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Uncovering the Hippocampal Mechanisms Underpinning Spatial Learning and Flexible Navigation

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Review of Pfeiffer

Navigating toward food, shelter, or mates is crucial for animals' survival. This process requires accurate estimates of both one's current self-location and intended goal location, as well as the ability to plan a traversable path between these sites. Tolman (1948) was the first to propose that mammals can latently learn the spatial layout of experienced spaces, akin to forming internal cognitive maps, from which spatial locations and relations can be deduced in service of navigation. The discovery that an intact hippocampus is required for storing and retrieving episodic memories in humans (Scoville and Milner, 1957) suggested a potential locus for such mnemonic-based maps, which gained further support from the subsequent discovery of place cells in the CA1 subfield of the rat hippocampus (O'Keefe and Dostrovsky, 1971). Place cells fire preferentially in particular environmental locations (called place fields), and thus in particular sequences as the animal is traversing the space, which suggests that they collectively encode the animal's continuous self-location. It has therefore been proposed that place cells provide a neural substrate of cognitive maps (O'Keefe and Nadel, 1978), now a central tenet in the neuroscience of spatial navigation. However, despite continuous progress in uncovering mechanisms of self-location in the last half century, it remains debated whether place cells also encode goal-related information, such as goal locations and goal-directed paths, owing to conflicting results in the literature (for a recent review, see Nyberg et al., 2022).

As one example, many studies have reported that the overall firing rate, or total number of place fields, across place-cell populations increases near goal locations relative to other equally sized locations in the environment (e.g., Dupret et al., 2010), potentially allowing these sites to become distinctly tagged and memorized within cognitive maps. However, this phenomenon has not been reported across all studies (e.g., Spiers et al., 2018), and it remains unclear whether, and how, such localized activity supports navigation when away from the goal.

Some navigation studies have also reported that, during movement, activations of overlapping place fields within each local field potential theta cycle (~6-12 Hz) can be biased to represent short paths leading to goal locations (e.g., Papale et al., 2016), suggestive of an online (i.e., during movement) planning mechanism. However, other studies have found that place cells equally alternate between different available route options that may or may not lead to the current goal (e.g., Tang et al., 2021). More recently, it has been discovered that, during immobility, when fast-oscillating sharp-wave ripples (SWRs) become evident in the local field potential, another form of sequential activation of place cells can occur that either represents connected paths ("replay") or jumps between multiple disparate locations ("reactivation") in the environment. Some studies have reported that, when replay sequences occur before navigation, goal-directed paths can become overrepresented (i.e., represented at a disproportionately higher rate relative to other possible traversable paths through the environment) (e.g., Pfeiffer and Foster, 2013), suggestive of an offline (i.e., before movement) planning mechanism. However, other studies have instead found a bias toward overrepresentation of previous, instead of current, goal-directed paths (e.g., Gillespie et al., 2021).

What might explain these discrepancies? For one, studies have used different types of navigation tasks, with varying levels of spatial processing demands. For example, some tasks have required that the animal make left-right choices to reach goal locations in track-based mazes (e.g., Papale et al., 2016; Tang et al., 2021), while others have required that the animal navigate to remembered goal locations in open fields (e.g., Dupret et al., 2010; Spiers et al., 2018). Furthermore, the animals' stage of learning has also varied across studies. For example, in some tasks, the goal locations

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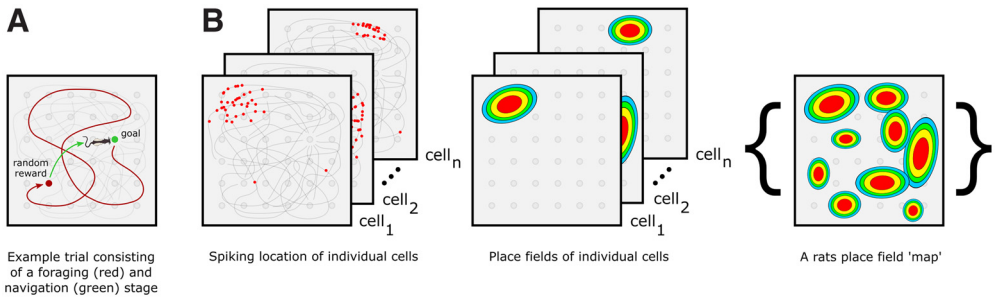

Figure 1. The flexible navigation task and creation of each rat's place field "map" used for analyses. ***A***, Illustration of the arena and task, with one example trial consisting of a foraging and navigation stage. The random reward location (red circle) changed each trial, whereas the goal location (green circle) stayed constant. ***B***, Illustration of how each rat's place field "map" was created. For each cell, the spiking location was determined, and the spiking activity (spikes/s) above a certain threshold was then used to define place fields. The total set of each rat's place cell fields was used for all analyses.

have remained constant across both training and recording sessions (e.g., Papale et al., 2016; Tang et al., 2021), while in others they have changed in each new session (e.g., Dupret et al., 2010; Pfeiffer and Foster, 2013). All of these factors may influence the extent and manner in which hippocampal processes become recruited. Further complicating previous findings is the fact that, in the vast majority of tasks, the starting locations and the goal locations have remained constant within a session, leading to stereotyped navigation behavior. It is possible that this contributes to a strengthening of the connections between place cells that become sequentially activated *en route* to goal locations via spike-timing-dependent mechanisms. In turn, this strengthening may "pull" place fields toward the goal locations, increasing activity at these sites, or bias the reactivation of the same cell assemblies during theta- or SWR-based sequences, without influencing goal-related neural computations per se.

In a recent study in the *Journal of Neuroscience*, Pfeiffer (2022) resolved many of these methodological issues by recording CA1 place cells from rats as they formed, and subsequently used, spatial goal memories in a flexible, naturalistic navigation task (Fig. 1). The task took place in a 2 m × 2 m arena containing 36 evenly spaced wells that were level with the floor and into which reward (chocolate milk) could be released. One trial consisted of two stages: First, chocolate milk was released in an unknown well location (that changed each trial), which required that the rat forage to find and obtain the reward. Second, finding the unknown reward location triggered the release of chocolate milk at a predictable well location (i.e., the goal, which remained constant across trials), that the rat now had to learn and navigate to. Each new trial began automatically on completion of a previous trial, without any signaling or interference by the experimenter. Importantly, the goal location changed without repetition across sessions, meaning the rats had to always learn its new location before relying on this newly formed memory in order to navigate.

The study presented four main findings related to goal coding. In order to investigate learning effects, Trials 1-4 (of 15) were conservatively defined as the Learning phase, during which asymptote performance was reached, while Trials 8-11 were defined as the Retrieval phase, during which peak performance was sustained. As a first analysis, Pfeiffer (2022) investigated whether place cells changed their activity patterns at the goal location relative to other locations. No evidence for this was found, as both the population firing rate and the spatial tuning of place fields at the goal location were comparable to that observed at other locations, across both Learning and Retrieval phases. A complementary pattern has recently been reported in the medial entorhinal cortex (mEC), which is generally regarded as a major input structure to the hippocampus, although reciprocal communication exists between these regions (Cappaert et al., 2015). Specifically, medial entorhinal cortex grid cells were shown to increase their activity around goal locations in a stereotyped navigation task (Boccara et al., 2019), but this was less clear in a flexible navigation task (Butler et al., 2019). These findings strongly suggest that previous reports of goal-localized activity changes were a consequence of stereotyped navigation behavior.

Next, Pfeiffer (2022) investigated whether learning might evoke a global rather than a local change in population firing rates. During both navigation and foraging, in-field firing rates of excitatory but not inhibitory cells increased throughout the Learning phase and plateaued during the Retrieval phase. The increased firing rate of excitatory cells also correlated with navigation but not foraging performance. Computational work has suggested that the specific balance between excitatory and inhibitory networks underlies memory formation and retrieval (Zhou and Yu, 2018). Recent empirical work has further suggested that excitatory hippocampal cells instantiate memory traces via LTP, while inhibitory cells reduce background noise and the threshold for LTP induction (Sharma et al., 2020). The current result complements these findings, by demonstrating how the excitation-inhibition balance in the hippocampus becomes specifically modulated during flexible spatial learning and retrieval.

Lastly, Pfeiffer (2022) investigated whether the representational content of theta and ripple-based sequences also underwent learning-related changes. No evidence for this was found for theta sequences, as the represented paths were generally more aligned with the rats' movement direction than with the direction to the goal location. This finding points to other potential roles for theta sequences during navigation, such as in informing the deliberation (vs outcome) aspect of a planning process. Indeed, this is in line with recent work suggesting that theta sequences in medial prefrontal cortex (mPFC) receive deliberative information from the hippocampus, which it in turn uses to represent the final path choice (Tang et al., 2021).

In terms of SWR-based sequences, previous analysis of the current dataset demonstrated that replay events occurring just before navigation became biased to represent paths to the goal location (Pfeiffer and Foster, 2013). However, this analysis was based on session-averaged data. When Pfeiffer (2022) analyzed the data on a trial-by-trial basis, it turned out that this bias only emerged during the Retrieval and not the Learning phase.

Interestingly, the opposite pattern was found for reactivation sequences, as the goal location became overrepresented in the content of these sequences during the Learning but not the Retrieval phase. This initial bias also seemed to directly influence learning, as the rats reached the goal location faster when navigation was preceded by SWR sequences that encoded this site, but only during the Learning phase.

What may explain these results, and what does it tell us about the potential roles of replay and reactivation sequences in goal coding? A deeper understanding of how the hippocampus communicates with downstream structures will help shed light on these questions. For example, it is known that both mPFC and orbitofrontal cortex (OFC) cells can form firing fields around goal locations (Feierstein et al., 2006; Hok et al., 2007), and the firing patterns of OFC cells can additionally keep track of goal locations when the animal is away from them (Basu et al., 2021). It has also recently been demonstrated that mPFC cells can form replay sequences, and their coherence with CA1 replay sequences increases when goal-directed paths become represented (Shin et al., 2019). One possible interpretation from these findings is that the initial goal-biased reactivation sequences discovered by Pfeiffer (2022) may activate downstream PFC cells, which then become involved in representing the goal location. Since there may be an increased need for cognitive control to successfully navigate during the Learning phase, which is believed to be a mainly PFC-dependent process (Menon and D'Esposito, 2022), PFC networks may exclusively take on the role of determining goal-directed paths during this time. During the Retrieval phase, when navigation may become less cognitively demanding, a more efficient delegation of functions and information transfer may occur between the hippocampus and cortical regions, with the hippocampus taking on a more substantial role in determining paths to the goal location. However, this hypothesis remains to be tested, and the specific roles of mPFC, OFC, and other PFC regions during spatial learning and flexible navigation remain to be delineated.

Another question raised by the current findings is how the brain might distinctly tag and memorize goal locations within cognitive maps. One largely unexplored locus that might be involved in forming such representations is the subiculum, which is regarded as a main output structure of the hippocampus, although reciprocal connections also exist between these regions (Cappaert et al., 2015). It was recently discovered that the subiculum contains vector-trace cells that can form a "memory" firing field near objects, that is retained even after the objects are removed (Poulter et al., 2021). However, whether these cells are also involved in forming mnemonic representations of goal locations remains to be determined.

In conclusion, the results of Pfeiffer (2022) offer important contributions toward our understanding of how the hippocampus supports spatial learning and flexible goal-directed navigation, reinforcing some current conceptions while challenging others. For example, the current results suggest that the hippocampus may have roles in the initial learning of goal locations via reactivation sequences, in planning goal-directed paths offline via replay sequences, and in deliberating over possible paths online via theta sequences. However, the results equally suggest important roles for extrahippocampal regions. Indeed, the findings raise many new questions, such as: do goal locations become distinctly memorized within regions of the hippocampal formation; and if so, how? How does this information become communicated to, and used by, extrahippocampal regions, such as the mPFC and OFC? Future studies investigating these questions will surely benefit from recent developments in multisite electrophysiological recording techniques (e.g., Shin et al., 2019; Steinmetz et al., 2019). The ultimate goal is for such multisite data to enable a more integrated understanding of how the whole brain, not just any specific region, contributes to different stages of spatial learning and flexible navigation.

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