

COMMENTARY

From the GPS to HM: Place Cells, Grid Cells, and Memory

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ABSTRACT: A longstanding debate in hippocampus research has revolved around how to reconcile spatial mapping functions of the hippocampus with the global amnesia produced by hippocampal damage in humans. Is the hippocampus primarily a cognitive map used to support spatial learning, or does it support more general types of learning necessary for declarative memory? In recent years, a general consensus has emerged that the hippocampus receives both spatial and nonspatial inputs from the entorhinal cortex. The hippocampus creates representations of experience in a particular spatial and temporal context. This process allows the individual components of experience to be stored in such a way that they can be retrieved together as a conscious recollection. © 2015 Wiley Periodicals, Inc.

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INTRODUCTION

In 1971, a brief report by John O'Keefe and Jonathan Dostrovsky described a small number of units in the rat hippocampus that “responded solely or maximally when the rat was *situated in a particular part of the testing platform facing in a particular direction*” (O'Keefe and Dostrovsky, 1971, p. 172, original italics). These units supported a theory that the hippocampus “provides the animal with a cognitive, or spatial, map of its environment” (O'Keefe and Dostrovsky, 1971 p. 171). Garnering a respectable, but unremarkable, number of literature citations (20) over the next 5 years, from these humble beginnings arose a scientific juggernaut that is arguably the most successful model system for understanding the neural basis of cognition at the level of brain systems. O'Keefe's discovery of the remarkable place cells led directly to the discovery by Marianne Fyhn, Torkel Hafting, May-Britt Moser, and Edvard Moser of an even more remarkable cell: the grid cell (Hafting et al., 2005). Located in the medial entorhinal cortex, a major input to the hippocampus, grid cells fire in a hexagonally arranged lattice of locations, an almost inconceivably regular, crystalline pattern that is unlike any other neural response property yet discovered. O'Keefe, Moser, and

Moser shared the 2014 Nobel Prize in Physiology or Medicine “for their discoveries of cells that constitute a positioning system in the brain... an ‘inner GPS’ in the brain that makes it possible to orient ourselves in space, demonstrating a cellular basis for higher cognitive function” (http://www.nobelprize.org/nobel_prizes/medicine/laureates/2014/press.html).

Fourteen years prior to O'Keefe and Dostrovsky's report, another seminal paper appeared that had an equal or greater impact on current thinking about the hippocampus. This article was a case report by Brenda Milner and William Scoville (Scoville and Milner, 1957) about the famous patient H.M., who developed a dense, global amnesia after bilateral removal of his hippocampus and surrounding cortex. Milner and Scoville's description of H.M.'s amnesia originated the idea that the hippocampus was critical for the formation and transfer to long-term storage of *declarative memories*: memories that could be brought to consciousness and verbalized, as opposed to procedural memories such as habits, motor skills, or simple Pavlovian or instrumental responses (Squire, 1987).

The relationship between the “inner GPS” and the declarative memory function of the hippocampus has been the subject of much debate among hippocampal experts—and the source of much confusion among the general neuroscience community. If the hippocampus is primarily a spatial mapping system, how does this system explain the global amnesia of H.M. and other hippocampal patients, who exhibit profound memory deficits that are not obviously spatial in nature? Drawing on the pioneering work of Edward Tolman and Donald Hebb, O'Keefe and Lynn Nadel (O'Keefe and Nadel, 1978) published one of the most influential books in the history of cognitive neuroscience, *The Hippocampus as a Cognitive Map*. O'Keefe and Nadel formulated a specific theory about the primary function of the hippocampus in forming cognitive maps and the role of these maps in memory: “We shall argue that the hippocampus is the core of a neural memory system providing an objective spatial framework within which the items and events of an organism's experience are located and interrelated” (O'Keefe and Nadel, 1978, p. 1). A key point was their distinction between a *locale* system and a *taxon* system. The locale system, identified with the

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hippocampus, created cognitive maps that allowed the animal to develop and evaluate place hypotheses that were flexible, changed rapidly, and specific to particular contexts. The taxon system, which in modern times might be identified with habit systems such as the striatum or neocortex, learned incrementally, was inflexible, and produced stereotypic, route-like behavior that was unable to adapt to different contexts. According to the cognitive map theory, lesions to the hippocampus caused deficits in behavioral flexibility by damaging the locale system, leaving the rigid taxon system to guide the animal's behavior.

Since 1978, the hippocampal research community was mostly split into two fields. Although there was much overlap, one line of research concentrated on the properties of place cells (mostly in rodents) and the computations that allowed the hippocampus to form the "objective spatial framework," which was its core function in memory. The other line of research concentrated on how the "items and events of experience" are interrelated and stored as a memory by hippocampal processing, not necessarily within a spatial framework. After many years of debate over these approaches, a general consensus has emerged that there are two input streams into the hippocampus (Manns and Eichenbaum, 2006; Knierim et al., 2006; Eichenbaum et al., 2007; Knierim et al., 2013). One stream (through the medial entorhinal cortex [MEC]) appears largely dedicated to spatial (and perhaps temporal) processing. The other stream (through the lateral entorhinal cortex [LEC]) appears to process information about individual items in the world. These input streams are merged in the hippocampus, which creates conjunctive object + place (or item + context) representations that are crucial for creating the spatial- and temporal-specific representations of experience that can be stored and retrieved as a specific, episodic memory.

THE MEC STREAM

The MEC is part of a brain circuit that appears largely devoted to representing the location of the animal. It is connected with a number of other regions (the parasubiculum, the dorsal presubiculum, and the retrosplenial cortex) that contain cell types that carry space- or motion-related signals (Taube et al., 1990; Cho and Sharp, 2001; Hafting et al., 2005; Boccaro et al., 2010). These cell types include grid cells, head direction cells, boundary cells, speed cells, theta cells, and conjunctive grid \times head-direction cells (Sargolini et al., 2006; Solstad et al., 2008; Savelli et al., 2008). The identification of this specialized, spatial processing system as one of the two major inputs to the hippocampus confirms one aspect of the cognitive map theory: space is fundamental to hippocampal function. The MEC and its related structures are believed to perform a path integration computation (McNaughton et al., 2006; Burgess et al., 2007; Hasselmo et al., 2007), by which an animal's movement vector (speed and direction) is integrated over time to continually update a representation of the animal's position

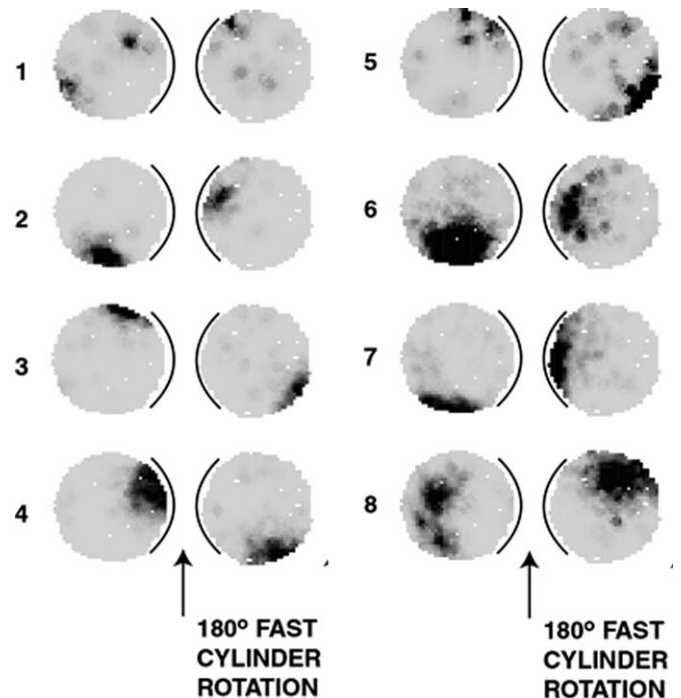


FIGURE 1. Internally coherent population of place cells. Eight place cells were recorded simultaneously in a cylinder with a white cue card (denoted by the black arc). In the middle of the session, the cylinder was abruptly rotated 180° with the rat inside. All 8 place fields rotated coherently $\sim 120^\circ$. Note that this rotation does not correspond to any sensory cues either in the cylinder or in the external lab environment. The ability of the system to maintain an internally coherent spatial representation decoupled from external sensory landmarks indicates the presence of specialized computational circuits using self-motion to update the spatial signal. (Modified with permission from Knierim, 2002).

in an allocentric spatial framework. A path integration input would explain certain properties of place cells that demonstrate the fundamental, spatial nature of place cells. Under certain experimental manipulations, place fields can become completely dissociated from any external sensory cues while maintaining internally coherent spatial relationships among each other (Fig. 1). The place cells, under these conditions, act as a purely cognitive, internal map of position that can assume any arbitrary orientation relative to the external world. This phenomenon must reflect specialized circuitry and spatial computations unrelated to external sensory input, and it argues for a dedicated spatial processing input to the hippocampus. Recent results have suggested that both nonhuman primates and humans may also have similar grid-like correlates in the entorhinal cortex (Doeller et al., 2010; Killian et al., 2012).

THE LEC STREAM

In contrast to the MEC, there is no evidence that space is a particularly fundamental component of processing in the LEC. The LEC does not appear to contain grid cells or head

direction cells, and under typical experimental conditions there is little evidence of robust spatial selectivity (Hargreaves et al., 2005; Yoganarasimha et al., 2011) or strong theta modulation of units in the LEC (Deshmukh et al., 2010). The computational function of LEC is not well understood. However, LEC cells fire more strongly than MEC cells when rats investigate individual objects (Deshmukh and Knierim, 2011). This result is consistent with notions that the LEC is part of the “what” stream of sensory processing, providing input to the hippocampus about the individual items in an environment. Although this description may be accurate to a first approximation, LEC can show a spatial signal related to objects under some conditions. First, in the presence of salient objects, a small fraction of LEC cells fire in specific locations that look just like hippocampal place fields; this property does not appear to be present in environments without objects (Deshmukh and Knierim, 2011). Second, when an item is moved in an environment or removed entirely, a small fraction of LEC cells fire in the former location(s) of that object, potentially maintaining this “memory trace” of object location for days (Deshmukh and Knierim, 2011; Tsao et al., 2013). Thus, spatial information of some kind is represented in LEC, although it is of a qualitatively distinct nature than the spatial representation of MEC and not as prevalent. If the MEC is thought to be primarily a computational circuit for path integration, the LEC may be usefully described as encoding information about items in the external world, including (but not limited to) spatial information about the locations of those items (Manns and Eichenbaum, 2006; Knierim et al., 2006; Lisman, 2007; Knierim et al., 2013).

PLACE CELLS AND MEMORY: INTEGRATING THE MEC AND LEC INPUT STREAMS

Remapping and Context

Early studies of place cells emphasized their spatial stability relative to the distal landmarks in an environment (Knierim and Hamilton, 2011). This emphasis on stability begged the question of how they could be used for memory, which requires neural plasticity and changes in neural representations. Knierim et al. (1995) showed that the stability between the orientation of landmarks and the firing of place cells and head direction cells was plastic and depended on the prior experience of the animal. If animals were trained to regard the landmarks as unstable, then the place cells and head direction cells could adopt arbitrary orientations relative to the landmarks between visits, even though they maintained internal consistency between themselves (presumably via path integration computations). Another early demonstration of hippocampal representational plasticity was the remapping phenomenon, in which different subsets of place cells are active in different environments (Muller and Kubie, 1987). This remapping phenomenon is a potential mechanism underlying the

hippocampal role in context-dependent learning (Nadel et al., 1985). Place cells active in one environment could organize the “items and events of experience” that occur in that context, and a different subset of place cells could organize potentially overlapping “items and events” that occur in a different context, thus allowing segregation of the memory traces and reducing interference during recall. Further work showed that remapping was not limited to different environments. For example, changes in the animal’s task within the same environment, or changes in the animal’s internal, motivational state, could also trigger remapping (Markus et al., 1995; Kennedy and Shapiro, 2009). Grid cells in MEC do not appear to remap like place cells (Fyhn et al., 2007). Rather, they appear to maintain the same spatial firing patterns relative to each other across environments. This difference between grid cells and place cells may be the most important functional difference between the two sets of cells.

Splitter Cells

Related to remapping is the splitter-cell phenomenon (Wood et al., 2000; Frank et al., 2000; Ferbinteanu and Shapiro, 2003). When animals run a T-maze (or similar) task, place cells can fire more strongly in a place field on the central arm when the animal is about to choose one turn than the other. One interpretation of this phenomenon is that the hippocampus remapped the two trial types, with one map encoding the behavioral context of a “turn right” trial and the other the context of a “turn left” trial. Interestingly, when the task is changed from a continuous alternation task to a delayed nonmatch-to-place task, with discrete sample and test phases, fewer place cells encode the left-choice/right-choice trials. Instead, they fire differently at the same location based on whether the rat is performing a sample trial or a test trial, regardless of the motor behavior (Griffin et al., 2007). It appears that the hippocampus creates separate maps based on the structure of the task at hand. This plasticity in encoding the different task-dependent contexts demonstrates that the formation of these maps is influenced by the learning parameters and/or the behavioral regularities of the task.

Sequences

A hallmark of episodic memory is the recollection of a sequence of events, and correspondingly, place cells encode sequence information (Jensen and Lisman, 2005; Foster and Knierim, 2012). During slow-wave sleep, the hippocampus replays sequences of place cells that were active in the preceding behavioral session, which may be related to memory consolidation (Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996). The backward shift and expansion of place fields has been modeled as encoding memory for sequences, as spike-timing dependent plasticity mechanisms strengthen asymmetrically the connections between neurons that are active in a particular spatiotemporal order (Mehta et al., 1997, 2000). This effect is dependent on NMDA receptors (Ekstrom et al., 2001) and is more long-lasting in CA3

than in CA1, suggesting that CA3 is the site of long-term storage of memories of sequences (Lee et al., 2004a). Head direction cells also display similar phenomena (Yu et al., 2006). Place cell sequences are related to the animal's decision making during behavioral tasks. During early training when animals pause at the choice point of a modified T-maze task, they look left and right as they make their decisions about which way to turn (called *vicarious trial and error*). During this time, hippocampal population activity reflects position sweeps down each choice arm, as if the animal were imagining the consequences of runs down each arm (Johnson and Redish, 2007). Similarly, on an open platform, hippocampal activity replays precise trajectories toward a goal location (Pfeiffer and Foster, 2013).

PATTERN SEPARATION AND PATTERN COMPLETION

Classic computational theories of associative memory emphasized two complementary processes (McNaughton and Morris, 1987; O'Reilly and McClelland, 1994; Rolls and Treves, 1998). Pattern separation refers to the ability of a network to orthogonalize similar input patterns before storing them, in order to minimize interference and errors during subsequent recall. Pattern completion refers to the ability of a network to retrieve complete patterns of activity when presented with partial or corrupted input patterns. These operations have been associated with the dentate gyrus (pattern separation) and the recurrent collateral network of CA3 (pattern completion/error correction/generalization). Studies of place cells have provided compelling evidence in favor of the notion that the DG performs a pattern separation function on its inputs (Leutgeb et al., 2007; Neunuebel and Knierim, 2014), whereas CA3 displays attractor dynamics that results in a sigmoidal relationship between input similarity and output similarity (Leutgeb et al., 2004; Lee et al., 2004b; Neunuebel and Knierim, 2014). When inputs are similar, CA3 does a pattern completion/generalization operation to "correct" the errors; when inputs are dissimilar, the CA3 region transitions to a different basin of attraction and reflects the pattern separation processing presumably imposed by the DG (Guzowski et al., 2004).

TEMPORAL CONTEXT AND TIME CELLS

The idea that place cells create a spatial framework used to organize the items and events of experience into memory is appealing, but what happens when one has an experience in a single location (e.g., having a discussion with a student in one's office, sharing a dinner conversation, writing a manuscript)? O'Keefe and Nadel (1978) suggested that the addition of time—the fourth dimension—to the cognitive map could explain episodic memory in humans. Recent studies have shown that time is represented even in rodent hippocampus,

however, on multiple time scales. Over the course of minutes to hours, the place cell map appears to gradually change, in accordance with models of "temporal context" (Manns et al., 2007; Mankin et al., 2012; Howard et al., 2014). Thus, just as the representation of place smoothly changes as an animal explores an environment, this spatial representation also changes gradually as time passes. This phenomenon may allow the cognitive map to encode different experiences in the same spatial context upon an evolving spatiotemporal framework.

On a more rapid time scale, Pastalkova et al., (2008) and MacDonald et al., (2011) have demonstrated a remarkable property of hippocampal cells when an animal remains in place but is actively engaged in the delay period of a task. Under these conditions, hippocampal neurons fire as a function of time, not place. Some cells will fire at the start of the delay period and others will have a peak firing at other times. The firing rate plots of these "time cells" (or "episode cells"), as a function of time when the rat is stationary, look just like the firing rate plots of place cells as a function of location when rats are running on a track. Moreover, they also appear to show the same "remapping" phenomena (MacDonald et al., 2013). Under other conditions, the cells appear to encode distance rather than space or time. Computational modeling has shown that the same network can produce time, distance, and place encoding by changing the composition of inputs to the network (Hasselmo, 2012). Intriguingly, preliminary data show that grid cells have time-encoding properties under the same conditions as place cells (Eichenbaum et al., 2014). The discovery of time-encoding properties of hippocampal cells is an enormous step forward to understanding how a spatiotemporal cognitive map can underlie episodic memory in humans and episodic-like memory in nonhuman animals.

NONSPATIAL CORRELATES OF PLACE CELLS

If the grid cells and place cells form a circuit for creating the spatiotemporal framework for memory (O'Keefe and Nadel, 1978; Eichenbaum, 2014), how are the "items and events of experience" incorporated onto this framework. As suggested earlier, it is likely that this information is conveyed to the hippocampus via the LEC input stream and becomes incorporated into the cognitive map. Early work on place cells showed that nonspatial cues could modulate the firing of place cells, in the form of cells that O'Keefe (1976) termed *misplace cells*: cells that fired in a specific location when the animal encountered an unexpected object at that location or failed to receive an expected reward at that location. Numerous examples of conjunctive representations of place and items have been shown over the years. In some cases, place cells form in locations previously occupied by objects (similar to examples of LEC cells discussed above), as if the hippocampus created a memory of the objects (Deshmukh and Knierim, 2013). Other experiments with objects have shown that the hippocampus encodes space as a primary variable, but with nonspatial cues encoded

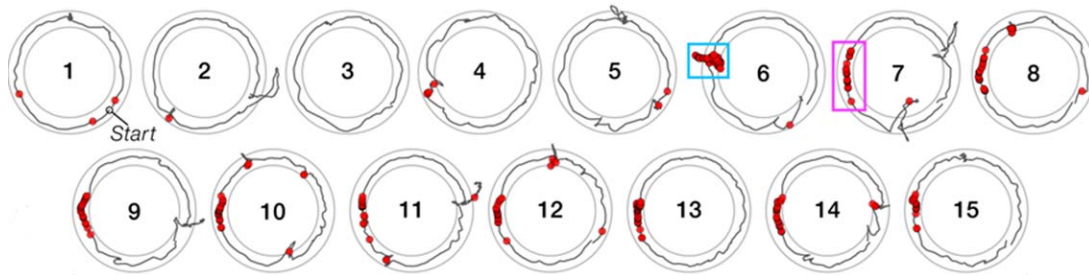


FIGURE 2. Place field formation and head scanning. A rat ran 15 laps around a circular track. The place cell was mostly silent during the first 5 laps. On lap 6, the rat paused and performed an investigatory, head-scanning behavior (cyan box), during which the cell fired vigorously (red dots). On the rat's next visit to that

location (lap 7, magenta box) a new place field appeared, which was stable for the rest of the recording session (laps 8–15). (Reproduced from Monaco et al., *Nat Neurosci*, 2014, 17, 725–731). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

as secondary correlates (Manns and Eichenbaum, 2009; McKenzie et al., 2014). In a fear conditioning task, place cells developed responses to the conditioned stimulus, but only when the animal was within the place field of the cell (Moita et al., 2003). Few examples exist in the literature of nonspatial firing of rodent hippocampal neurons that are clearly not somehow a modulation of an underlying spatial or temporal primary correlate.

Can we detect the real-time formation of a hippocampal memory? A recent study showed that new place fields can form immediately and robustly after the animal performs an attentive, exploratory behavior known as head scanning (Monaco et al., 2014). In this study, rats ran on a circular track, and a fraction of the hippocampal silent cells abruptly formed strong, new place fields in the middle of the recording session. For a significant minority, the place field formation was preceded by robust firing of the cell on the previous lap, when the rat paused at that location and moved its head laterally off the track, investigating the extra-track environment (Fig. 2). Although there is no evidence that the formation of this place field corresponds to the formation of an explicit memory, such one-trial, robust creation or strengthening of place fields is the type of plasticity seemingly required if the hippocampal cognitive map acts as a memory index to locate and interrelate cortical representations of the items and events of experience (Teyler and DiScenna, 1985; Schwindel and McNaughton, 2011).

MOVING FORWARD

With this selective review, I hope to have demonstrated that we are beyond the “spatial vs. nonspatial” controversies that characterized much of the debate in the field. There is a broad consensus that something like the ideas reviewed here are on the right track. Hippocampal computational processing on distinct MEC and LEC inputs allows the formation of context-specific, item + place/time representations that are critical to bind together the different components of an experience and

store them in a way that can be retrieved and experienced as a conscious recollection. Lively debate will continue about the details, but the main task now is to understand the precise neural mechanisms that might underlie this general consensus. What are the computations of the different hippocampal subregions? How do the LEC and MEC streams combine? Does the current consensus actually hold water in explaining the role of the hippocampus in human declarative memory? How do we test this specifically? Does the hippocampus perform the same computation along its longitudinal axis, but with different inputs and outputs, or is ventral hippocampal processing fundamentally different from dorsal hippocampal processing? Does the hippocampus do the same computation across species (bats, rats, mice, birds, monkeys, and humans), but with different inputs and outputs appropriate for the ethological niche of that species? These are the types of questions that are under active investigation by a myriad of hippocampal investigators. Hopefully, the answers will ultimately lead to an understanding of how the “inner GPS” is related to the “inner HM,” our memories that define us as unique individuals with specific life experiences that molded us into our current identities.

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