The hippocampus - from memory, to map, to memory map

Kate J Jeffery*

Institute of Behavioural Neuroscience, Department of Experimental Psychology, University College London, 26 Bedford Way, London WC1H 0AP Tel: +44 7753 305526 email k.jeffery@ucl.ac.uk twitter @katejjeffery

*Correspondence: k.jeffery@ucl.ac.uk (K.J. Jeffery).

Keywords spatial learning; memory; hippocampus; maze; rat; place cells

Abstract

The hippocampus is one of the brain's great mysteries. Historically, theories of its function included emotion, response inhibition, general memory, and spatial perception/learning, with memory vs. space emerging as a particular focus of more recent debates. A 1978 paper by Olton and colleagues (Brain Res. 1978 Jan 13;139(2):295-308) captured this dichotomy by exploiting their newly developed radial maze task to reveal a profound deficit in the ability of hippocampally lesioned rats to execute a spatial memory task. This finding supported the emerging spatial map theory of hippocampal function, and helped pave the way for the subsequent uncovering of an entire brain system linking space and memory.

Main text

In the late 1950s, the neuroscience world was tilted on its axis by a clinical case report that led to profound changes in thinking about memory. Scoville and Milner published a report of a neurosurgical patient, Henry Molaison (known for many years as HM), who had developed a deep and permanent anterograde amnesia following therapeutic bilateral temporal lobe resection [1]. They described his condition as follows:

> “After operation this young man could no longer recognize the hospital staff nor find his way to the bathroom, and he seemed to recall nothing of the day-to-day events of his hospital life. There was also a partial retrograde amnesia, inasmuch as he did not remember the death of a favourite uncle three years previously, nor anything of the period in hospital, yet could recall some trivial events that had occurred just before his admission to the hospital. His early memories were apparently vivid and intact”.

Until then, neuroscientists had thought that memory is probably distributed across the brain: this report seemed to suggest that it might be more modular. In particular, Scoville and Milner concluded “… that the anterior hippocampus and hippocampal gyrus, either separately or together, are critically concerned in the retention of current experience.”

From memory to map

This finding of a possible specific memory module in the brain electrified the field, and neuroscientists immediately turned to animal experiments to try to find out what the hippocampus might be doing for memory, and how. It is interesting to look back on the literature of the 1960s and 1970s and see the growing puzzlement over the data emerging from hippocampal lesion studies, in both monkeys and rats. Lesion techniques at that time were blunter instruments than today, with the use of surgical removal, aspiration and radiofrequency coagulation. Such methods produce large holes in the brain and also destroy fibres of passage, and we now know that many of the early findings from hippocampal lesion studies were side-effects of extra-hippocampal damage. Even so, replications of HM’s surgery in either monkeys or rodents were, in the words of the behavioural neuroscientist Helen Mahut, “disappointing”, with rodents showing “a complex profile of post-operative behavioural changes, none of which reflect a selective memory deficit”, and monkey studies also revealing consistently negative results [2] with preserved object discrimination and object reversal learning. However, Mahut was seeing in her own work the glimmerings of an answer as to what the hippocampus might be doing in animals. In a series of studies of monkeys with medial temporal lobe ablations, including hippocampus and sometimes amygdala, she found a consistent impairment in tasks having a spatial component, particularly if this involved a reversal [2]. Meanwhile, studies in rodents were also beginning to find that some tasks did appear to be affected by hippocampal lesions, and prominent among these were, again, those having a spatial component [3,4]. Pieces of the developing picture seemed to fall into place in the early 70s, when John O'Keefe and Jonathan Dostrovsky reported initial findings indicating that single hippocampal neurons in rats were selectively active for places in the environment [5]. O'Keefe and Lynn Nadel made a detailed and compelling argument for the hippocampus being a spatial processing structure in their famous 1978 book *The Hippocampus as a Cognitive Map* [6].

This left a conundrum unaddressed, however. The amnesia of HM and other similar human cases was not for space alone; in fact, it seemed to affect virtually all events of daily life. HM's memory span was only as long as his attention span – the moment he was distracted, the events of the past disappeared into oblivion, whether or not they involved a spatial aspect. For this and other reasons, many continued to stoutly defend the argument that the roles of the hippocampus go beyond that of merely spatial memory or spatial representation. Perhaps one of the firmest voices of this viewpoint is Larry Squire's, who argued, and continues to argue, that spatial memory is a subtype of a more general type of memory that he called (in humans) "declarative" [7]. Similarly, Neal Cohen and Howard Eichenbaum suggested that the multifarious firing correlates of hippocampal neurons indicate that they "…represent various relationships among multiple stimuli and contingencies or responses, including configurational properties of items simultaneously present in the environment and significant relationships between temporally separated items” [8].

Into the debate between spatial and more generally-oriented memory functions of the hippocampus came the 1978 paper by David Olton, together with John Walker and Fred Gage, that is the focus of the present article [9]. They employed a new method for assessing memory capabilities of animals, using a task introduced a few years earlier by Olton and his student Robert Samuelson [10]. In the standard version of the so-called radial maze, or Olton maze, task, animals start from a central platform and make their way to the ends of several – usually 8 – arms to find food, until all the arms have been depleted (Figure 1). At its core, this is a working memory task, because the animal needs to keep a running record of which arms it has visited and which it has not, with the arms being defined by their locations in the room. Somewhat oddly, rats (in contrast to mice) do not generally use an algorithm for making arm choices (e.g., enter the arm immediately to the left of the current one) but seem to make their next choices at random. In a variant of this task, only some of the arms are ever baited, and the animal thus has to maintain both a longer term “reference” memory of which are the sometimes-baited arms, as well as a working memory record of which arms it has visited in this session.

Using this task, Olton et al. tested the effects of several types of brain lesion that share the characteristic of de-afferenting or de-efferenting the hippocampus. Lesions to the fornix and septal nuclei deprive the hippocampus of the bulk of its subcortical connections, while lesions of entorhinal cortex remove its cortical connections. Lesions of the septal area also remove a rich source of cholinergic input to hippocampus, as well as (we now know) disrupting oscillatory hippocampal activity in the 8-11 Hz theta range. Control animals with lesions to postero-lateral (i.e, parietal) cortex, as well as ones with sham surgery or no surgery, were also tested. The results were striking – all lesions that interfered with the hippocampus and its communication with other brain structures, including septum, fornix and entorhinal cortex, induced profound and enduring deficits on the task, whereas the neocortical lesions did not. Thus, overall, the findings seemed to support the idea that the hippocampus, in the authors' words "plays a major role in spatially organized behaviors."

From map to memory map

The space/memory debate did not end with this study; in fact it continued to gain force. The study's findings were provocative and influential, but did not settle once and for all the question of space vs. memory, because the radial maze could in theory be solved non-spatially by remembering the extra-maze cues associated with each arm (although with hindsight, this is probably not what rats do). The findings did, however, galvanise thinking about how one *could* distinguish between a purely spatial vs. a more mnemonic explanation for the hippocampal dependence of such tasks. Shortly afterwards, to circumvent the possibility of non-spatial cue learning during navigation, Richard Morris devised the watermaze, which relies entirely on processing the spatial relations between extra-maze cues, and showed that hippocampal lesions profoundly affected performance on this task too [11].

Even with these clear demonstrations of its contribution to spatial processing, the idea that the hippocampus might have a more general role in memory remained alive and kicking. As mentioned, Squire and Eichenbaum were among the most enthusiastic proponents of this idea, but were by no means the only ones. As neurophysiologists picked up on O'Keefe's method for recording place cells and began to extend it, an increasing number of reports emerged presenting correlates of hippocampal neuronal activity that were not entirely spatial. A robust debate ensued, with Cohen and Eichenbaum calling the cognitive map theory, with evident frustration, the “theory that wouldn’t die” [12]. Defenders of the spatial mapping theory, particularly O’Keefe himself, argued that many apparently non-spatial correlates, such as firing near goals or rewards, were artefacts of behavioural changes occurring at those places. Since place cells were by this time known to be modulated by movement [13], it can be hard to refute these arguments. However, as evidence accrued for non-spatial correlates that were clearly not movement artefacts, the notion of “place” began to be extended to take these findings into account. Place cells on the Olton maze, for example, proved to be highly directional, firing differently when the animal traversed an arms outwards vs. when it returned – “place” was thus modulated by other task-relevant demands. Place cells could even be modulated by the differing intentions of the animal at a place, even when all other factors were accounted for, and so “place” has eventually morphed into the extended concept of “spatial context”.

The hippocampus as a memory map

Despite all these other non-spatial modulators, place seems somehow fundamental to place cells. Even after decades of experiments, there are few reports of place cell activity that does not also have a spatial component, whereas if the cells were part of a more general memory mechanism then we might expect to see some cells with non-spatial firing correlates (e.g., cells that fire everywhere in a black box but nowhere in a white one, cells that fire when one experimenter is present but not a different one, etc). The ubiquity of the spatial modulation of hippocampal cells has led to speculation that the hippocampal spatial map might be a way for the brain to organise memories, thus being a critical component of them. This idea has emerged several times in the decades since HM, and takes two different but related, and sometimes partially overlapping forms. One is that the brain uses space, via hippocampal place cells, as the organising framework for associating episodic memories, the idea being that returning to a place, or thinking of a place, can activate associative links that retrieve memories of things that have happened there. This idea was advanced by O'Keefe and Nadel who noted that the cognitive map – what they called the "locale system" – could order representations in a structured context, and thus be central to representation of context-specific experiences.

The other memory map idea is that the hippocampus itself *is* a map, or organises a map, of where memories are stored in the brain. The best known of these so-called indexing theories was proposed by Teyler and DiScenna [14] who suggested that the hippocampus is a coordinate system for neocortical loci, the links to which are formed by Hebbian strengthening of the synapses between coactive neurons. Their ideas borrowed from a number of earlier ones including Hebb's rule for creating cortical cell assemblies, and Marr's ideas about the simple memory function of hippocampus ("archicortex"). The indexing theory finds support in the discovery of reactivation of hippocampal-neocortical links during offline processing periods such as sleep. Collectively, these ideas have led to the emerging view that the hippocampus is a "memory map" – at once a map of space, a map of the brain, and a register of the links between these [15].

The Olton maze and its variants continue to be popular to this day. Although none of the studies based on it was able, on its own, to prove (or refute, for that matter) the spatial theory of hippocampal function, the paradigm taps into many broad questions pertaining to cognitive navigation, and does so at a level of concreteness that helped retain the task's appeal over the years. What are, for instance, the algorithms that animals use for deciding which order to visit arms in? Where are the working vs. reference memory traces located? What methods does the brain use for updating these traces? And where is the site of decision-making at choice points? The Olton maze is also notably easy to run and score, and lastly, given that rats are foragers, it taps into a relatively natural behaviour for these animals. With the growing recognition of the importance of ethologically-relevant experimental design, the Olton maze is likely to be with us – like the wider debates on hippocampal functions that it helped propel – for years to come.

Acknowledgements

KJJ is supported by grants from the Wellcome Trust (WT103896AIA) and BBSRC (BB/R004765/1).

References

1 Scoville, W.B. and Milner, B. (1957) Loss of recent memory after bilateral

hippocampal lesions. *J. Neurol. Neurosurg. Psychiat.* 20, 11–21

2 Mahut, H. (1971) Spatial and object reversal learning in monkeys with partial temporal lobe ablations. *Neuropsychologia* 9, 409–424

3 Kimble, D.P. (1963) The effects of bilateral hippocampal lesions in rats. *J. Comp. Physiol. Psychol.* 56, 273–283

4 Plunkett, R.P. *et al.* (1973) Place learning in hippocampectomized rats. *Bull. Psychon. Soc.* 2, 79–80

5 O'Keefe, J. and Dostrovsky, J. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. , *Brain Res.*, 34. (1971) , 171–175

6 O'Keefe, J. and Nadel, L. (1978) *The Hippocampus as a Cognitive Map*, Clarendon Press.

7 Squire, L.R. and Zola, S.M. Structure and function of declarative and nondeclarative memory systems. , *Proc.Natl.Acad.Sci U.S.A*, 93. 13515–13522

8 Eichenbaum, H. and Cohen, N.J. (1988) Representation in the hippocampus: what do hippocampal neurons code? *Trends Neurosci.* 11, 244–248

9 Olton, D.S. *et al.* Hippocampal connections and spatial discrimination. , *Brain Res*, 139. (1978) , 295–308

10 Olton, D.S. and Samuelson, R.J. (1976) Remembrance of places passed: Spatial memory in rats. *J. Exp. Psychol. Anim. Behav. Process.* 2, 97–116

11 Morris, R.G. *et al.* Place navigation impaired in rats with hippocampal lesions. ,

Nature, 297. (1982) , 681–683

12 Cohen, N.J. and Eichenbaum, H. The theory that wouldn't die: a critical look at the spatial mapping theory of hippocampal function. , *Hippocampus.*, 1. (1991) , 265–268

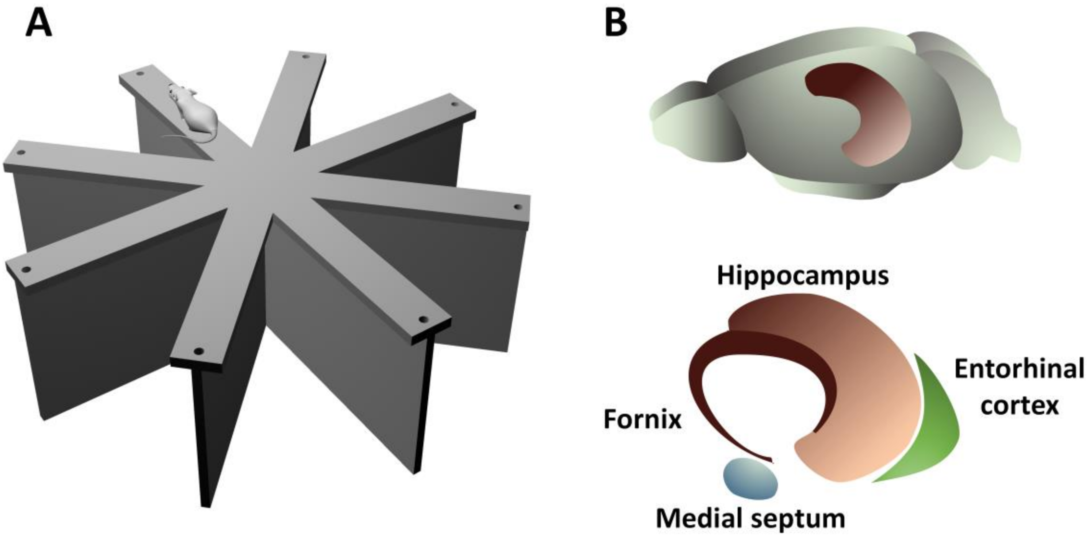
13 McNaughton, B.L. *et al.* The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. , *Exp.Brain Res.*, 52. (1983) , 41–49

14 Teyler, T.J. and DiScenna, P. The hippocampal memory indexing theory. , *Behav Neurosci*, 100. (1986) , 147–154

15 Buzsáki, G. and Moser, E.I. (2013) Memory, navigation and theta rhythm in the hippocampal-entorhinal system. *Nat. Neurosci.* 16, 130–138

Figure legend

Figure 1: (A) Schematic of the radial maze, showing the spoke-like configuration, and food wells at the ends of the arms. (B) Schematic of the rat brain (top) showing the location of the hippocampus, and (below) the relationship of the hippocampus to medial septum and fornix (conveying subcortical inputs) and entorhinal cortex (cortical inputs).


A
B
Hippocampus
Entorhinal cortex
Fornix
Medial septum