

Has the hippocampus really forgotten about space?

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Abstract

Several lines of evidence, including the discovery of place cells, have contributed to the notion that the hippocampus serves primarily to navigate the environment, as a repository of spatial memories, like a drawer full of charts; and that in some species it has exapted on this original one an episodic memory function. We argue that recent evidence questions the primacy of space, and points at memory load, whether spatial or not, as the challenge that mammalian hippocampal circuitry has evolved to meet.

Highlights

Spatial correlates have been identified for neural activity in several places in the brain

Hippocampal activity can be seen to be selective for many other variables, besides spatial ones

Hippocampal involvement is typically needed when the memory load is massive

The mammalian dentate gyrus appears to be specialized to set up new memories when there are many already

A long-term partnership, but not exclusive

Spatial memory has long been associated with the hippocampus. In food-storing birds, the association has been reviewed in this journal over a quarter of a century ago (1), and the avian hippocampus continues to be the object of current research, broadening in scope from new species (2) to aging in pigeons (3), to memory not just for goal locations but also for how to get there (4).

If spatial learning in birds (and also in reptiles, with the attendant difficulties of getting them to demonstrate it behaviorally; 5) reminds us that memory for space does not require a medial pallium with the exact internal organization of the mammalian hippocampus, ray-finned fish have long indicated an even looser relationship. Due to a different forebrain development, their homologous structure is not in the medial but in the lateral pallium, and is not cortex-like. Yet, the pioneering work of the Seville group of Fernando Rodríguez and Cosme Salas has shown a striking functional similarity with the medial pallium in advanced vertebrates (6). Anatomical homology suggests that we might be dealing with a relation that goes all the way back to our common ancestors with agnathans (7), making it a very long-term form of evolutionary memory – half a billion years. Intriguing recent work has suggested an internal differentiation, within the fish hippocampal homologue, reminiscent of the one observed in mammals (8). Further studies have looked at neural activity patterns in other fish species (9), while in goldfish a diversity of neural selectivity types has been characterized (10).

Fish can also contribute to place in an evolutionary perspective the recent excitement about neurogenesis in the mammalian dentate gyrus. Indeed, given that the size of the hippocampal

homologue correlates with the complexity of the spatial environment, as shown in species of gobiids that live in different habitats (11), one might expect extraordinary hippocampal neurogenesis in species living in complex and dynamic environments. In this respect, Augusto-Oliveira and colleagues (12) argue that it is surprising *how few* are the new neurons born in the dentate gyrus of adult mammals, and in particular of primates – suggesting a need to actually *suppress* neurogenesis in complex brains.

Given a partnership lasting half a billion years, one could well ask: what is it, that spatial cognition still finds so attractive in the hippocampus? Wait a minute, not spatial cognition as a whole, there are parts that seem to do just fine *without* the hippocampus: in humans, at least, scene construction and shifts in perspective, which require several coordinate transformations (13), appear to depend more on the integrity of parahippocampal regions (14). Further, Robin et al (15) find that ‘schematic’ spatial memory is not impaired in patients with medial temporal lobe lesions, in contrast with detailed scene memory, which is impaired, like episodic memory. Moving from the analysis of impairments in patients to imaging in healthy subjects, while a study emphasizes the role of visual inputs to an amodal ‘core’ network including the hippocampus (16), another reports no specific activation in the human hippocampus in goal-directed navigation, but only in the posterior parahippocampal region (17), in line with an extensive meta-analysis, that finds bits and pieces of spatial cognition distributed across many cortical areas, but not in the hippocampus (18).

It is not just human deviance: more ‘posterior’ neural representations of spatial variables are increasingly found in other species, in particular in rodents. A plurality of studies has focused on the retrosplenial cortex (19, 20, 21, 22); but also in the thalamus (23), including the visual thalamus (24), in visual cortex, as reviewed in this journal (25), as well as in higher-order visual areas (26). Brain mapping studies highlight a broad network of cortical and subcortical regions, including the ventral striatum – one of the main output stations of the hippocampus – as progressively engaged in spatial navigation, depending on the degree of familiarity of the routes (27). Finally, a recent study has reported a variety of spatially tuned cells, including place, grid, boundary vector/border and head direction cells, also in the somatosensory cortex (28).

The hippocampus is interested in other forms of memory

As other neural populations ‘invade’ its space, it seems as if the hippocampus is almost pushed out: Poulter et al (29) find a condition in which hippocampal lesions actually facilitate learning the location of the platform in a Morris water maze. Luckily, there are other variables it can get involved with. A series of studies have described how it codes for odors, e.g., articulated in temporal sequences (30), particularly in the dentate gyrus (31); while other recent trends deal with visual categorization (32) and, increasingly, social memories (33, 34, 35). In parallel, its role in memory is fortified by the observation that hippocampal reactivation can extend much longer than previously demonstrated (36).

The analysis of the complex effects of relevant and irrelevant feature density in visual categorization (32) seems relevant to understand, in humans, the role of long-term memory and of the hippocampus in goal directed search (37) and probably in the construction of scene-based mental representations (38). In this framework, the ‘spatial’ nature of scenes, as opposed to simple arrays of objects, might effectively be a shorthand for a complex set of features, with their conjunctions, pairwise relations, ternary, etc. to be recalled from long-term memory and used in short-term memory. In other words, physical space, and more recently social space, might have offered researchers the opportunity to probe

the effects of memory load without having to solve the challenging task of explicitly quantitating memory load itself, making do with the qualitative characterization of ‘spatial relations’.

But short-term memory load has in fact been probed explicitly in a series of studies that capitalize on the tendency of rodents to spontaneously demonstrate object recognition through decreased exploration (39), with a paradigm that allows an analysis of the molecular mechanisms involved (40). Memory load determines the recruitment of structures adjoining the hippocampus proper, such as the subiculum and lateral entorhinal cortex, in rats presented with 5 to 10 odors (41). Also in humans, activity within the hippocampus, subiculum and surrounding medial temporal cortices is modulated in a load-dependent manner in a working memory task (42).

It is possible that the short-term memory span is determined by the need to organize the exchanges between the hippocampus and the surrounding cortex along the temporal dimension. This could account for the prominent role that sharp wave ripples, which compress the temporal dimension as much as possible, have been assigned in memory, recently also in primates (43). In humans, there is neuroimaging evidence that visual sampling predicts hippocampal activity (44), and it may well be that the recently reported ‘time cells’ in the hippocampus and entorhinal cortex (45) play an important role in the ordering of sequence information, which has been theorized to be a central organizing principle for memories in the hippocampus (46).

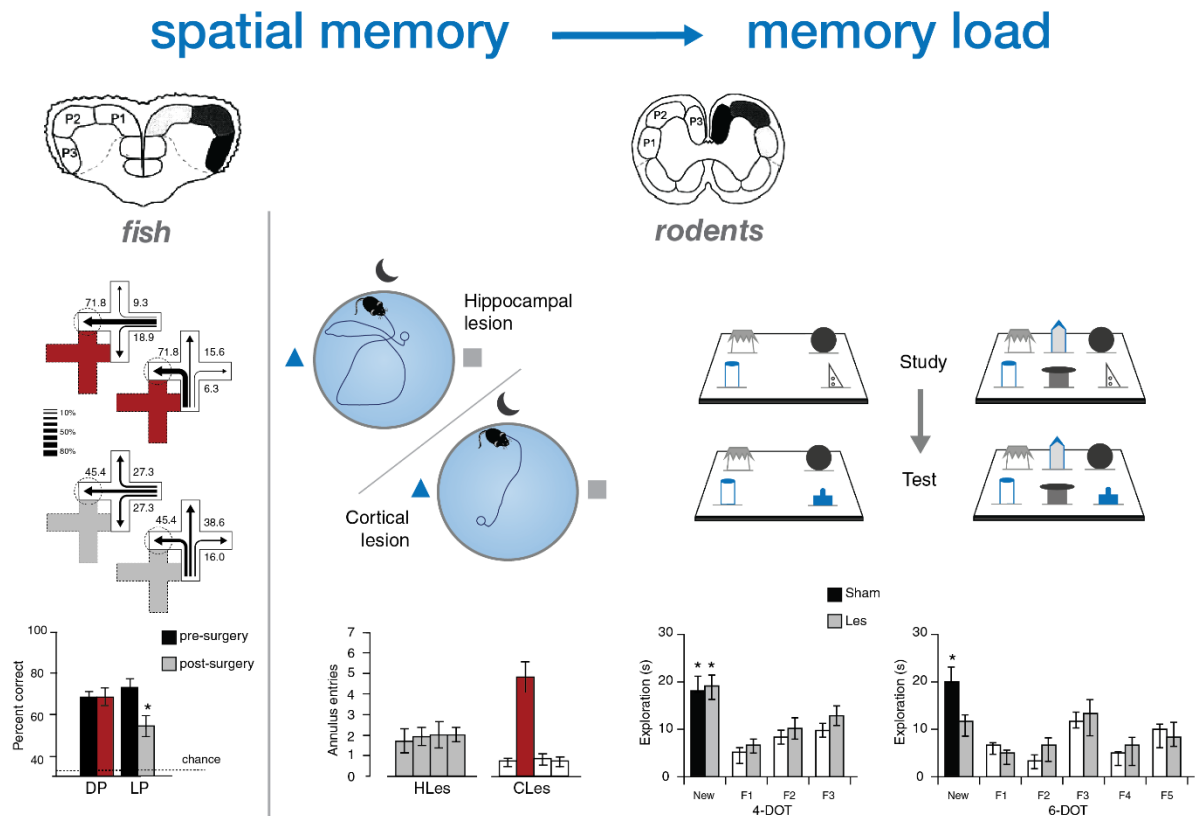


Fig.1. Shifting perspectives on hippocampal specialization. In the leftmost panels, redrawn from Rodriguez et al (6), fish with lesions in the lateral pallium (LP, the fish hippocampal homologue) have trouble selecting, post-surgery, one of 3 spatial alternatives. This appears to fit with the spatial account of the deficit observed in rodents 40 years ago (next right, redrawn from Morris et al, 48); but it can be

interpreted also as an effect of memory load, which in mice is observed not with 4 but with 6 DOT alternatives (see Sannino et al (39), from which the rightmost panels are redrawn).

In other words, theoretical perspectives on hippocampal function have gradually shifted from emphasizing spatial memory to coping with the challenge of memory load. Is that an evolutionary shift, or just an emerging reappraisal by the scientific community? It appears that much of the consolidated evidence can be reinterpreted as the hippocampus selecting perceptual elements on the basis of previous knowledge, in emotionally relevant contexts, in order to re-organize already formed mental representations, to form new ones or to manage the flow of incoming information along a sequential-temporal axis (47). However, it seems that it comes into play, as part of a widespread network, only when the game gets tough (Fig.1).

When the hippocampus looks at space, it is through the fragments of a spin glass

In what ways do spatial representations stand out among other complex representations of relations? In the possibility of realizing them as compact *charts*, at least in 2 dimensions, for one thing. Also, in their stability over time, one may argue, and find a neural correlate of such stability in the impressive rigidity of co-activation patterns among grid cells in entorhinal cortex (49). That is medial entorhinal cortex and not hippocampus, however; and even there, grid cells appear to ‘patch up’ their maps when the environment changes (50) and to deform them depending on where the animal wants to go (51). A comprehensive theoretical view suggests that such changes in the collective *network attractor* expressed by a tightly knit entorhinal module may be driven in fact by the hippocampus (52), even without taking into account that ‘entorhinal modules’ themselves are likely not as hardwired as initially assumed to be (53).

The remarkable plasticity of hippocampal representations, erstwhile regarded as stable *charts*, which had been observed with Calcium imaging (54), has been dramatically corroborated by the finding, in the Ziv lab, that multiple charts can represent the same environment at the same time (55), perhaps because they disorderly recycle small pre-wired fragments (56). Surprisingly, theoretical modelling indicates that multiple unrelated charts could coexist also among grid cells (57), with irrepressible disorder and inability to express long-range coherence as the hallmark of such multiplicity (58).

If charts are not stable and not unique to a spatial context, are they really spatial maps, or just ‘concept maps’ of complex relations? And how can they be set up, on the go? Recent evidence points, again, at the dentate gyrus (59). Dentate inputs to CA3 had long been shown at the behavioral level to be necessary to establish new memories (60, 61) and new research shows what they do at the neural level (62). Seen from the grand angle of evolution, the dentate gyrus, although rooted in a very ancient genetic imprint (63) and showing indications of going its own way in very distant species (8), appears to be, with its intrinsic and highly peculiar excitatory outputs a distinctly mammalian invention (64).

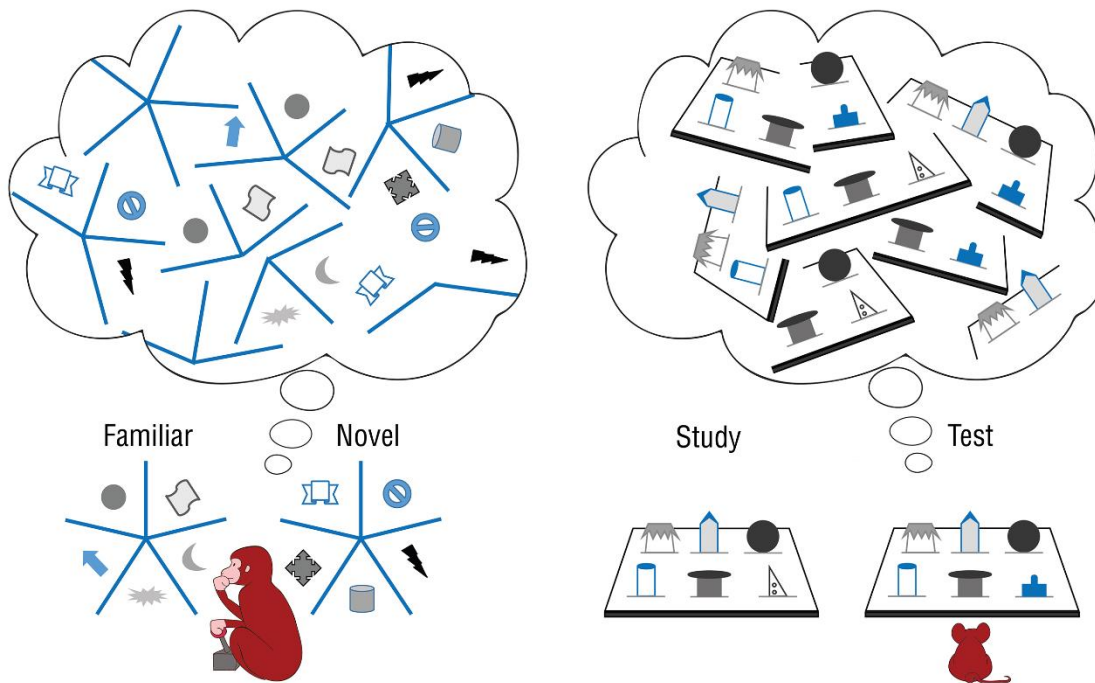


Figure 2. **Charts might be stitched together from disorderly fragments.** Both the familiar and novel mazes of Baraduc et al (67) and the study and test object arrays of Sannino et al (39) could be represented in the hippocampus as overlapping and partially incongruent fragments (top) or, if recurring, schemata, which are not necessarily ever composed into a single holistic chart which fully integrates current perception (bottom).

Having a dentate gyrus with its special characteristic may have been the extra trick that, independently of other ‘tricks’ invented by other classes of vertebrates (65), has endowed the mammalian hippocampus with the ability to generate concept charts of sufficient complexity as to face the challenges of the spatial and social reality we are immersed in, and in which we form episodic memories (66). Rather than charts we should perhaps refer to them as clusters of schemata (67), or aggregations of fragments of memory, multiple and not necessarily consistent with each other (Fig.2; this distinguishes them from the ‘schematic spatial memories’ of Robin et al, 15). They can be acquired in the hippocampus and then be reactivated in seemingly random sequences (68) and, particularly in primates, be consolidated elsewhere, e.g. in prefrontal cortex (69), and let behavior emerge from a motley of complex, incongruent, overlapping memories.

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(* a subpopulation of hippocampal cells is shown to express a complex activity pattern – not a simple place field – that is similar in two environments with the same layout but different landmarks, indicating one type of ‘fragment’ used to construct charts, perhaps like the top left fragment in Fig.2.)

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(** when rats are quiet and immobile, decoded hippocampal activity appears to describe Brownian motion in a recently explored environment – which could be interpreted as really encoding a novel, purposeless random trajectory on a complete chart, or as the random juxtaposition of chart fragments.)

69. Ciaramelli, E., De Luca, F., Monk, A. M., McCormick, C., & Maguire, E. A. (2019). What "wins" in VMPFC: Scenes, situations, or schema? *Neuroscience & Biobehavioral Reviews*, 100, 208-210.