COMMENTARY

Navigating the Human Hippocampus Without a GPS

Halle R. Zucker,* and Charan Ranganath*

ABSTRACT: The award of the Nobel Prize to Professors John O'Keefe, May-Britt Moser, and Edvard Moser brings global recognition to one of the most significant success stories in modern neuroscience. Here, we consider how their findings, along with related studies of spatial cognition in rodents, have informed our understanding of the human hippocampus. Rather than identifying a "GPS" in the brain, we emphasize that these researchers helped to establish a fundamental role for cortico-hippocampal networks in the guidance of behavior based on a representation of the current place, time, and situation. We conclude by highlighting the major questions that remain to be addressed in future research. © 2015 Wiley Periodicals, Inc.

KEY WORDS: context; perirhinal; parahippocampal; binding; time

INTRODUCTION

We, along with the rest of the neuroscience community, are delighted to celebrate the award of the Nobel Prize to John O'Keefe, May-Britt Moser, and Edvard Moser. Their studies have unequivocally demonstrated that a complex, self-directed behavior can be understood at the level of computations implemented by specific neural circuits. As a result, research on the hippocampus has become the most significant success story in modern neuroscience.

In this commentary, we will take a step back to reflect on how their contributions have fundamentally affected our understanding of the hippocampus (HC), spatial cognition, and memory. Although the Nobel Prize press release and corresponding media coverage credited O'Keefe and the Mosers with finding the brain's "internal GPS" system, we argue that this description obfuscates the innovation and significance of their work. Here, we aim to provide some context for their scientific accomplishments and explain how research on spatial cognition in rodents has

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informed our understanding of human HC function. Finally, we will outline major unresolved questions and directions for future research.

SPACE AND A SENSE OF PLACE

Thomas Kuhn, in his study of the history of science, argued that major scientific advances come about through the establishment of a new paradigm that enables systematic progression towards an answer to a fundamental question (Kuhn, 1996). In the case of the HC, this paradigm was a recording apparatus and experimental approach to systematically investigate neural correlates of self-initiated, complex behavior in an awake, naturally behaving animal (O'Keefe and Dostrovsky, 1971; Ranck, 1973). Although they were not the first to record HC unit activity in awake, behaving animals (e.g., Komisaruk and Olds, 1968; Olds et al., 1969), O'Keefe and Dostrovsky (1971) were the first to relate HC neural firing to the rat's position while it moved freely through the environment. Rather than examining firing during an experimentally controlled behavior, O'Keefe and Dostrovsky controlled the *environment* and examined how the environment affected *spontaneous behavior* and neural firing. Their modest report, focused on a subpopulation of 8 of 76 neurons that responded "solely or maximally when the rat was *situated in a particular part of the testing platform facing in a particular direction*" (p. 172; italics from original). O'Keefe and Dostrovsky related these cells to the concept of the "cognitive map" (Tolman, 1948), and proposed that "it is the loss of this spatial reference map which results in all or most of the behavioral deficits reported for hippocampectomized rats" (p. 175).

O'Keefe and Nadel (1978) further advanced this line of thinking by summarizing a vast body of evidence from lesion and physiology studies in rodents, neuropsychological research in humans, and theoretical ideas from philosophy and linguistics. According to their model, HC representations exhibit the following properties: "(1) preservation of spatio-temporal context; (2) single occurrence storage; (3) minimal interference between different representations of the

same item; (4) multiple channels of access for the retrieval of any, or all, of the relationships embodied in the map" (p. 384). As we will describe below, these ideas remain central to virtually every viable contemporary theory of HC function.

Research on place cells has revealed many important insights, but perhaps the most significant is that place cells can "remap," such that they exhibit distinct firing fields when the rat is in different spatial contexts (Muller and Kubie, 1987; Thompson and Best, 1989). The fact that place cells remap in different environments indicates that HC place cells indicate one's location within a specific context. Subsequent work has shown that context (both spatial and non-spatial) may be the most fundamental attribute that is encoded by HC ensembles and that even slight changes to a context can result in significant remapping (O'Keefe and Burgess, 1996; Leutgeb et al., 2005).

A second key insight is that the timing of HC firing is temporally organized relative to the phase of ongoing population-level theta oscillations (O'Keefe and Recce, 1993). The discovery of phase precession is important for at least two reasons. First, it suggests that oscillations, which reflect rhythmic network-level changes in excitability, play a role in shaping HC activity. Second, it highlights the fact that spike timing carries a great deal of information and that it is essential to consider this variable in addition to overall changes in HC place cell firing.

PATHS BEYOND THE HIPPOCAMPUS

Many researchers now accept that the HC influences behavior by interacting with specific cortical and subcortical networks. Nonetheless, until recently, single-unit recording research on navigation focused almost exclusively on the HC with the overwhelming majority of recordings coming from the dorsal third of subfield CA1. The Mosers and their team helped to move the field forward by taking a broader view of HC function. Their recordings and parallel work with lesion and inactivation methods helped to characterize differences along the longitudinal axis of the HC (Moser and Moser, 1998; Kjelstrup et al., 2002) and between different HC subfields (e.g., Leutgeb et al., 2004, 2007). Most importantly, they broadened the perspective of the entire field through their investigations of cortico-hippocampal networks. Guided by the detailed anatomical observations of Menno Witter, they recorded from the medial entorhinal cortex (MEC), the source of projections thought to drive place cells. Recording from MEC while rodents foraged in large environments allowed them to identify grid cells and to capture their regularly spaced firing fields (Hafting et al., 2005).

The relationship between grid cells and place cells is still an area of active research (Krupic et al., 2015), but it is fairly clear that place fields do not emerge solely via downstream integration of grid cell input (Bush et al., 2014). Instead, place cells

seem to integrate input from at least two circuits. One of these circuits includes grid cells, head direction cells (see Muller et al., 1996 for a review), and border (or "boundary vector"; Hartley et al., 2000) cells in the retrosplenial cortex, distal subiculum, MEC, dorsal presubiculum, anterior thalamus, and mammillary bodies. The other circuit provides information about the locations of salient objects and landmarks integrated from sensory inputs to lateral entorhinal cortex.

THE BROKEN GPS

All of the work described above points to the fact that cells in cortico-hippocampal circuits in rodents are sensitive to spatial position relative to the external environment. Using virtual reality paradigms, researchers have identified cells with place fields in the human HC with intracranial recordings (Ekstrom et al., 2011) and fMRI (Hassabis et al., 2009). Furthermore, HC activity patterns can be used to decode information about context and location within a virtual environment (Bonnici et al., 2012; Stokes et al., 2015). Given the parallels in HC anatomy between humans and rats, and the functional parallels identified above, it would be tempting to conclude that the HC, like a GPS, encodes spatial position in a metric fashion.

There are at least two reasons, however, to reject the GPS analogy. First, studies of place cells in rodents do not capture some essential features of spatial cognition in adult humans (see Ekstrom, this issue for further discussion of this issue). Most studies of place cells involve rats with little knowledge of environments outside of their home cages with recordings performed when the rat is exploring relatively small environments. Thus, typically, a rat has limited semantic knowledge but a highly detailed spatial representation of the environment. This is not the case for humans who have extensive semantic knowledge and thus rely on schemas to inform spatial navigation and orientation.

Second, even if the human HC encodes space in a metric fashion, humans have an extensively developed neocortex that likely plays a dominant role in guiding spatial navigation and orientation. Indeed, navigation in learned environments, along with many forms of new spatial learning, can be performed in patients with HC lesions (Bohbot et al., 2004; Teng and Squire, 1999). For instance, one study reported the case of a taxi driver with bilateral HC lesions who could navigate routes in London by relying on major artery roads but not when required to use minor roads (Maguire et al., 2006). The emerging conclusion seems to be that neocortical areas can support schematic or "semanticized" spatial representations whereas the HC adds further precision to spatial cognition.

If the neocortex encodes schematic representations of space, and if humans rely on these schematic representations, it follows that people probably do not have a sense of space that is analogous to a GPS. Indeed, human spatial representations are probably no more analogous to a GPS than episodic memory
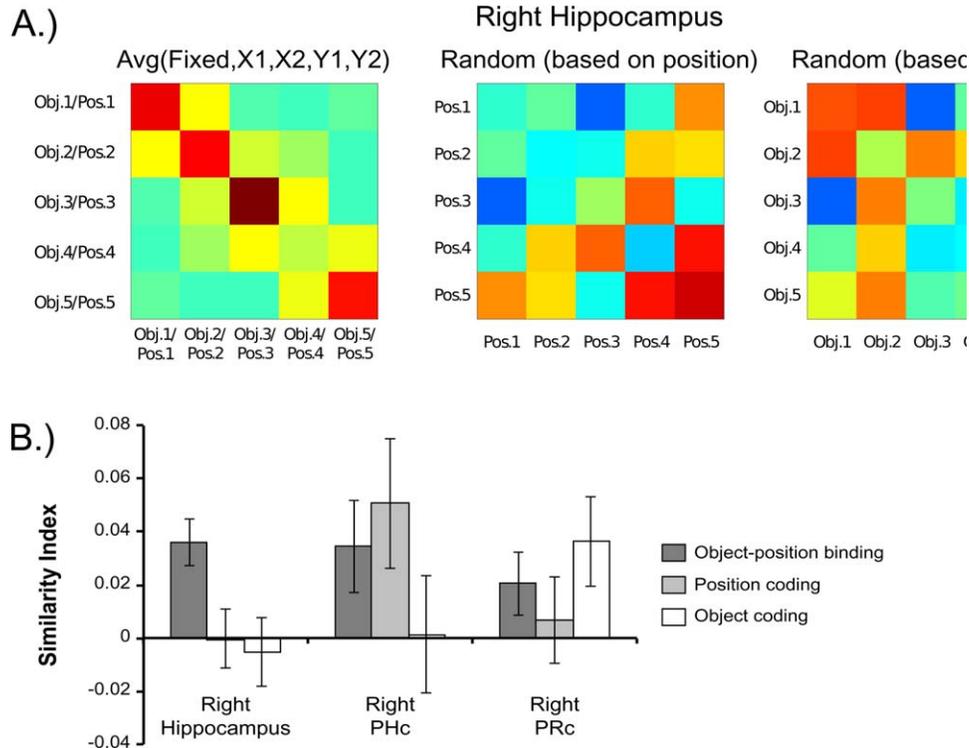
FIGURE 1. Temporal coding in the human hippocampus (adapted from Hsieh et al., 2014): In this study, participants learned sequences of objects and were scanned while viewing objects in sequence as well as random object sequences. (A) Right hippocampal activity patterns were compared across repetitions of objects in a learned sequence (upper left), repetitions of the same serial position (upper middle) or same object (upper right) in a random object sequence. (B) The exclusive sensitivity of the hippocampus to items in context (lower left) can be distinguished from the more generalized sensitivity of the parahippocampal cortex ("PHc," lower middle) to temporal position, and the sensitivity of perirhinal cortex ("PRc," lower right) to object identity. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

representations are analogous to photographs. Furthermore, by exclusively focusing on metric representations of the external world, the GPS analogy misses fundamental aspects of HC function. This will become apparent as we consider non-spatial influences on HC activity.

MOVING OFF THE MAP

Single-unit recording studies have generally revealed that non-spatial variables can influence HC coding. Recent work has highlighted the fact that the HC is exquisitely sensitive to temporal context, even when spatial factors are held constant. For instance, several studies have found that HC cells code for temporal intervals during delay periods in memory tasks, even when the animal is running on a wheel (Pastalkova et al., 2008), treadmill (Kraus et al., 2013), or is stationary (MacDonald et al., 2011).

Behavioral context also strongly influences HC representations. For instance, place cells recorded from CA1 during delayed alternation tasks depend not only on the animal's current location but also on the journey and anticipated goal (Wood et al., 2000; Shapiro and Ferbinteanu, 2006; Ainge et al., 2007). In a similar vein, the temporal selectivity of time cells is also sensitive to the structure and rules of a memory task (MacDonald et al., 2011). Reward and motivational states are also known to substantially shape HC context representation (Kennedy and Shapiro, 2009; Mizumori, 2013; McKenzie et al., 2014). In contrast to the robust coding of time, place, or situational context, object coding is relatively weak. Although HC ensembles are sensitive to the identity of specific odors (Eichenbaum et al., 1987; McKenzie et al., 2014), HC encoding of real objects requires extensive experience, and cells typically encode objects in a location or context-specific manner (Manns and Eichenbaum, 2009).

Results from imaging studies in humans strongly converge with the single-unit recording data from rodents. FMRI studies have typically examined learning or retrieval of words or objects, and these studies have shown that activation is enhanced during successful encoding or retrieval of the association between these items and contextual information (see Diana et al., 2007; Howard et al., 2007; Ranganath, 2010, for reviews). More recently, fMRI studies have used multivariate activity patterns to decode HC representations in a manner
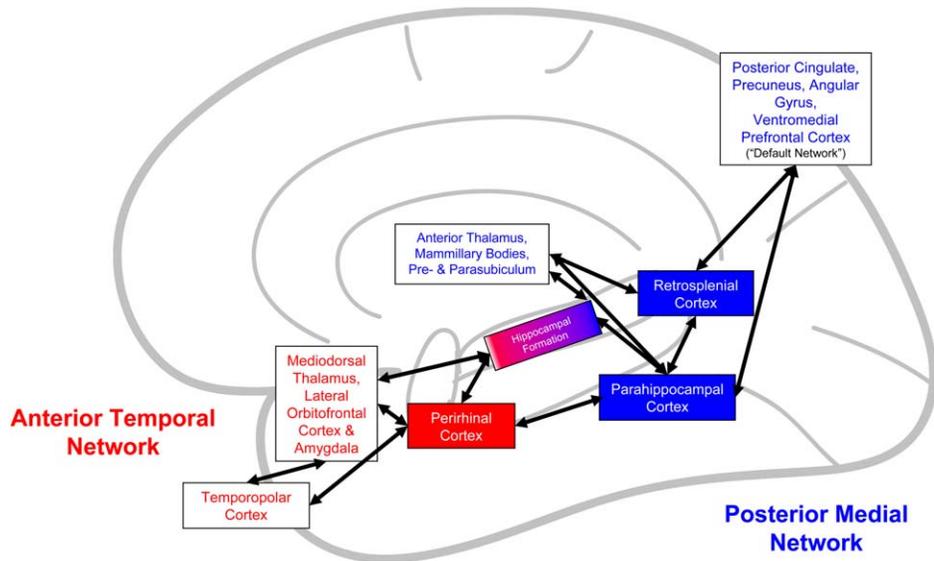
FIGURE 2. **Cortico-hippocampal networks for memory-guided behavior (adapted from Ranganath and Ritchey, 2012). The cortical and subcortical regions that interact with the hippocampus can be subdivided into posterior medial (PM; shown in blue) and anterior temporal networks (AT; shown in red). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]**

similar to population vector analyses in single-unit recording studies. These studies have found that human HC activity patterns carry no detectable information about objects (Hsieh et al., 2014; Libby et al., 2014), some information about spatial and non-spatial context (Libby et al., 2014; Stokes et al., 2015; Ritchey et al., 2015), and substantial information about the association between an item and its spatio-temporal context (Hannula et al., 2013; Copara et al., 2014; Hsieh et al., 2014; Libby et al., 2014; see Fig. 1).

THE HIPPOCAMPUS AS A COGNITIVE STATISTICIAN

O'Keefe and Nadel (1978) stated that, "memory comes in two basic varieties: (1) memory for items, independent of the time or place of their occurrence; (2) memory for items or events within a spatio-temporal context" (p. 381). They proposed that the HC is specifically central to "the representation of experiences within a specific context" (p. 381), an idea supported by over 35 yrs of subsequent research on the HC in rodents and humans (Ranganath, 2010). But, as often happens in science, the answer to this question raises a new question: How does the HC identify and differentiate contexts? Although there is no single answer to this question, we suggest one hypothesis below:

O'Keefe and Nadel (1978) emphasized that the HC encodes contexts in order to generate predictions about upcoming stimuli and events in the environment. Fuhs and Touretzky (2007)

expressed this idea in terms of a balance between two computational goals: "minimiz[ing] the variability of the distribution of experiences within a context and minimiz[ing] the likelihood of transitioning between contexts." (p. 3173). Put another way, HC representations should be optimized to identify the most informative and temporally stable features in the environment (Ranganath, 2010). Conversely, sudden changes in the flow of information over time should lead to establishment of a new context representation (remapping). This nicely explains the sensitivity of the HC to spatial context, because distal cues, landmarks, and borders in a particular environment are temporally stable, and the relationships between them are highly predictable. This view also explains the essential role of the HC in memory tasks that require the integration of information over time (Eichenbaum, 2013; Hsieh et al., 2014).

Taking this view further, one can extend the role of the HC from representation of physical space to the representation of a "state space," or a set of probable events and contingencies linked to a particular context (see Eichenbaum et al., 1999 for a similar idea). Ranganath and Ritchey (2012) previously argued that the HC influences behavior by modulating activity in a posterior medial (PM) network that encodes mental models about places and situations and an anterior temporal (AT) network that encodes representations of entities. Accordingly, once a stimulus or environmental cue activates a HC representation, HC pattern completion results in strong feedback to these networks, enhancing activation of episodically related items and contexts, and dampening activation of competing representations. Thus, the hippocampus may act like a Bayesian statistician, by using contextual cues to bias the prior probability that a cortical representation of an entity or situation

will be activated. Learning about familiar entities and situations might not require a HC, although we would expect that HC feedback would help to resolve competition amongst related representations, affording more precision during memory retrieval. This idea accords with findings in rodents showing that new information that is accommodated within an existing schema can rapidly become HC independent (Tse et al., 2007) and with demonstrations of semantic knowledge acquisition in humans who experienced HC damage early in childhood (Baddeley et al., 2001).

INTEGRATING AND A PATH FORWARD

Moving forward, what are the major questions that need to be addressed by the next generation? One important question concerns the relationship between spatial and temporal coding in the HC (Eichenbaum, 2013). Temporal context is thought to be critical for episodic memory representation (Tulving, 1972), but so is spatial context (Burgess et al., 2002). In everyday experiences, spatial context is learned, at least in part, through temporal integration of motion signals and sensory cues. Likewise, verbal references to the temporal order or duration of events inevitably involve spatial descriptors (Boroditsky, 2000). We anticipate that, in coming years, researchers will devise new ways to disentangle hippocampal representations of space and time (cf., Ekstrom et al., 2003; Kraus et al., 2013) and clarify how they interact. Additionally, researchers will need to specify how space and time are represented at different scales (Howard and Eichenbaum, 2014), and whether some HC subfields might be more involved in encoding spatial context (Mankin et al., 2012) and others in temporal context (Mankin et al., 2015).

A second direction for new research will be to better understand HC interactions with subcortical and neocortical regions. At the time of O'Keefe and Nadel (1978), little was known about the extended networks that interact with the HC. It is now clear that the HC is not the only player when it comes to memory, and that it is no longer tenable to assume that the HC interacts with memory networks distributed across the entire brain. The HC directly interacts with a few semi-modular small-world networks of cortical areas and subcortical nuclei (Ranganath and Ritchey, 2012; Ritchey et al., 2014; see Fig. 2). As these networks become more extensively characterized, we expect the emerging findings to fundamentally challenge existing models of systems consolidation (Ritchey et al., 2015), and to emphasize the importance of cortico-hippocampal interactions in several cognitive domains, including perception, action, semantic cognition, and decision-making (Ranganath and Ritchey, 2012; Mullally and Maguire, 2013; Nadel and Peterson, 2013; Wang et al., 2015). We anticipate that future studies will highlight the role of functional connectivity (Ritchey et al., 2014), perhaps mediated by oscillatory synchrony (cf., Gordon, 2011) in coordinating cortico-hippocampal interaction.

A third emerging area is the interaction between motivation and memory in the HC. Although it has long been known that emotional arousal modulates HC encoding and consolidation, it is now clear that arousal enhances the gist of an event, but not specific details (Kensinger et al., 2007). We therefore hope that upcoming research will clarify how arousal and/or stress *alters* the HC representation of an episode. We also hope to see more research on how extrinsic rewards (Singer and Frank, 2009; Shohamy and Adcock, 2010) and intrinsic motivation (Gruber et al., 2014) modulate HC encoding, offline reactivation, and consolidation. Finally, it will be important for researchers to understand how the HC influences behavior related to anxiety (Kjelstrup et al., 2002; Bannerman et al., 2004) and assessments of value (Shohamy and Adcock, 2010).

Whatever the paradigm shift of the next generation happens to be, we are optimistic that it will stimulate the emergence of anatomically principled theories, exciting new research approaches, and findings that challenge us to remap our views on the cortico-hippocampal networks that support memory-guided behavior.

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