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Preserved spatial memory after hippocampal lesions: effects of extensive experience in a complex environment

Gordon Winocur[1–3], Morris Moscovitch[2–4], Stuart Fogel[3], R Shayna Rosenbaum[1] & Melanie Sekeres[3]

Damage to the hippocampus typically impairs spatial learning and memory in animals, but humans with hippocampal lesions retain spatial memories of premorbidly familiar environments. We showed that, like humans, normal rats reared in a complex environment and then given hippocampal lesions retained allocentric spatial memory for that environment. These results, which ruled out dependency on single cues, landmarks or specific routes, suggest that extensive premorbid experience leads to spatial representations that are independent of the hippocampus.

Converging evidence from lesion, electrophysiological and neuroimaging studies implicates the hippocampus in spatial memory and navigation[1–4]. Less is known about the effects of hippocampal damage on premorbidly acquired spatial memories. In animals, hippocampal lesions typically lead to memory loss, extending as far back as 9 months preoperatively[4,5]. In contrast, patients with bilateral hippocampal lesions retain accurate allocentric spatial representations of familiar environments[6,7].

A crucial difference between the studies is that the humans had extensive experience with the environment before hippocampal damage, whereas the animals did not. To model the human condition, we reared rats in a complex environment or 'village' and studied the effects of hippocampal lesions on allocentric spatial memory (**Fig. 1a**).

The village ($1.2 \times 1.2 \times 1.2$ m) was located in the center of a room with standard laboratory furniture (for example, desks and book shelves) and pictures on the walls. The room was dimly and uniformly illuminated by overhead lighting. The village contained two levels, with interconnected walkways within and between the levels. Two walkways leading to the lower levels were situated across from the entrance to the reward compartments in the northeast and northwest corners. The walls and ceiling were made of wire mesh, and the walkways of aluminum sheet metal. The upper level, also constructed of sheet metal, consisted of a gathering area in the middle of the upper level with four walls each containing a central opening. This area served as a start box for training and test trials. A compartment containing food (southeast corner), water (northwest corner), an assortment of toys (northeast corner) or a female rat (southwest corner) was attached to each of four

corners on the lower level (**Fig. 1a**). The compartment containing the female rat was separated from the village by a wire mesh screen, whereas the other compartments could be accessed freely.

Preoperative training consisted of five daily trials in which rats were placed individually in the start area and allowed to find the reward compartment. On each trial, the rat was forced to enter the village through a different doorway, thereby ensuring the use of different routes to the reward. The floors and walkways of the village were divided into imaginary zones demarcated by intersections, from which the rat could move closer to the reward compartment or farther from it. A rat was considered to have made an error when it arrived at a choice point and turned away from the reward compartment (**Supplementary Methods**, online). After each training session, the rats were returned to individual cages where they had access to food or water for 1 h.

Three-month-old male Long-Evans rats were assigned to Rearing + Training (RT) and Training-Only (TO) conditions. For 3 months, rats in the RT condition spent 8 h per day in groups of five or six in the village during their high-activity cycle. The rats were allowed to explore the entire village, with access to various reward sites, including food and water, which were always available at the same locations. After each session, the rats were returned to individual cages, where they were deprived of food and water. TO rats were on the same deprivation schedule, but they remained in individual cages except for brief daily periods during which they were handled and given food and water.

After this three-month period, RT and TO rats were placed on a 23-h food or water deprivation schedule. Preoperative training to find the appropriate reward compartment began 1 week later. All rewards were available in the compartments where they had been found during rearing. Rats required 9.86 d (RT) and 9.21 d (TO) to reach a criterion of 80% errorless trials over 2 d, $t < 1$. There were no differences between rats motivated to find food or water on these or subsequent tests, so this variable was collapsed into a single reward condition.

Within 48 h of reaching criterion, rats received bilateral NMDA hippocampal lesions or a surgical control procedure. At this time, surgery was also done on a third group (Postoperative testing–Only (PO)) with no previous exposure to the village. Fifty-one rats survived and met inclusion criteria. Twenty-seven rats had an acceptable hippocampal lesion, at least 50% damage to dorsal and ventral regions (**Fig. 2**), and completed the study. There was no relationship between extent of lesion and performance (**Supplementary Results**, online). Seven days postoperatively, rats were deprived of food or water, and their ability to find the reward was assessed. Testing procedures were the same as in preoperative training in the RT and TO conditions, except that they lasted 10 d.

Rats with hippocampal lesions in the RT condition found the appropriate reward compartment efficiently from the beginning, and made no more errors than controls (**Fig. 1b**). This was confirmed by a significant Lesion × Rearing interaction ($F_{2,53} = 3.17$, $P = 0.050$). Hippocampal and

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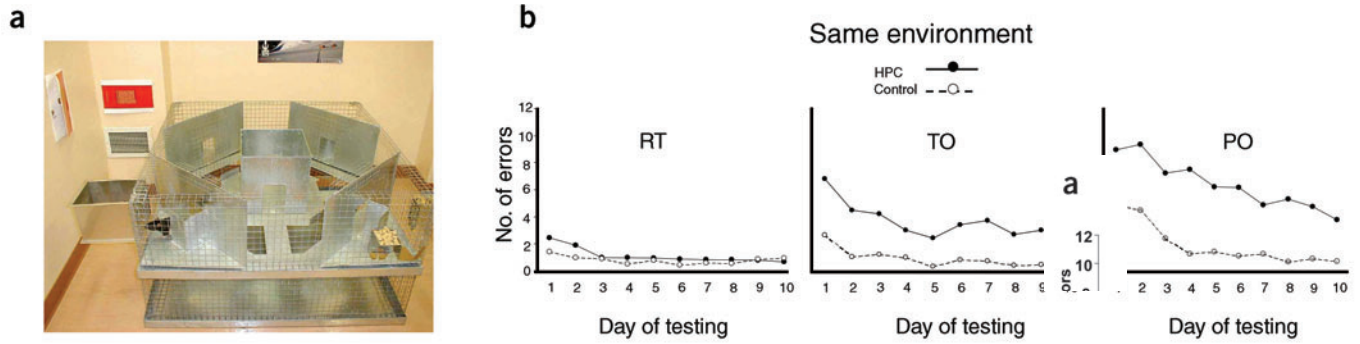
Figure 1 The village and postoperative test results for the first series of experiments. (**a**) The village apparatus. (**b**) Performance of hippocampal (HPC) and control groups in the three rearing conditions, tested in the familiar environment. Error bars indicate s.e.m. RT: Rearing + Training (HPC, $n = 8$; control, $n = 6$). TO, Training-Only (HPC, $n = 10$; control, $n = 9$). PO, Postoperative testing–Only (HPC, $n = 9$; Control, $n = 9$). This study was approved by the Trent University Animal Care Committee, and the rats were cared for in accordance with the ethical standards of that committee.

control RT animals did not differ significantly ($F < 1$), but there were significant group differences in TO ($F_{1,53} = 5.00, P = 0.030$) and PO ($F_{1,53} = 13.22, P < 0.001$) animals. Rats with more experience in the environment, including those with lesions, performed well initially; those with less experience started poorly and then improved (Rearing × Days interaction, $F_{2,477} = 7.92, P < 0.001$).

To ensure that rats were relying on allocentric spatial cues, we did experiments on a subset of hippocampal and control rats from the RT condition (**Supplementary Results**). We first moved the village to a new room with entirely different cues and tested the animals as before. The reward compartments remained in the same relationship to the village and to each other. The room change led to severe impairment in the hippocampal group ($F_{1,6} = 19.10, P = 0.005$), indicating that the rats had used distal cues rather than local village cues to navigate in the familiar environment (**Fig. 3a**). Hippocampal and control groups were similarly affected by the change, as shown by Day 1, Trial 1 responses. Both groups showed substantial increases in average errors (hippocampal, 7; control, 5), over the last test in the original environment. Only one animal in each group selected the correct reward compartment on the first trial, indicating that, initially, both groups responded randomly in the new environment. The overall Group × Days interaction was not significant ($F_{9,54} = 1.51, P = 0.17$), but by the seventh day of testing, the lesioned rats had improved substantially and performed as well as controls. Both groups were impaired after room change, relative to the original test, but only the control group showed some savings compared with their performance in the preoperative training condition.

If successful postoperative navigation depended on configural, allocentric representations, then some of the environment could be altered without affecting performance. Thus, we returned the rats to the initial environment, but removed most of the distal cues (for example, pictures and chairs) and introduced new ones, while retaining elements of the original array in the same relationship to each other (**Supplementary Methods**). All rats with hippocampal lesions continued to perform well (**Fig. 3b**; $F < 1$), indicating that performance in the original condition was attributable to a minimal configuration of cues, including room geometry, and their relationships to the reward compartments.

To determine whether the rats could learn new spatial relationships between the village and the familiar, external environment, we rotated the village and the attached compartments by 180° relative to the distal cues and tested the rats as before. Whereas controls learned quickly, a significant Group × Days interaction ($F_{9,54} = 2.07, P = 0.048$) indicated that the hippocampal group was severely impaired in locating the correct compartment (**Fig. 3c**). This deficit was related to a strong tendency in lesioned, but not control, rats to continue visiting the compartment's original location, especially at the beginning of each test trial (**Supplementary Results**). Thus, both groups retained considerable spatial memory of the familiar environment, but rats with hippocampal lesions could not assimilate the changed location of the compartment within their retained knowledge. This deficit was also apparent when we compared rats' preoperative performance with their scores on the village rotation (as well as the room-change test). Although both groups' performance declined postoperatively, only the control group showed savings relative to preoperative training (**Supplementary Results**).

Two additional experiments ruled out the possibility that rats relied on sensory cues within the village or olfactory cues outside the village. Rotating the floor of the village by 180°, while holding constant the location of the compartments, had no effect on performance ($F < 1$), confirming that neither lesioned nor control rats depended on sensory cues within the village (**Supplementary Results**, online). Rendering rats anosmic with zinc sulfate nasal treatment did not affect either group's ability to locate the reward compartment (**Fig. 3c**; all t values < 1.0), indicating that navigation was not guided by olfactory cues (**Supplementary Methods** and **Supplementary Results**).

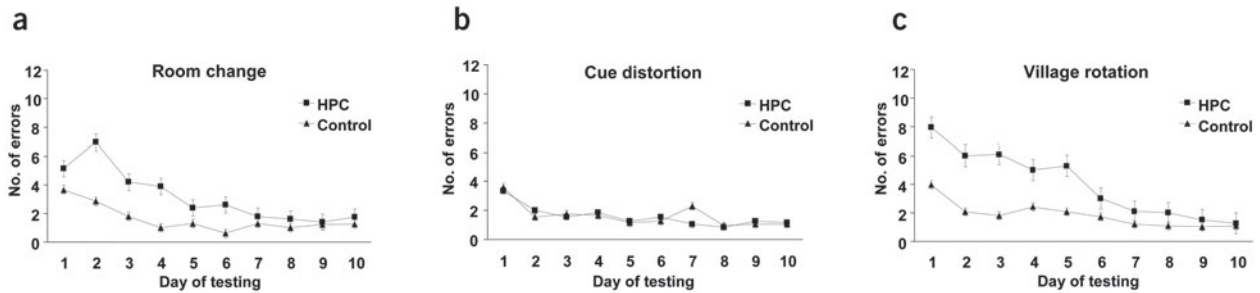**Figure 2** Maximal and minimal extents of hippocampal lesions.

Figure 3 Test results for second series of experiments. (**a**–**c**) Performance of RT hippocampal (HPC; $n = 4$) and control ($n = 4$) groups, tested in different environmental conditions.

Efficient performance of the hippocampal rats in the RT condition could be related to preservation of spatial learning abilities, rather than spatial memories. We ruled this out by finding that hippocampal, RT rats were severely impaired when tested in a new room on the radial arm maze, a test of spatial learning and memory[8] (**Supplementary Methods**; $F_{1,6} = 25.75$, $P = 0.002$, **Supplementary Results**).

The results provide strong evidence that a map-like or allocentric spatial representation of a complex environment, gained through extensive preoperative experience, can survive hippocampal damage and support navigation. Because some hippocampal tissue was spared, we cannot rule out the possibility that the residual tissue mediated the spared performance. We consider this highly unlikely because there was no correlation between performance and lesion size, and no difference in performance between rats with more than 80% of the hippocampus removed and those with smaller lesions in any of the conditions (**Supplementary Results**). These results show a notable parallel between humans and rats with hippocampal lesions in the retention of spatial memories of a familiar environment, and point to similar underlying mechanisms.

There was a noteworthy finding in the room-change and village-rotation conditions, where the hippocampal group, despite their initial impairment, eventually improved to the level of controls. These findings are analogous to patterns observed in the amnesic patients H.M. and K.C., both of whom have extensive hippocampal damage but eventually learned to navigate in new environments as they became increasingly familiar[7,9]. Future work will determine whether the representations acquired with difficulty after hippocampal lesions resemble those acquired before the hippocampus was damaged.

The distinction between premorbid spatial memories acquired through extensive experience and newly acquired spatial memories has received scant attention in theories of hippocampal function. Insights into this issue come from recent considerations of anterograde and retrograde amnesia after hippocampal lesions in humans and rats[4]. In humans, old semantic memories (such as general knowledge concerning facts, events and public figures) are retained normally after hippocampal lesions, whereas postmorbid semantic memories are acquired in adulthood with difficulty[9–11]. By analogy, the preserved spatial memories may also be considered 'semantic' in the sense that they represent the gist or core of spatial knowledge without the extraneous details that accompany its acquisition. The core of a well-established spatial memory, therefore, may consist of the bare topographical elements of the environment such as the geometry of a room or a small array of specific landmarks: a schematic cognitive map that can support navigation and that is represented in extrahippocampal structures (for example, the superior-medial parietal, posterior cingulate, retrosplenial, frontal and parahippocampal cortices, the latter sometimes bordering on the hippocampus[12,13]). This indeed is what our experiments showed: changing details had little effect on performance, whereas altering the topography entirely led to severe impairment.

It has yet to be determined how experience alters both the nature of the spatial representation and their neural substrates. One possibility is that spatial memories are laid down independently in the hippocampus and in extrahippocampal structures, with the hippocampus reinforcing the weaker connections until this structure is no longer needed[6,10]. Another alternative is that the allocentric representations in the hippocampus may be different in nature from those in extrahippocampal structures[4]. Whereas hippocampal representations may code information about details of the environment in an allocentric framework and details of the events that occurred there[3], extrahippocampal representations may simply abstract coarse information that is sufficient to support navigation but not sufficient to support a rich re-experiencing of the environment (in humans) or detailed recognition (in rats)[7]. The mechanisms needed to transform spatial memories from detailed to schematic representations have yet to be elucidated, though conscious recollection or rehearsal combined with offline reactivation of hippocampal-cortical networks may be involved[14,15].

Note: Supplementary information is available on the Nature Neuroscience website.

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Erratum: Preserved spatial memory after hippocampal lesions: effects of extensive experience in a complex environment

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In the published version of this article, the y-axis of the right panel in Figure 1b on page 274 was obscured by a fragment of another graphic. The corrected figure is reproduced below.
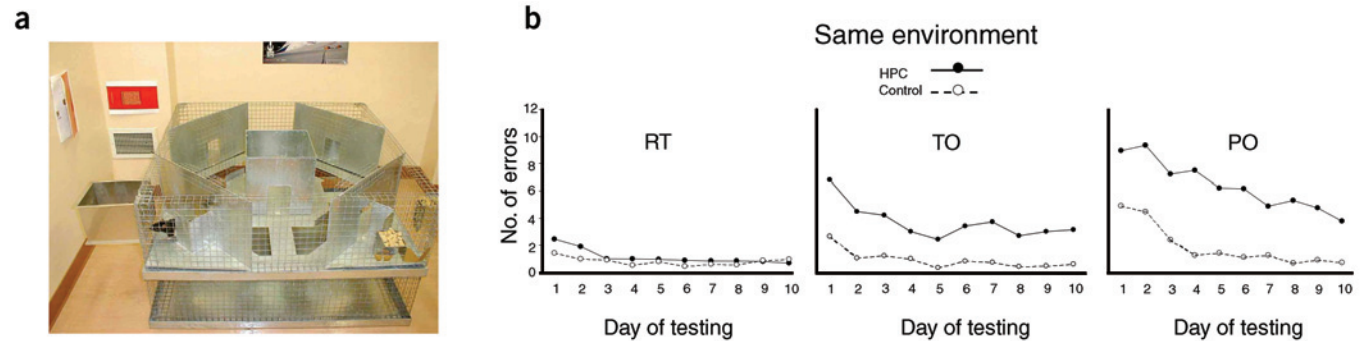
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