Decoding the cognitive map: ensemble hippocampal sequences and decision making

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Tolman proposed that complex animal behavior is mediated by the cognitive map, an integrative learning system that allows animals to reconfigure previous experience in order to compute predictions about the future. The discovery of place cells in the rodent hippocampus immediately suggested a plausible neural mechanism to fulfill the 'map' component of Tolman's theory. Recent work examining hippocampal representations occurring at fast time scales suggests that these sequences might be important for supporting the inferential mental operations associated with the cognitive map function. New findings that hippocampal sequences play an important causal role in mediating adaptive behavior on a moment-by-moment basis suggest specific neural processes that may underlie Tolman's cognitive map framework.

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Introduction

A long-standing conjecture in the study of animal learning, memory, and decision making is that adaptive behavior is supported by a cognitive map, a flexible, generative learning system that allows animals to reconfigure previous experience to make inferences about the future and plan forthcoming behavior [1–3]. While the spatially tuned firing patterns of hippocampal pyramidal neurons (place cells) provide an intuitive neural substrate for the mapping component of the cognitive map [4–6], understanding how hippocampal computations relate to the more cognitive aspects of Tolman's construct has proven challenging. Work in human and non-human species suggests that the hippocampus underlies both retrospective, mnemonic processes as well as prospective, future-oriented mental abilities [7–11], raising an interesting question: how can place cell representations, which undoubtedly form a reliable representation of the animal's actual location in an environment (e.g. [12]), also support the more complicated cognitive processes associated with the cognitive map? Recent work suggests that the answer lies in the sequential activation patterns of hippocampal pyramidal neurons.

Hippocampal network states

The information represented within hippocampal sequences differs as a function of the hippocampal network state. The computations performed by hippocampus change in the presence and absence of neuromodulators [13–15] and state-input processes [4]. These network states are reflected in patterns of local field potential (LFP) oscillations, which are often divided into theta and non-theta states [4,16–19]. The *theta state* accompanies active behavior or attentive processes, during which the LFP exhibits prominent oscillations in the theta frequency band (6–12 Hz). Theta oscillations organize the spiking of place cells. Within each theta cycle, place cells fire in a sequential order: cells with place fields behind the animal fire first and cells with place fields farther ahead of the animal fire later. Consequently, over the course of the theta cycle, place cells trace out an ensemble representation of spatial trajectories near the animal. During slow wave sleep and awake quiescence (e.g. grooming, food consumption), the hippocampal LFP is less orderly; instead of regular oscillations, broad band voltage fluctuations typify the large, irregular activity (LIA) state. In LIA, place cells activate in fast sequences during sharp-wave ripple (SWR) complexes, so named for the characteristic high-frequency ripple waveforms that punctuate the otherwise irregular LFP. Place cell spiking during SWRs does not necessarily represent the animal's current location in space. Instead, ensemble firing sequences trace out trajectories that may traverse regions of space the animal does not currently occupy [20,21].

Ensemble sequence representations

Hippocampal sequences were first identified through changes in the firing of place cells relative to the theta rhythm (Figure 1a). When running through a place field, place cells were observed to *precess* through phases of theta, so that on entry, spikes occurred late in the cycle, but, on exit, they occurred early in the cycle [22,23]. It was immediately recognized that this *phase precession* implied
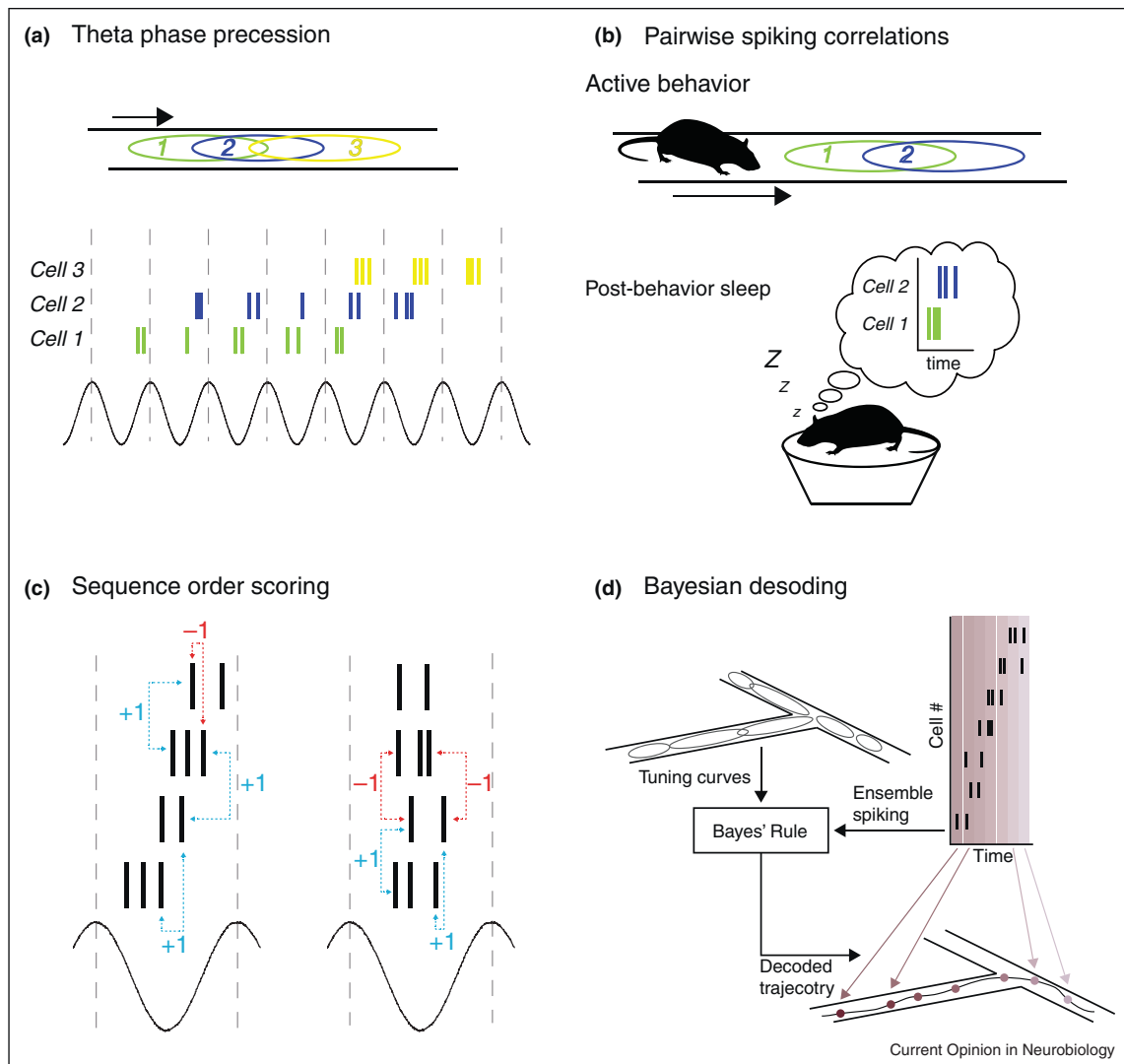
Methods of sequence extraction. A variety of analytical approaches have been developed to identify and quantify temporally structured spiking in hippocampal ensembles, ranging from techniques that examine one or a few neurons **(a,b)** to approaches that leverage ensemble activity **(c,d)**. (a) Early work [22,23] identified that hippocampal place cell spiking phase precesses against the theta cycle. This phase precession implies the existence of orderly, temporal patterns within theta cycles; however, certain types of sequences might not result in phase precession [26]. (b) Other early work (e.g. [27]) noted that the correlations that were established between place cell spiking during exploration persisted during subsequent sleep, suggesting that place cell firing patterns recurred during offline states. (c) Sequence scoring methods like the one developed by Lee and Wilson [76] or Gupta and colleagues [47,58] quantify the temporal structure of neural activity in a given time window. Pairs of spikes with an order of activation matching the order in which the animal passes through their fields during behavior are scored +1, while pairs of spikes whose activation order is opposite their ordering in space are scored −1. Summing across all spike pairs results in a metric of both the direction of the sequence (sign of the sequence score) and the temporal precision of the sequence (magnitude of the sequence score). The activity in the left panel exhibits temporal structure characteristic of theta sequences; the ordering of many spike pairs is consistent with a forward-directed representation. Unpatterned ensemble spiking (right panel) is consistent with both forward-ordered and backward-ordered representations equally often, resulting in a net sequence score near zero. (d) Bayesian decoding methods [77] use the tuning curves of hippocampal neurons measured during active behavior (i.e. place fields) to estimate which positions in space are most likely being represented by ensemble spiking activity. Decoding hippocampal sequence representations reveals the spatial trajectories that sequence events encode.

a sequential firing representation along the path of the animal [23,24]; it has since become clear that the phase precession is a consequence of sequences changing as an animal progresses through a task [25,26].

Although hippocampal sequences were originally characterized by assessing pairwise correlations in spiking of place cells [27,28] (Figure 1b), sequences are fundamentally an ensemble phenomenon, and the recent advances