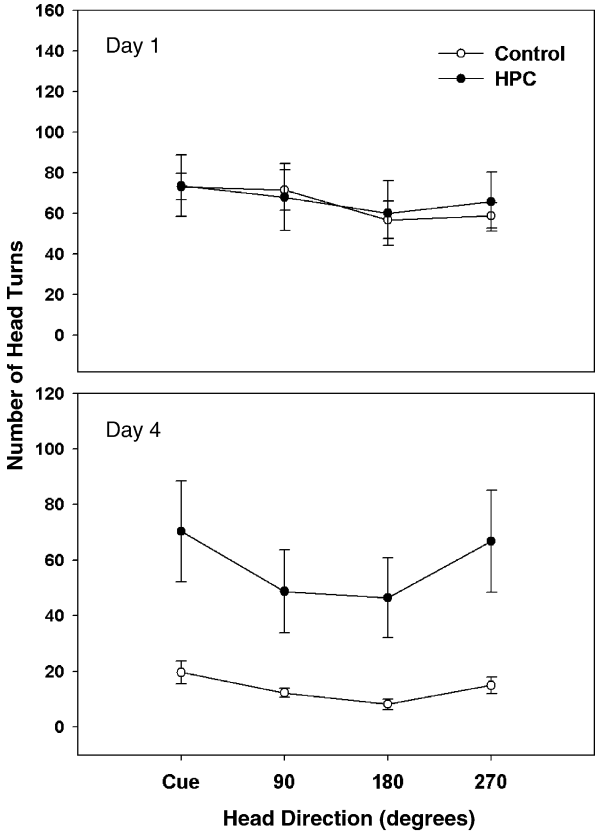

Fig. 10. The number of head turns (mean ± S.E.M.) made toward the cue, 90° from the cue, 180° from the cue, and 270° from the cue for control and hippocampal (HPC) rats on Days 1 and 4.

and 90°, 180°, and 270° away from the cue, indicated that the two groups made comparable numbers of head turns on Day 1, while the control group displayed a reduced number of head turns on Day 4 (Fig. 10). This result was confirmed by a significant group-by-day interaction, $F(1, 10) = 7.651$, $P < 0.05$.

4. Discussion

The present study examined the prediction [31] that rats with hippocampal lesions should display an absence of exploratory behavior. On 4 successive days, control and hippocampal rats were placed onto a circular table near which was a large salient cue and their movements were measured in the light of an ethogram (comprehensive description) of exploratory movements. Both control and hippocampal rats formed a home base, a location in which they made long stops, near a proximal cue, made excursions consisting of progressions, punctuated by stops, away from the home base, visited most regions of the table, and made head scans directed to different portions of the environment and to the cue. Control rats and hippocampal rats were not different on the first test day on these measures, but on the fourth day control animals were less active on all measures, except immobility near the

home base, while the behavior of hippocampal rats was unchanged. These results show that the exploratory movements of control and hippocampal rats are similar. The failure of hippocampal rats to display "habituation" across the test sessions cannot of itself indicate an absence or even an abnormality in movement organization. Nevertheless, it is consistent with previous evidence that rats with hippocampal lesions are different, especially in sustaining reactivity to salient aspects of a testing situation.

O'Keefe and Nadel's [31] conclusion that rats with hippocampal lesions display no exploratory behavior was based upon the hypothesis that the hippocampus serves as a cognitive map requiring environmental information derived from exploration. The conclusion was supported by a literature review that was interpreted as showing that: (1) hippocampal rats are unresponsive to unfamiliarity, (2) explore novel items less than control animals, (3) are hyperactive, and (4) and do not spontaneously alternate. Whereas the hypothesis that the hippocampus serves as a cognitive map has received extensive examination [23,35], there has not been similar interest in the predication that the hippocampus is required for exploration. Furthermore, only recently has an objective ethogram of rat exploratory behavior been developed [2,7,16,17], which could allow a direct assessment of the behavioral profile of hippocampal rats in novel situations. The present study took advantage of this ethogram to reassess the idea that exploratory behavior is absent in rats with hippocampal lesions.

Control rats were compared to rats that received NMDA neurotoxic lesions of the hippocampus, which remove most of the pyramidal cells of the CA regions of Ammon's horn and the granule cells of the dentate gyrus [21]. The rats were placed on a large open table. A salient cue was placed near the table as a landmark for home base formation. Both control and hippocampal rats spent a majority of their time in the quadrant adjacent to the landmark and made excursions and returns to the quadrant adjacent to the cue. Additionally, when they were relatively immobile (not walking) it was in the quadrant adjacent to the landmark. This pattern of behavior suggests that this quadrant of the table becomes their home base [2,16,17].

On the measures of exploratory movements obtained from the first test, control and hippocampal rats were surprisingly similar. Similar behavior included the distance that they traveled, area of the maze that was traversed, the time spent near the cue, number of stops and stopping time, and number of head turns directed to the room and to the cue.

Despite the overall pattern of the main effects of the behavioral measures, there were interesting individual differences in the behavior of the rats. One control rat established a home base about one quadrant away from the proximal cue. We have observed that in the absence of a salient proximal cue, rats will establish a home base adjacent to a distinctive room cue [2,16,17], and this animal established its home base proximal to a book case. In all other respects, this animal's behavior was similar to that of the other control rats. One hippocampal animal also failed to engage in any locomotor activity in any test situation, and rather remained close to the proximal cue. It is possible that for this animal the cue was so dominant as to suppress locomotor activity, as occurs when an animal is given a refuge [44]. Future research could examine the significance of the salience of ambient cues to control and hippocampal rats.

In so far as behavioral measures used in this study indicate exploratory behavior, these results do not support the hypothesis that hippocampal rats do not explore and additionally they are inconsistent with most of the evidence upon which that hypothesis was based. On the first test day the hippocampal rats made the same movements used by control rats. They made many alternating head movements directed toward and away from the cue, movements that suggest they evaluated room cues [8,12,18,25]. They walked to novel regions of the table and they visited as many regions of the table as did the control rats. In order to visit all regions of the table, rats had to make many trips away from their preferred "home base" along novel routes. Additionally, the hippocampal rats were no more active than were the control rats.

These results are consistent with many other studies that show that rats with hippocampal lesions are responsive as control rats to both proximal cues that serve as landmarks and to distal cues that mark the rats' own position or the position of objects in the room. For example hippocampal rats do respond to ambient cues, and display both instrumental [10,14,46] and latent [16,48] learning in response to ambient cues. Furthermore, rats with hippocampal lesions do explore novel objects [29,30,37], and respond to changes in the arrangement of those objects [9,28,40]. The contribution of the present study is the finding that in response to the configuration of room cues provided by the novel test situation, both the control and hippocampal rats formed home bases near a salient landmark, made trips characterized by progressions and stops in relation to the home base, and examined the test room equally using both head movements and locomotion. In short, the ethogram of both groups was similar.

What was distinctive about the behavior of the hippocampal rats in the present study was that they displayed an almost unchanged pattern of behavior after a number of successive exposures to the table, whereas the control rats showed reductions in the incidence of all behaviors except time spent immobile in the region of the table near the cue. The persistent activity of the hippocampal rats cannot be taken as an indication that hippocampal rats do not explore, however. Rather, because their pattern of behavior on the fourth day resembles that of both groups on the first day, it could be argued that they display hyperexploratory behavior. Such behavioral persistence is symptomatic of hippocampal rats in many test situations [31, Table A14]. For example, hippocampal rats display faster running speeds in maze tests [5], show higher peaks of activity in tests of circadian activity [19,51], are more responsive in tests of amphetamine induced locomotion [52,53], schedule induced behavior [4,38,39],

adjunctive behavior [26], and to administration of electrical brain stimulation [24].

Although the exploratory ethogram used by hippocampal rats is not obviously abnormal in terms of the expression of movements, it is nevertheless relevant to consider whether the animals profit from their exploratory experience. Using a similar experimental design to that used here, Hines [16] and Hines and Whishaw [17] have found that when the visual cue was removed after control and hippocampal rats were exposed to the test apparatus for four days, both groups established their home base in the same location. This result demonstrates that hippocampal animals had learned the location of the home base relative to surrounding room cues even though not required to do so. That is, they profited sufficiently from their exploratory experience to learn the location of their home base in relation to other room cues. This conclusion is consistent with other work showing that hippocampal rats can learn about places in their environment even when not required to do so [3,46,48].

Even though hippocampal rats display hyperresponsivity to many test situations [31, Table A14], this aspect of their behavior is not invariant. In an exploratory test situation very similar to that used in the present study, except that the rats were provided with a refuge box from which to explore, no differences in activity were observed over a number of test days in control versus hippocampal rats because neither group made many excursions from the refuge [44]. Thus, it is not clear whether rats in "exploratory" tests situations, such as that described here, are exploring as opposed to attempting to find an exit from the test situation. It is interesting in this respect that the hippocampus has many cortisone receptors, which have been implicated in responses made to stress-inducing stimuli [36]. Thus, it is possible that control and hippocampal animals display differential responses to "stress-inducing" features of certain testing situations [13], as opposed to displaying differences in habituation of "exploratory" behavior. This idea could be systematically examined in future work.

In conclusion, in considering the issue of whether hippocampal rats explore, it is important to note that what constitutes exploration is inferential [47]. The present findings only show that hippocampal rats display a behavioral pattern that is very similar to that of control animals in an open field test. This pattern of behavior has been hypothesized to be exploratory in nature. Thus, if the test and behavioral measures used here define exploration, the results do not confirm the prediction that hippocampal lesions abolish exploratory behavior. This is not to say that hippocampal rats do not display behaviors that are different from those of control rats. In the present study, they displayed sustained "exploratory" behavior across repeated tests. They also tended to spend more time near the edges of the table than did control rats [44]. In other studies, hippocampal rats have been shown not to display the dead reckoning homing of control rats [44,50]. In sum, although the behavioral measures used in the present study do not support the prediction that all exploratory behavior in an open field test is abolished by hippocampal lesions, they nevertheless raise the interesting question of what contribution the hippocampus makes to time-dependent features of testing [45].

Acknowledgments

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References

[1] Bardgett ME, Jacobs PS, Jackson JL, Csernansky JG. Kainic acid lesions enhance locomotor responses to novelty, saline, amphetamine, and MK-801. Behav Brain Res 1997;84:47–55.
[2] Clark BJ, Hines DJ, Hamilton DA, Whishaw IQ. Intact organization of exploratory behaviour in rats with hippocampal lesions? Soc Neurosci 2004:434.8.
[3] Day LB, Weisand M, Sutherland RJ, Schallert T. The hippocampus is not necessary for a place response but may be necessary for pliancy. Behav Neurosci 1999;113:914–24.
[4] Devenport LD. Schedule-induced polydipsia in rats: adrenocortical and hippocampal modulation. J Comp Physiol Psychol 1978; 92:651–60.
[5] Diaz-Granados JL, Greene PL, Amsel A. Selective activity enhancement and persistence in weanling rats after hippocampal X-irradiation in infancy: possible relevance for ADHD. Behav Neural Biol 1994;61:251–9.
[6] Drai D, Golani I. SEE: a tool for the visualization and analysis of rodent exploratory behavior. Neurosci Biobehav Rev 2001;25:409–26.
[7] Eilam D, Golani I. Home base behavior of rats (*Rattus norvegicus*) exploring a novel environment. Behav Brain Res 1989;34:199–211.
[8] Ellard CG, Goodale MA, Timney B. Distance estimation in the Mongolian gerbil: the role of dynamic depth cues. Behav Brain Res 1984;14:29–39.
[9] Ennaceur A, Aggleton JP. Spontaneous recognition of object configurations in rats: effects of fornix lesions. Exp Brain Res 1994;100: 85–92.
[10] Gaffan EA, Bannerman DM, Healey AN. Learning associations between places and visual cues without learning to navigate: neither fornix nor entorhinal cortex is required. Hippocampus 2003;13: 445–60.
[11] Golani I, Benjamini Y, Eilam D. Stopping behavior: constraints on exploration in rats (*Rattus norvegicus*). Behav Brain Res 1993;53: 21–33.
[12] Goodale MA, Ellard CG, Booth L. The role of image size and retinal motion in the computation of absolute distance by the Mongolian gerbil (*Meriones unguiculatus*). Vis Res 1990;30:399–413.
[13] Gray JA. The neuropsychology of anxiety. Oxford, UK: Clarendon Press; 1982.
[14] Hannesson DK, Skelton RW. Recovery of spatial performance in the Morris water maze following bilateral transection of the fimbria/fornix in rats. Behav Brain Res 1998;90:35–56.
[15] Harley CW, Martin GM. Open field motor patterns and object marking, but not object sniffing, are altered by ibotenate lesions of the hippocampus. Neurobiol Learn Mem 1999;72:202–14.
[16] Hines DJ. The role of cues and hippocampus in home base behavior. In: Masters dissertation under the supervision of Ian Q. Whishaw. Lethbridge, AB: University of Lethbridge; 2004.
[17] Hines DJ, Whishaw IQ. Development of a virtual home base influenced by cues in control and hippocampectomized rats. Soc Neurosci 2003:938.7.

[18] Hu D, Amsel A. A simple test of the vicarious trial-and-error hypothesis of hippocampal function. Proc Natl Acad Sci USA 1995;92:5506–9.
[19] Jarrard LE. Behavior of hippocampal lesioned rats in home cage and novel situations. Physiol Behav 1968;3:65–79.
[20] Jarrard LE. On the role of the hippocampus in learning and memory in the rat. Behav Neural Biol 1993;60:9–26.
[21] Jarrard LE. Use of excitotoxins to lesion the hippocampus: update. Hippocampus 2002;12:405–14.
[22] Jarrard LE, Meldrum BS. Selective excitotoxic pathology in the rat hippocampus. Neuropathol Appl Neurobiol 1993;19:381–9.
[23] Jeffery KJ. The neurobiology of spatial behaviour. Oxford, UK: Oxford University Press; 2003.
[24] Kelley SP, Mittleman G. Effects of hippocampal damage on reward threshold and response rate during self-stimulation of the ventral tegmental area in the rat. Behav Brain Res 1999;99:133–41.
[25] Legg CR, Lambert S. Distance estimation in the hooded rat: experimental evidence for the role of motion cues. Behav Brain Res 1990;41:11–20.
[26] Mittleman G, Whishaw IQ, Jones GH, Koch M, Robbins TW. Cortical, hippocampal, and striatal mediation of schedule-induced behaviors. Behav Neurosci 1990;104:399–409.
[27] Morris RGM. Neural subsystems of exploration in rats. In: Archer J, Birke LIA, editors. Exploration in animals and humans. Berkshire, England: Van Nostrand Reinhold (UK); 1983.
[28] Moses SN, Sutherland RJ, McDonald RJ. Differential involvement of amygdala and hippocampus in responding to novel objects and contexts. Brain Res Bull 2002;15:517–27.
[29] Mumby DG. Perspectives on object-recognition memory following hippocampal damage: lessons from studies in rats. Behav Brain Res 2001;127:159–81.
[30] Mumby DG, Gaskin S, Glenn MJ, Schramek TE, Lehmann H. Hippocampal damage and exploratory preferences in rats: memory for objects, places, and contexts. Lear Mem 2002;9:49–57.
[31] O'Keefe J, Nadel L. The hippocampus as a cognitive map. Oxford, UK: Clarendon Press; 1978.
[32] Osborne B, Seggie J. Behavioral, corticosterone, and prolactin responses to novel environment in rats with fornix transactions. J Comp Physiol Psychol 1980;94:536–46.
[33] Paxinos G, Watson C. The rat brain in stereotaxic coordinates. New York, NY: Academic Press; 1998.
[34] Poucet B. Spatial cognitive maps in animals: new hypotheses on their structure and neural mechanisms. Psychol Rev 1993;100:163–82.
[35] Redish AD. Beyond the cognitive map: from place cells to episodic memory. Cambridge Mass: MIT Press; 1999.
[36] Sapolsky RM. Stress and plasticity in the limbic system. Neurochem Res 2003;28:1735–42.
[37] Save E, Poucet B, Foreman N, Buhot MC. Object exploration and reactions to spatial and nonspatial changes in hooded rats following damage to parietal cortex or hippocampal formation. Behav Neurosci 1992;106:447–56.
[38] Schmelzeis MC, Mittleman G. The hippocampus and reward: effects of hippocampal lesions on progressive-ratio responding. Behav Neurosci 1996;110:1049–66.
[39] Shull RN, Holloway FA. Behavioral effects of hippocampal system lesions on rats in an operant paradigm. Brain Res Bull 1985;14:315–22.
[40] Sutherland RJ. The navigating hippocampus: an individual medley of movement, space and memory. In: Buzsaki G, Vanderwolf CH, editors. Electrical activity of the archicortex. Budapest: Ajadenuau Juadi; 1985.
[41] Tchernichovski O, Benjamini Y, Golani I. The dynamics of long-term exploration in the rat. Part I. The dynamics of long-term exploration in the rat. Part I. A phase-plane analysis of the relationship between location and velocity. Biol Cybern 1998;78:423–32.
[42] Thinus-Blanc C, Save E, Buhot MC, Poucet B. The hippocampus, exploratory activity, and spatial memory. In: Paillard J, editor. Brain and space. Oxford: Oxford University Press; 1991.
[43] Wallace DG, Hines DJ, Whishaw IQ. Quantification of a single exploratory trip reveals hippocampal formation mediated dead reckoning. J Neurosci Methods 2002;113:131–45.
[44] Wallace DG, Whishaw IQ. NMDA lesions of Ammon's horn and the dentate gyrus disrupt the direct and temporally paced homing displayed by rats exploring a novel environment: evidence for a role of the hippocampus in dead reckoning. Eur J Neurosci 2003;18:513–23.
[45] Wallace DG, Whishaw IQ. Dead reckoning. In: Ian Q, Whishaw, Bryan Kolb, editors. The behavior of the laboratory rat: a handbook with tests. Oxford: Oxford University Press; 2004.
[46] Whishaw IQ. Place learning in hippocampal rats and the path integration hypothesis. Neurosci Biobehav Rev 1998;22:209–20.
[47] Whishaw IQ, Brooks BL. Calibrating space: exploration is important for allothetic and idiothetic navigation. Hippocampus 1999;9:659–67.
[48] Whishaw IQ, Cassel JC, Jarrard LE. Rats with fimbria-fornix lesions display a place response in a swimming pool: a dissociation between getting there and knowing where. J Neurosci 1995;15:5779–88.
[49] Whishaw IQ, Cassal JC, Majchrzak M. "Short-stops" in rats with fimbria-fornix lesions: evidence for change in the mobility gradient. Hippocampus 1994;4:577–82.
[50] Whishaw IQ, Hines DJ, Wallace DG. Dead reckoning (path integration) requires the hippocampal formation: evidence from spontaneous exploration and spatial learning tasks in light (allothetic) and dark (idiothetic) tests. Behav Brain Res 2001;127:49–69.
[51] Whishaw IQ, Jarrard LE. Similarities vs. differences in place learning and circadian activity in rats after fimbria-fornix section or ibotenate removal of hippocampal cells. Hippocampus 1995;5:595–604.
[52] Whishaw IQ, Mittleman G. Hippocampal modulation of nucleus accumbens: behavioral evidence from amphetamine-induced activity profiles. Behav Neural Biol 1991;55:289–306.
[53] Wilkinson LS, Mittleman G, Torres E, Humby T, Hall FS, Robbins TW. Enhancement of amphetamine-induced locomotor activity and dopamine release in nucleus accumbens following excitotoxic lesions of the hippocampus. Behav Brain Res 1993;55:143–50.