

REVIEW | *Where are you Going? The Neurobiology of Navigation*

The role of the hippocampus in navigation is memory

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Eichenbaum H. The role of the hippocampus in navigation is memory. *J Neurophysiol* 117: 1785–1796, 2017. First published February 1, 2017; doi: 10.1152/jn.00005.2017.—There is considerable research on the neurobiological mechanisms within the hippocampal system that support spatial navigation. In this article I review the literature on navigational strategies in humans and animals, observations on hippocampal function in navigation, and studies of hippocampal neural activity in animals and humans performing different navigational tasks and tests of memory. Whereas the hippocampus is essential to spatial navigation via a cognitive map, its role derives from the relational organization and flexibility of cognitive maps and not from a selective role in the spatial domain. Correspondingly, hippocampal networks map multiple navigational strategies, as well as other spatial and nonspatial memories and knowledge domains that share an emphasis on relational organization. These observations suggest that the hippocampal system is not dedicated to spatial cognition and navigation, but organizes experiences in memory, for which spatial mapping and navigation are both a metaphor for and a prominent application of relational memory organization.

cognitive map; hippocampus; memory; navigation

A MAJOR DIRECTION in research on navigation concerns how the spatial coding properties of hippocampal area neurons support cognitive maps and maintenance of trajectories through space. I will review this work from several related viewpoints, beginning with considerations of the features of cognitive maps, how the hippocampus came to be associated with cognitive maps, and the dilemma of differing viewpoints on the role of the hippocampus in navigation and memory.

Cognitive Maps Are Maps of Cognition

Edward Tolman (1948) introduced the idea that behavior is driven by memory representations that are organized as a cognitive map. He was opposed to the then current emphasis on behavior as supported by the learning of rigid stimulus-response associations. Instead, he argued, rats have something like an old-fashioned switchboard control room where “the stimuli, which are allowed in, are not connected by just simple one-to-one switches to the outgoing responses. Rather, the incoming impulses are usually worked over and elaborated in the central control room into a tentative, cognitive-like map of the environment. And it is this tentative map, indicating routes and paths and environmental relationships, which finally determines what responses, if any, the animal will finally release” (Tolman 1948, p. 192). Although Tolman’s experiments fo-

cused on rats and maze learning, his ideas extended to a broad range of normal and disordered cognition in humans (Tolman 1948), thus clarifying that cognitive maps were not solely for mapping physical space but for a broad range of “cognitive space.” Thus Tolman employed a model of rodents and maze learning to demonstrate that animals and humans learn facts about the world, integrate them into a framework of relations among those facts, and then subsequently remember and deploy the network in a flexible manner; and this conception of cognitive maps applies across domains of cognition.

The Hippocampus and Cognitive Maps

The connection between the hippocampus and cognitive maps was argued in O’Keefe and Nadel’s (1978) pioneering treatise that reviewed the literature on hippocampal function and physiology. Consistent with Tolman, they distinguished mapping of relationships among experiences within a spatial framework and support of flexible behavior in navigating the relational space, and they presented a large body of evidence that the hippocampus is selectively involved in this kind of spatial learning and memory. Strong evidence was provided in a review of experiments showing that damage to the hippocampus usually results in impairments on some types of spatial learning and memory tasks, whereas learning of a variety of nonspatial tasks as well as other types of spatial learning did not require the hippocampus. In considering the literature on which their review is based, it is critical to realize that the spatial and nonspatial tests that O’Keefe and Nadel reviewed

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differed not only in the focus on spatial vs. nonspatial cues and responses but also in the relational organization and flexible expression of memories vs. rigid stimulus-response associations. As discussed below, careful examination shows that the hippocampus is not required whenever spatial cues and responses are essential and the hippocampus is required for learning and memory of nonspatial memory organizations, indicating it is the features of relational organization and not space per se that requires hippocampal function (e.g., Bunsey and Eichenbaum 1996; Preston et al. 2004; see Eichenbaum et al. 1999).

The discovery of “place cells,” neurons that fire when an animal passes through a specific location in its environment, was viewed as providing neural instantiation of the hippocampal map of space (O’Keefe and Dostrovsky 1971). Furthermore, subsequent work revealed other types of spatial coding neurons in areas connected with the hippocampus. These discoveries included neurons that fire in association with head direction (Ranck 1984; Taube et al. 1990) and grid cells in the medial entorhinal cortex (MEC) that fire when rats traverse a spatially periodic array of locations, as well as MEC head-direction cells and cells that signal borders and speed (see Hartley et al. 2013; Kropff et al. 2015). In 2014, the Nobel Prize in Physiology or Medicine was awarded to John O’Keefe and May–Britt and Edvard Moser for their discoveries of hippocampal place cells and MEC grid cells. The Nobel committee described their combined discoveries as “a comprehensive positioning system, an inner GPS, in the brain.” This view is argued in detail in papers entitled “Place cells, grid cells, and the brain’s spatial representation system” (Moser et al. 2008) and “Space in the brain: how the hippocampal formation supports spatial cognition” (Hartley et al. 2013). Furthermore, hippocampal system neurons briefly continue to code for specific locations as animals move in the dark, suggesting that this system tracks movement via internally generated cues to integrate a path through the cognitive map (McNaughton et al. 2006). Taken together, these findings have led to the prominent view that the hippocampus and associated areas compose a brain system dedicated to spatial navigation via path integration. In this review I will examine this claim, and in doing so, highlight evidence showing that the hippocampus plays an essential role in navigation, but does so via its general role in memory.

Hippocampus: Spatial Mapping or Maps of Cognition?

The narrow view taken in many place cell studies contrasts with Tolman’s idea of cognitive maps as extending broadly to maps of cognition. Consistent with Tolman’s view, there is extensive evidence that the hippocampal system performs a more general memory function such that damage to the hippocampus results in global amnesia including both spatial and nonspatial domains in both humans and animals (Eichenbaum et al. 1999; Squire et al. 2004). Correspondingly, neuronal activity in the hippocampus reflects memory processing across a range of spatial and nonspatial domains both at the level of fMRI signals in humans and neuronal activity patterns in humans and animals (Eichenbaum 2017).

Can we reconcile these findings with the robust spatial coding properties of hippocampal system neurons in animals? Toward that goal, previous reviews have drawn parallels be-

tween the cognitive maps for space and other domains (Buzsáki and Moser 2013; Eichenbaum 2004; Eichenbaum and Cohen 2014; Eichenbaum et al. 1999; Milivojevic and Doeller 2013; Schiller et al. 2015). In this review, I will add to the reconciliation by focusing on the literature that describes navigational strategies in animals and humans, the essential role of the hippocampus in navigation, and the spatial firing properties of hippocampal system neurons associated with different navigational strategies. I will describe evidence that hippocampal networks represent multiple navigational strategies and its mappings support a broad range of cognitive maps, as Tolman envisioned. A convergence of recent findings in these areas indicates that the hippocampus does play a fundamental and essential role in navigation, but as an expression of its more general role in the organization of memories relevant to diverse spatial and nonspatial domains.

Navigation: What Is It?

According to Gallistel (1990), “Navigation is the process of determining and maintaining a course or trajectory from one place to another” (p. 35). The phenomenology of navigation has generated considerable interest in those who study how humans (e.g., Dudchenko 2010; Huth 2013; Wolbers and Hegarty 2010) and animals (e.g., Poucet 1993; Trullier et al. 1997) find their way through environments and in the development of robots that navigate (e.g., Franz and Mallot 2000; Levitt and Lawton 1990). Reviews on the topic distinguish two general domains of navigational strategies, one involving local navigation, where one can approach a directly observed goal location in the currently perceived environment, and the other by wayfinding, where the goal must be reached by moving beyond immediately perceived space via learned routes or by referring to an internalized cognitive map (Franz and Mallot 2000; Trullier et al. 1997). Both domains of navigation involve multiple cognitive and behavioral mechanisms that together have been characterized as a hierarchy of navigational strategies (Franz and Mallot 2000; Trullier et al. 1997). In this review I will introduce strategies that are particularly relevant to experiments on the role of the hippocampus.

Local navigation. At the lowest level within local navigation strategies is “search” without an active orientation toward the goal, which involves simply locomotion and goal recognition without any need for spatial representation (Franz and Mallot 2000). Even though it is arguable whether search constitutes navigation, Franz and Mallot included this strategy in the hierarchy because it is often used when other strategies fail. Next in the hierarchy is “target approaching” (Trullier et al. 1997) or “taxis” (O’Keefe and Nadel 1978), which involves orienting and maintaining a body orientation while reaching toward an observable goal (e.g., a visible escape platform in the water maze) or proximal landmark as a surrogate of the goal (e.g., a visible flag over a submerged platform). O’Keefe and Nadel (1978) and Morris (1981) considered taxis as supported by stimulus-response behavior, falling short of consideration as true navigation, although it is kept within the hierarchy of navigational strategies discussed here.

When the goal itself is not directly observable but instead its location is defined by a spatial configuration of observable nonproximal cues, navigation can be accomplished at the next level by “guidance” toward the precalculated goal location. Examples

of guidance include approaching a goal that lies at a particular distance between two landmarks that are not contiguous with the goal (Collett et al. 1986) and the submerged escape platform in a water maze that lies at a location defined by distant cues on the walls of the room (Morris 1981). Under these situations, a spatial computation must be performed to identify the goal location before navigating. However, once the goal location is defined, it is directly observable in the local environment. Subsequently, the required strategy for navigating, which according to Gallistel (1990) is focused on the trajectory to the observed goal in the local environment, and therefore the execution of navigation itself is not different from that in taxis.

Wayfinding. Three wayfinding strategies for navigating to goals that are not within the local environment have been identified. The first of these strategies involves “recognition-triggered responses” wherein the goal is reached by recognizing and approaching sequential landmarks or places within local environments (Franz and Mallot 2000; Trullier et al. 1997).

The second strategy is a concatenation of multiple recognition-triggered responses called a “route,” and when multiple distinguishable routes intersect while maintaining their distinctive paths, they can support “topological navigation” or “route following.” Importantly, whereas topological navigation distinguishes multiple and overlapping routes, it supports navigation only along already traversed paths and does not support flexible navigation via novel paths.

The third and highest level strategy of wayfinding is “survey” or “metric” navigation, which requires embedding all known places and their spatial relations into a common frame of reference, and can support navigation through novel routes, including detours and shortcuts to a goal (Franz and Mallot 2000; Trullier et al. 1997). Survey navigation involves precisely the relational organization of a cognitive map described by Tolman (1948) and adopted by O’Keefe and Nadel (1978). It is important to emphasize that survey navigation employs the same map regardless of the goal or other cognitive demands. In the navigation literature, the cognitive map is employed just as we use maps in the glove compartment of a car or electronic maps in our smart phones; the structure of the map is identical regardless of the goal location or the reason for the trip. One employs the map in our heads, as if on paper or on the phone, to plot a route and follow progress to any goal for any purpose.

This brief survey indicates a consensus that there are many different strategies in navigation that engage different cognitive processes to solve the problem of getting from one place to another. Next, I will consider the role of the hippocampus in the navigational tasks that are examples of levels of the navigation hierarchy. Many view the role of the hippocampus as selectively involved in survey navigation using a cognitive map, and not topological navigation (route following) or any of the forms of local navigation lower in the hierarchy. However, considerable evidence is contrary to this view in that the hippocampus is engaged in multiple navigational strategies and in the relational organization of nonspatial memories, as discussed below.

Role of the Hippocampus in Navigation: Two Approaches

The role of the hippocampus in navigation has been pursued by two general approaches. One approach involves evaluating navigational performance following damage to, or inactivation of, the hippocampus, with the expectation that navigational

strategies that depend on hippocampal processing will be challenged when the hippocampus is inactivated or removed. The second approach involves monitoring the activity patterns of hippocampal neurons, with the expectation that hippocampal firing patterns reflect a specific type of spatial representation that the hippocampus supports. One would hope that evidence from these two approaches would complement one another such that the navigational strategy that depends on the hippocampus is reflected in selective hippocampal activation and corresponding neural activity patterns. As described below, the evidence indicates a complicated picture that does not match the ideal expectancy and suggests that the hippocampus is engaged in multiple navigational strategies rather than just the one for which it is necessary.

When is Hippocampal Function Essential for Navigation?

In their treatise on the hippocampus as a cognitive map, O’Keefe and Nadel (1978) famously reviewed a large literature on the effects of hippocampal damage on performance of rats in a variety of tasks and concluded that the hippocampus is required only in tasks that require a cognitive map and survey navigation. More specifically, they distinguished navigation by recognition-triggered responses and their concatenation as routes (topological navigation by route following) as independent of the hippocampus from cognitive maps that support survey navigation as hippocampal dependent. I will review some of the classic and recent experiments that are consistent with the idea that the hippocampus is essential to a cognitive map and survey navigation, and not to other navigational strategies. Although the data support the notion that the hippocampus is essential to the acquisition and performance on tasks that involve survey navigation, further considerations later in this review will show that hippocampal networks are engaged in a broader range of spatial as well as nonspatial memory tasks.

A remarkably useful classic experiment examined two navigational strategies employed to solve a simple T-maze problem where animals learn to choose a path involving a specific turn direction (e.g., head north and then turn left) to reach food in a particular location (e.g., the west goal of maze). Packard and McGaugh (1996) trained rats for different numbers of days and then probed the navigational strategy used by rotating the maze 180° and allowing a free choice. The expectations were that if animals used a route-based strategy, then in the probe test they should follow the turn-left route even as it takes them to the east rather than the west goal location. However, if they used survey navigation, they should employ a cognitive map that guides them to the west goal even as it requires taking a right-turn route. After 1 week of training, normal rats in the probe test turned right at the choice point and approached the west goal, consistent with flexible survey navigation in a cognitive map to the remembered goal location, and this performance was dependent on the hippocampus. Then, after an additional week of training, rats turned left in the probe test, consistent with a rigid route-following strategy, and this performance was dependent on the striatum. These findings strongly support O’Keefe and Nadel’s notion that navigation using a cognitive map requires the hippocampus and route following does not. It is important to emphasize that the structure of the training task (a particular path guided by spatial cues) does not dictate whether the hippocampus is required;

rather, the critical features that drive hippocampal involvement are the representation of spatial relations among cues that define the organization of the environment and the flexibility of behavioral expression in paths taken. Also, notably, the switch between survey navigation and route following was driven by the amount of training and not by a change in spatial cues or navigational demands.

Hippocampal cognitive maps even when survey mapping is not required. Consistent with the findings described above, hippocampal lesions do not impair learning to turn in a particular direction in a T-maze, presumably because learning can be accomplished using a recognition-triggered response that does not require a cognitive map. Furthermore, if the task is extended to include continuous alternation between left and right turns at the choice point, wherein an animal switches between left and right turn paths without any delay between those paths, the hippocampus is still not required (Ainge et al. 2007a), supporting the idea that topological navigation involving the following of two intersecting routes also does not depend on hippocampal involvement. However, when a delay is imposed between alternations, animals with hippocampal damage fail. This finding indicates that the critical feature of the task that requires hippocampal involvement is the demand for recalling the immediately preceding trial, rather than the demands to use spatial cues or to express memory by taking a particular path through the maze, both of which are central to both task strategies. It appears that the memory demand imposed by the addition of a delay engages performance driven by a cognitive map supported by the hippocampus.

In the Morris water maze task, animals must compute and remember an escape location defined by distal cues in the environment. However, once the goal location is defined, they simply need to orient toward the goal and approach it, fitting the description of guidance as the required navigational strategy (see above). A considerable literature indicates that guidance is supported by nonhippocampal mechanisms (McDonald and White 1994). Indeed, consistent with this expectation, the water maze task is successfully learned in animals with hippocampal damage when they can guide navigation along a single route (Eichenbaum et al. 1990).

However, in contrast to learning a single route, the standard water maze task involves concurrent learning of multiple routes, and animals with hippocampal damage fail under this protocol (Morris et al. 1982). The demand to disambiguate multiple learned routes suggests that topological navigation also depends on the hippocampus. However, after single-route learning, intact rats can swim along novel routes, whereas animals with hippocampal damage cannot (Eichenbaum et al. 1990). This flexibility of expression suggests that normal rats employ a cognitive map supported by the hippocampus in learning the water maze even when guidance or topological navigation are available. The engagement of hippocampal function may be caused by the open field structure of the water maze such that the paths taken in searching for the platform vary considerably even from a small number of fixed starting points; essentially, the rats are learning to find the platform via many routes. Another possibility is that rats without a hippocampus cannot learn or remember the location of a platform defined by distant cues; this is not a deficit in navigation per se, but rather a deficit in recalling the unmarked target location. These findings further extend the evidence in favor of an

essential role for the hippocampus in cognitive mapping and survey navigation and show that even in tasks that are constructed as solvable by strategies lower in the navigational hierarchy, cognitive mapping and survey navigation supported by the hippocampus are employed.

Path integration. Finally, with regard to direct evidence on whether the contribution of the hippocampus is specifically the integration of a path along a route through the cognitive map, the evidence is mixed. Some studies have shown that hippocampal damage impairs path integration (Whishaw and Maaswinkel 1998; Whishaw et al. 2001), and others have reported intact path integration in animals with hippocampal damage (Alyan and McNaughton 1999; Benhamou 1997). A compelling study involved a comparison of performance between humans and rats on the classic path integration task where subjects initially traverse paths of differing lengths and with differing numbers of turns, and then must return to the start location in the dark (Kim et al. 2013). The most striking finding was how poor normal humans and rats are in path integration. In humans path integration was limited to paths of 8–10 m over 20–30 s and 2–3 turns, and in rats path integration was limited to paths of 2 m over 6 s and 1 turn. So, although guidance by path integration is applicable for short distances in local navigation, it does not support meaningful route or survey navigation in global space. It is important to acknowledge that path integration is not advised in real-world navigation, precisely for the reason that it is so prone to accumulated error (Dudchencko 2010; Huth 2013).

Notably, humans with hippocampal damage were not impaired in path integration, whereas rats with hippocampal damage were, suggesting species differences in either path integration or the role of hippocampus-dependent memory for the origin or course of routes taken. Importantly, some of the earlier studies that observed impairment in path integration following hippocampal damage also reported that animals with hippocampal damage were impaired on the task even when visual cues were available, that is, when path integration based on internal cues was unnecessary, suggesting that the hippocampus plays an essential role in remembering a goal location rather than in integrating idiothetic signals about direction and distance (Whishaw and Maaswinkel 1998; Whishaw et al. 2001).

In addition, recording studies have not provided compelling evidence of a path integration signal in hippocampal neural activity. Multiple hippocampal areas have neurons that signal location, heading direction, and speed of movement (Hartley et al. 2013; McNaughton et al. 1983). Also, in some tasks where distance is a salient dimension, hippocampal and MEC neurons signal distance traveled along a linear path (Gothard et al. 1996; Kraus et al. 2015). These signals could provide the substrates for calculating vectors that support path integration. Moreover, grid cell firing patterns degrade in the dark, indicating their activity does not solely reflect self-generated cues argued to be the basis of path integration (Chen et al. 2016). Cells that signal a vector toward an intended goal have been observed in bats (Sarel et al. 2017), and a vector from a journey origin should be readily observable in current data from rats performing maze tasks. Nevertheless, there is no evidence of neural activity patterns that correspond to a vector from the origin of a path to a current position, or any other information that would correspond to a path integration or memory-of-

origin signal per se. Ferbinteanu and Shapiro (2003) have observed place cell coding of paths through a maze dependent on the origin (as well as destination) of a journey, suggesting that the hippocampus does contain a record of journey origins in the form of distinct paths through space. These findings suggest that, rather than integrating a path, hippocampal place cells represent the history and trajectory of paths through a spatial framework.

The hippocampus and spatial information processing in humans. A series of studies by Squire and colleagues have taken advantage of the well-known phenomenology of amnesia by which, following hippocampal damage, recalling newly acquired memories is impaired but online cognitive processing, working memory, and memory for remotely acquired knowledge are spared (Squire et al. 2004). These studies examined performance on a range of tasks where performance relies on different kinds of spatial information processing but can be solved without retaining newly acquired spatial memories, and therefore distinguish operations in spatial cognition from recalling recent spatial experiences. The results show that humans with hippocampal damage perform as well as normal control subjects in guiding movements through space by reading from maps, using online spatial computations that successfully orient them from the map to the real world (Urgolites et al. 2016). Amnesic patients also succeeded in tests of memory for previously seen targets from new viewpoints (Shrager et al. 2007), memory for a start location and distance from the start location (Shrager et al. 2008), and computations supporting path integration (Kim et al. 2013; discussed above), as long as the accumulated spatial information could be held in working memory. Also, a severely amnesic patient could describe short cuts and detours through the town in which he had grown up and had left long before sustaining hippocampal damage by using his intact remotely acquired memories (Teng and Squire 1999). Thus, in humans, the hippocampus is not essential to spatial cognition per se, unless there is a demand for establishing a new long-term memory.

Summary of the essential role of the hippocampus in navigation. Combining the findings described above, there is substantial evidence that the hippocampus is required to support memory for tasks that require survey navigation. In addition, the hippocampus plays an essential role in some tasks that can be solved by navigation that could be supported by strategies lower in the hierarchy, for example, delayed spatial alternation and the water maze. However, a memory demand in these tasks engages a survey strategy even when not required, so the most comprehensive accounting is that the hippocampus is essential whenever a survey strategy is engaged regardless of whether it is required. The hippocampus is not required for path integration per se, even though it plays an essential role when animals must remember past locations, such as the origin of a route.

Hippocampus Network Maps of Navigational Strategies

In view of the above-described evidence that the hippocampus is critical to behavior associated with a cognitive map and survey navigation, one would expect that studies on the firing properties of neurons in the hippocampal system would focus on tasks in which cognitive mapping and survey navigation are engaged. However, surprisingly few studies on hippocampal

system neurons actually require survey navigation, and it has been suggested that hippocampal spatial maps will be much more complex in real-world navigation (Derdikman and Moser 2010). Notably, a major exception to the focus on simple behavioral tasks is recent work on firing properties of hippocampal neurons in bats as they navigate long distances to find food in a real-world environment (e.g., Geva-Sagiv et al. 2015; Sarel et al. 2017). Furthermore, a major tenet of the cognitive map view is that survey navigation involves referring to the same map of the environment to solve any navigational problem and reach any goal, as discussed above. Yet, contrary to that expectation, considerable evidence indicates the hippocampal networks form distinct spatial mappings in tasks with differing cognitive and navigational demands within the identical environment.

Network representation of survey maps even when not required. The most commonly employed behavioral paradigm used to examine the firing patterns of hippocampal system neurons is foraging for food scattered in a local open field environment. This task could be supported by searching in a random walk or by taxis to food if it is seen at a distance. Neither requires a cognitive map or survey navigation. This task has been used to identify place cells in the hippocampus and grid cells, head direction cells, and border cells in the MEC, suggesting that the hippocampus represents space regardless of the task demands. Notably, in a guidance navigation task where rats traverse paths in an open field to obtain rewards at remembered goal locations, place cells identified during search behavior fire in sequence in anticipation of the taken path, suggesting that a map is used to read out a route to be taken (Pfeiffer and Foster 2013; see also Johnson and Redish 2007).

Furthermore, if the hippocampus creates a map of the environment and then employs that map to solve tasks in survey navigation, one would expect to observe the same representation of the spatial environment when goal locations are changed or added, perhaps with relatively minor alterations of the code for specific locations where new events occur. Indeed, consistent with maintaining a map and updating it to incorporate the locations of new memories are studies where an otherwise consistent mapping is locally altered to identify the addition or repositioning of goal locations on the otherwise consistent map (Dupret et al. 2010; McKenzie et al. 2013). In sum, during tasks that can be characterized as open field search or guidance navigation, it appears that hippocampal networks nonetheless form cognitive maps, employ a consistent survey map to remember goal locations, and update the map by adjustments to the code for new goals.

In addition, a recent study of the phenomenon of “reorientation” also indicates that the hippocampus employs a survey map even when a simpler strategy based on memory for individual landmarks is sufficient (Keinath et al. 2017). Reorientation refers to the ability of navigators to regain their sense of direction after becoming disoriented. By one view, reorientation is accomplished by employing a cognitive map based on available cues (Cheng 1986; Gallistel 1990), whereas by another view reorientation can be accomplished by matching the current view to a remembered, egocentrically defined landmark (Pecchia and Vallortigara 2010). The Keinath et al. study recorded from hippocampal neurons during spatial reorientation in mice foraging in chambers of various shapes and as

animals performed a spatial memory task. They found that after animals were disoriented, the realignment of the recovered place field map that predicted searching behavior was determined by the environmental geometry and not by a prominent nongeometric cue, even when the latter could have been used to distinguish the geometric ambiguities. These findings provide compelling evidence that a mapping of spatial relations predominates in spatial cognition over the use of specific cues (Gallistel 2017).

Network maps of multiple navigational strategies. In contrast to the evidence for hippocampal survey maps described above, findings from recordings of hippocampal system neurons in rats performing continuous and delayed T-maze alternation tasks challenge the assumption within the cognitive mapping view that the same spatial map is employed to pursue different navigational goals. As discussed above, performance in the continuous alternation task seems to be supported by topological navigation by alternating between distinct but overlapping routes, not requiring hippocampal function (Ainge et al. 2007a). Yet, hippocampal and MEC neurons have place fields in this task (Ainge et al. 2007a; Frank et al. 2000; Lipton and Eichenbaum 2008; Wood et al. 2000), consistent with the evidence introduced above that a hippocampal cognitive map is formed even when not required to solve the task as observed in the open field foraging and track running tasks. However, two other features of the observations on spatial alternation tasks bring into question whether a consistent survey map of the environment is developed in the hippocampal system and employed similarly under different cognitive demands in the same environment.

First, in continuous alternation, hippocampal and MEC neurons fire differently as animals traverse the overlapping segment of the routes through the maze. That is, these neurons form distinct spatial representations (“remap”) for each route (e.g., Ainge et al. 2007b). This finding is consistent with representation of distinct routes in topological navigation and inconsistent with employing the same survey map to guide paths to the two different goals. Importantly, however, the remapping between overlapping routes is partial: some neurons have very different firing patterns whereas others have the same firing pattern as animals traverse the overlapping maze segment. Thus the hippocampal representation of the continuous alternation task is constituted as a mapping of the distinct and common elements of two routes, allowing the animal to both distinguish and link its alternate paths toward goals.

Notably, the creation of distinct representations for overlapping maze routes is not universally observed, and specifically is not observed when rats are trained to run in both forward and reverse directions in a Y-maze (Lenck-Santini et al. 2001), when each leg of a journey is guided by signals and rewards (Bower et al. 2005), and when rats are trained only on delayed alternation (Ainge et al. 2007a). Although these findings do not identify a specific condition that dictates whether distinct maps are formed for overlapping routes, the combined observations strongly indicate that hippocampal networks develop distinctive maps for different routes through the same environment, that is, a representation of topological navigation and route mapping rather than a consistent survey map.

Second, when rats are trained to perform both continuous and delayed alternation in the same recording session, hippocampal neurons also remap between the two versions of the task (Robitsek et al. 2013). Thus, even in a situation where rats

follow the same paths through the identical maze under demands that vary only in the requirement for memory over a delay, the hippocampus forms distinct network representations. Similarly, when rats perform a variant of the T-maze task wherein each trial involves a sample phase when they are directed to take a left or right turn followed by a test phase when they are required to choose the alternate turn, hippocampal neurons dramatically remap between sample and test phases (Griffin et al. 2007; see also Hallock and Griffin 2013). In this situation the hippocampus also does not provide a single survey map that is consistently referenced across differing cognitive demands, but instead the findings indicate that the hippocampus forms distinct representations for memories associated with different cognitive demands (study vs. test) even when they involve the same route through the same maze. Another fascinating example is the observation of different place field maps in bats navigating to a target when guided by vision vs. ecolocation (Geva-Sagiv et al. 2016). In addition, hippocampal neurons change firing patterns quite dramatically when task contingencies are altered in other maze tasks (Bahar and Shapiro 2012; Kelemen and Fenton 2010; Markus et al. 1995; Muzzio et al. 2009; Smith and Mizumori 2006), as well as in open field foraging vs. guidance (Markus et al. 1995), and in simple fear conditioning or extinction where no navigation is involved (Moita et al. 2004; Wang et al. 2012, 2015).

The findings on place cell remapping across the various tasks described above have been characterized as reflecting the coding of distinct memories within the same environment (Colgin et al. 2008). In support of this view, Leutgeb et al. (2005) distinguished changes in firing rates, but not firing locations (rate mapping), when proximal cues were altered within a consistent room vs. qualitative changes in the location or presence of spatial firing between rooms (global remapping). This observation suggested that the hippocampus might indeed maintain the same cognitive map modified by firing rates at consistent locations to code for distinct memories. However, it is important to emphasize that this experiment involved partial changes in spatial cues resulting in modest recoding of the otherwise stable spatial environment and consistent demands for simple foraging behavior under all conditions compared. By contrast, in challenging cognitive tasks such as those described above, when the spatial cues are constant and cognitive demands are altered, a mix of rate mapping, global remapping, and stable place fields is typically observed (e.g., Markus et al. 1995; McKenzie et al. 2014; Smith and Mizumori 2006; Wang et al. 2012, 2015), suggesting that strong cognitive demands can drive a global reconfiguration of hippocampal networks to include both the consistent spatial information and distinct events and cognitive demands.

Summary of hippocampal network maps of navigation. The observations of distinct mappings of the identical environment under different cognitive demands challenges the view that the hippocampus forms a survey map of the environment and employs the same map to solve diverse navigational problems. Instead, these findings suggest that the hippocampus creates unique representations for the cognitive demands of each task, and the representation expresses the ongoing task performance as a sequence of place cell firings that is specific to that cognitive structure. Moreover, the observation of remapping for different cognitive demands under the identical spatial cues suggests that hippocampal neurons are not solely or even primarily driven by spatial cues, but rather by cognitive states

in which memories are expressed as specific firing sequences in space and time. Furthermore, these findings bring into question whether the hippocampal system is restricted to survey navigation or can represent diverse navigational strategies that guide behavior under different contingencies, consistent with the broader role in mapping spatial and nonspatial cognition envisioned by Tolman (1948).

The Hippocampus Also Maps Abstract Spaces

Recent reviews have provided substantial evidence that the role of the hippocampus extends beyond the spatial domain (Eichenbaum 2017; Eichenbaum and Cohen 2014; Milivojevic and Doeller 2013; Schiller et al. 2015). I will briefly summarize findings that highlight the generality of hippocampal function in relational organization and the flexibility of memory expression inherent in nonspatial domains, similar to that discussed above in the spatial domain.

The hippocampus plays an essential role in organizing memories. A substantial body of studies show that the hippocampus is essential to the building of cognitive maps of abstract spaces that link associations between nonspatial (object) stimuli and supports inferential expression of memories within the associational space. For example, in one experiment, normal rats and rats with hippocampal lesions were trained to associate overlapping pairs of objects (e.g., A–B and B–C) and then were tested for whether they inferred the indirect relationship between never-paired elements (A–C). All rats learned the direct associations, and normal rats made the inferential judgment, but rats with hippocampal lesions did not (Bunsey and Eichenbaum 1996). In a succeeding experiment, rats were trained on a set of overlapping choice judgments (choose A over B, B over C, C over D, and D over E) and then were tested on the transitive inference B vs. D (Dusek and Eichenbaum 1997). Again, all animals learned the direct choices, and normal rats made the inferential judgment, but rats with hippocampal lesions failed on the inference. Both of these studies show that the hippocampus is not required to learn specific responses to individual cues, but the hippocampus is essential to forming a representation of associative and hierarchical relations, two forms of cognitive maps that organize abstract spaces.

There is also compelling evidence that the hippocampus plays an essential role in organizing memories in time. In humans, hippocampal damage results in a greater deficit in memory for the order of events than in memory for the events themselves (Dede et al. 2016). Also, several functional imaging studies have shown that the hippocampus is activated during encoding and retrieval of the order of events in memories, independent of memories for the events themselves (reviewed in Eichenbaum 2014). Similarly, in rats, selective hippocampal lesions result in impairments in memory for the order of a sequence of nonspatial stimuli, even when memory for the stimuli themselves is spared (Fortin et al. 2002; Kesner et al. 2002). In these experiments, animals are presented on each trial with a unique series of odor stimuli, and then, following a delay, are required to judge which of a pair of stimuli arbitrarily selected from the list occurred earlier. Normal rats perform well at the task, but rats with hippocampal damage are impaired. Control tests have shown that animals with hippocampal damage could distinguish and identify the individual odors on the list, even as they could not remember

the order in which they had appeared. Importantly, the stimuli are all presented at the same locations such that spatial coding plays no role in performance of this task. Furthermore, the contrast between intact memories for the specific stimuli vs. impaired memory for their order strikingly reveals a selective impairment in the temporal organization of memories as a defining feature of hippocampal memory function in animals, as it is in humans.

These findings are complemented by recording studies in animals showing that hippocampal networks link associations among object memories by both spatial and nonspatial dimensions in rats (McKenzie et al. 2014) and organize memories via a mapping of the time course of events in a memory independent of space in rats, monkeys, and humans (Kraus et al. 2013, 2015; Naya and Suzuki 2011; Pastalkova et al. 2008; Paz et al. 2010; Spiers et al. 2001). Most recently, it was shown that hippocampal networks also map an auditory space in rats trained to identify a specific frequency in a signal composed of a tone ramping in pitch (Aronov et al. 2017).

The human hippocampus maps abstract spaces. Recent studies on humans have also indicated that the hippocampus builds cognitive maps of abstract spaces. Several recent studies have shown hippocampal activation in humans associated with linking events that overlap in content via common elements and consequent insight about indirectly related associations, including associations of events by common spatial context (Milivojevic et al. 2015) and/or by common nonspatial elements (Zalesak and Heckers 2009; Zeithamova et al. 2012). Additional recent studies have extended observations on hippocampal mapping of abstract spaces. In one study, participants were engaged in a social role-playing game in which they imagined they had arrived in a new town where they had to find a job and a place to live by interacting with the town's people during fMRI (Tavares et al. 2015). The participants' choices during the interactions positioned the game characters along the dimensions of power and affiliation. fMRI analyses showed that hippocampal activation tracked a vector metric, indicating the locations of the characters in social space relative to the participant. In yet another study, human participants learned arbitrary associations of a set of stick-figure birds that differed by dimensions of neck and leg length. fMRI analyses of activation patterns in the MEC reflected the existence of a spatially regular pattern that mimics grid cell activation also observed during viewing of scenes (Constantinescu et al. 2016). These findings suggest that the hippocampus supports "navigation" in social and abstract spaces.

The hippocampus supports cognitive maps of memories even when not required. It is notable that the range of hippocampal involvement in humans and animals extends to memory tests that superficially do not appear to require relational processing. A prominent example is recognition of recently experienced stimuli (reviewed in Eichenbaum et al. 2007). In these tests, humans and animals initially study a list of well-known stimuli and then later are tested for recognition where a distinction is made between those stimuli that evoke recall of the stimulus in the context of other items in the list (relational processing) and those stimuli that have individually become more familiar as a result of recent study (nonrelational). Across many studies, the hippocampus is required and activated selectively associated with recall, not familiarity. These results can be viewed as parallel to observations described above where animals with

hippocampal damage are impaired in spatial alternation with the same rules and in the same environment depending on a memory demand and not a specific demand for relational processing. Thus, in examples of both spatial memory and recognition memory, a specific memory demand engages hippocampal relational processing even when not explicitly required.

Combining these findings with the evidence on necessary involvement of the hippocampus in navigation, the critical task features that engage essential use of the hippocampal cognitive map are not the spatial cues or demands to calculate, select, or follow particular routes. Rather, in all of the tasks described above, the critical features are engagement by demands for, or a memory-driven preference for, a representation of the organization of events and for the flexible expression of memories, i.e., the defining properties of cognitive mapping across spatial and nonspatial domains as Tolman viewed them (see Eichenbaum 1999, 2004).

Real-World Navigation Requires Learning a Cognitive Map and a Large Body of Nonspatial Knowledge

The study of human navigation in real world applications (e.g., how hikers find their way in a forest) and in specific cultures (e.g., how the Norse sailed the seas), reveals that navigation in a broad variety of situations relies on myriad skills and knowledge obtained by learning to use a variety of tools and diverse and complex information about sun, wind, vegetation, celestial cues, memory for previous routes, and built-up knowledge about relationships between landmarks and layouts (Dudchenko 2010; Huth 2013). In particular, the learning and use of known routes (topological navigation) and cognitive maps (survey navigation) are prominent in descriptions of real-world navigation. Conversely, path integration is consistently described as associated with an accumulation of error that leads to getting lost.

Laboratory studies on navigation in humans and animals have provided strong evidence for the use of both topological navigation (route following) and survey navigation (cognitive maps). Brain imaging studies have identified hippocampal activation in London taxi drivers as they employ learned maps of the city to navigate (Maguire et al. 1997; Maguire et al. 1998), and these experiments have distinguished the activation of the hippocampus in wayfinding by survey navigation from activation of the caudate nucleus in route following (Hartley et al. 2003; Iaria et al. 2003). These studies provide exemplars of different forms of learning the natural environment (Chersi and Burgess 2015; Hartley and Burgess 2005; Voermans et al. 2004), as they are in complex maze learning in rats (Fouquet et al. 2013).

These studies suggest the human hippocampus is preferentially involved in survey navigation. However, more detailed examination of the role of the hippocampus in survey navigation has revealed that the hippocampus is primarily engaged during the building and updating of cognitive maps rather than the expression of well-learned maps (Rosenbaum et al. 2000; Suthana et al. 2009; Teng and Squire 1999; Wolbers and Büchel 2005; see McNamara and Shelton 2003), and these findings are confirmed in studies on rats (Tse et al. 2007; Winocur et al. 2005). Also, in an investigation of hippocampal activation over the detailed course of navigating a well-learned environment in humans, the hippocampus was not continu-

ously engaged, as might be expected if it is involved in integrating the ongoing path or a continuous guiding of movement through a map, but rather is engaged only briefly during the planning of routes to a new destination or altering an already specified route (Spiers and Maguire 2006, 2008).

These findings indicate that human navigation involves the building of a complex knowledge space and learning how to use tools to read it, and after learning, the role of the hippocampus is to support remembering prior experiences in the space as a guide to planning navigational decisions (Brown et al. 2016). Navigation in humans can be aptly characterized as a highly complex memory task supported by the hippocampal system.

On the Evolution of Cognitive Maps

Some have suggested that the hippocampus evolved to map space and support navigation and that these functions were co-opted during evolution to also support the organization and navigation of abstract spaces in memory. For example, O'Keefe and Nadel (1978) viewed the rodent hippocampus as dedicated to mapping physical space; they allowed that the human left hemisphere evolved to map semantic space. Buzsáki and Moser (2013) raised a similar argument, suggesting that the hippocampus and closely associated areas originally evolved as a dedicated spatial navigational system, but in humans was co-opted to support a broader role in mapping memories. They specifically emphasized that the form of representation originally developed to represent routes was the basis for later evolution of the ability to remember the flow of events in episodic memory. They also argued that the form of representation used in the creation of cognitive maps was the basis for later evolution of the ability to represent structured conceptual organizations in semantic memory.

Of course, we do not have access to evidence in the fossil record, so these conjectures cannot be empirically tested. However, there is substantial evidence that hippocampus is essential to creating cognitive maps of physical and abstract space in nonprimates, including birds (Lazareva et al. 2015) as well as rats (Bunsey and Eichenbaum 1996) and mice (Devito et al. 2010), indicating a general role in cognitive mapping across spatial and nonspatial domains among diverse mammalian species. Context-dependent memory, a nonnavigational exemplar of hippocampus-dependent relational memory in mammals, has already evolved in crabs and is supported by a potential analog of the hippocampus, suggesting a very early evolution of relational memory dependent on a hippocampal prototype (Maza et al. 2016). These findings challenge the idea that navigation preceded relational memory in evolutionary appearance.

Deciding this issue is a bit like the “chicken and egg” problem, and so is unlikely to achieve consensus. It is, perhaps, more useful to consider whether processes in navigation can straightforwardly support relational memory or, vice versa, whether a general capacity for relational memory can straightforwardly support spatial navigation. To the extent that the hippocampus is viewed as contributing to navigation via spatial-geometric computations (e.g., computation of physical distances and angles, path integration), the translation to relational memory is not straightforward. By contrast, the above review is consistent with the alternative conclusion that the hippocampus supports both memory and navigation by mapping and flexible expression of a relational organization of events, in-

cluding contributing to spatial memory and navigation. Consistent with this interpretation of the evidence, remembering a route taken is simply a prominent example of episodic memory, and a cognitive map of the environment is simply a prominent example of a semantic memory structure. These considerations support the idea that the role of the hippocampus in spatial navigation evolved as an application of the relational organization of memories.

Concluding Comments: The Role of the Hippocampus in Navigation is Memory

Navigation has a simple definition: “the process of determining and maintaining a course or trajectory from one place to another” (Gallistel 1990). However, the implementation of navigation is highly complex, because many different strategies can support the process of getting from one place to another. It is clear that all recognized strategies involve a strong memory component, from remembering that rewards can be found by random searching, to learning landmarks or places that are associated with goals, to remembering routes or survey maps. In real-world navigation, several of these forms of learning and memory are brought to bear in combination. It is remarkable that the complexity of navigation is seldom acknowledged in research on the role of the hippocampus and that physiological studies that are aimed to understand the highest level of navigation (survey navigation) are focused on the lowest level tasks (searching and guidance). It is also remarkable that considerable attention is paid to potential spatial-geometric computations of the hippocampus (e.g., path integration) that evidence shows contributes so little to navigational success. Conversely, it is perhaps most remarkable that demands for memory that are broadly prevalent in navigational strategies are seldom considered, especially in view of overwhelming evidence for the role of the hippocampus in memory in both animals and humans.

Despite these shortcomings, the above-reviewed research supports some general conclusions about the role of the hippocampal system in navigation:

- The hippocampus is essential to survey navigation, which is most often engaged in tasks where there is high demand for remembering goals and recent experiences, for integrating multiple paths into an organization of places that compose a survey map, and for flexible expression of navigation guided by the map. Correspondingly, in these situations, even when survey mapping is not required, hippocampal networks map environments by parsing locations into place fields and can predict paths through these maps as reflected in sequences of place cell firings.
- At the same time, the hippocampus is also necessary for a broad range of memory tasks that do not involve survey mapping but do involve the organization and flexible expression of memories. Correspondingly, hippocampal networks map many nonsurvey spatial and nonsurvey organizations, including mapping of multiple intersecting routes (e.g., the continuous alternation task), distinct spatial mappings for different cognitive operations in the same environment (e.g., delayed vs. continuous alternation), mapping of temporal organizations (e.g., remembering the order of events in episodes), and abstract relations between events that form a continuity of associations

(e.g., hierarchical organizations, social space).

This evidence should lead us to conclude that the role of the hippocampal system in navigation is to support a particular form of memory organization characterized by Tolman’s broader view of a mapping of memories into a cognitive space of the navigational task, and therein the contribution of the hippocampus to navigation is memory.

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AUTHOR CONTRIBUTIONS

H.E. conceived and designed research; H.E. interpreted results of experiments; H.E. drafted manuscript; H.E. edited and revised manuscript; H.E. approved final version of manuscript.

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