Spotlight Article

Does the hippocampus map out the future?

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Summary

Decades of research have established two central roles of the hippocampus - memory consolidation and spatial navigation. Recently, a third function of the hippocampus has been proposed: simulating future events. However, claims that the neural patterns underlying simulation occur without prior experience have come under fire in light of newly published data.

Main text

Much of our understanding of the hippocampus comes from neural recordings in behaving rodents. Neurons within the hippocampus, known as place cells, are tuned to the rodent's spatial position, such that each place cell increases its neural activity when the rodent is in a specific location within its environment [1]. However, when the rodent stops running, the hippocampus exhibits brief high-frequency oscillations, referred to as sharp-wave-ripple (SWR) events [2]. SWR events typically co-occur with the sequential firing of place cells that represent a spatial trajectory. These spontaneously reactivated 'trajectory events' can represent the spatial path that the animal has recently taken [2,3] or about to begin [3,4]. Trajectory events are not limited to when the animal is awake and static; during non-REM sleep, SWR events trajectory events depicting past journeys can also be observed [2]. Substantial evidence supports the phenomenon of trajectory events, commonly referred to as "replay" or "reactivation", demonstrating that these events are coordinated with reactivation events in brain regions beyond the hippocampus, and are influenced by both rewards and external cues [2,5].

A common assumption about 'trajectory events' is that they are a by-product of experience. During exploration of a novel environment the hippocampus is thought to create a cognitive map of that environment, which can be reactivated to recall this map [1]. However, in 2011 a break with this standard view occurred [6]. The sequential pattern of hippocampal place cells during a sleep session were recapitulated while the animal was subsequently running on a linear track (after waking up), despite no prior experience of the track [6]. This phenomenon of *de novo* 'pre-play', argues for the existence of pre-configured

sequential patterns in the hippocampus that the hippocampus "maps" onto a new environment.

In a challenge to these findings, a new study by Silva, Feng and Foster [7] reports that while it is possible to observe *de novo* pre-play events, the occurrence of these events do not happen at a frequency above what would be expected by chance. Secondly, while a significant increase in the number of trajectory events can be observed after the animal's spatial exploration, these effects are mitigated with a pharmacological blockade of NMDA receptors (disrupting synaptic plasticity), when administered prior to exploration. Together, these two observations suggest that trajectory events are experience dependent.

How can we resolve the conflicting results surrounding the existence of *de-novo* preplay? To answer this, we raise three main issues, which we will refer to as the good news, the bad news, and the ugly truth.

The good news: internal sequences exist in the hippocampus

For *de-novo* preplay to exist, the hippocampus must be able to generate an internal sequence, i.e. a sequential pattern of place cell activity in the absence of a spatial trajectory. Substantial evidence now supports this. Time cells in the hippocampus exhibit responses tuned to time rather than space [8]. If time cells do not require travel, then theoretically trajectory sequences can be generated without locomotion, and may not be fully determined by the spatial tuning of cells. Recently, hippocampal cells have been observed to exhibit repeated sequences of activation linked to the distance run on a wheel in the dark, providing further support for internal representations [9].

The bad news: we can't predict the future

Evidence suggests trajectory events can pre-play through previously explored space [2,3], and even through unexplored space, when the path leads to a visible reward [4]. However, can trajectory events occur without any experience or knowledge of the environment? To explore this, we can perform the following thought experiment. Imagine we observe two different trajectory events (A and B) repeating during sleep. If trajectories A and B do not share any place cells, we can assume that they represent different trajectories, while if instead the middle of both trajectories shares the same sequence of place cells, then this would imply the trajectories intersect. This means we can infer information about the environment's topology. This principle has already been demonstrated for replay events [10], and thus might apply to *de novo* pre-play trajectory events. Except, that in a pure *de novo* state you cannot predict the future. Thus either *de novo* preplay only works on specific topologies, limiting its overall utility, or we have identified the neural correlate of pre-cognition.

The ugly truth: Statistics

How do we even know that a pattern of neural activity is replaying or preplaying a trajectory? Since the discovery of hippocampal replay, we have observed a rapid evolution of statistical analyses to measure: 1) the similarity between

patterns of activity, and 2) whether a pattern occurs above chance levels. These statistical methods have moved from pairwise correlation, combinatorics of short sequences, rank-order correlation, to Bayesian inference [2], and most recently to using a multi-dimensional analysis of sequence correlation and jump distance [7].

Unfortunately, with the improved use of statistics has also come the misuse of statistics. For instance, it is important to compare like with like. Firing rates in place cells as well as the behavioural and sensory experience of the animal varies dramatically between sleep and awake states. Comparing trajectory events between these two states can be problematic, especially given that many of the methods employed depend on neuronal firing rates. Similarly, it is incorrect to compare the best correlations scores from multiple sequence templates with a single shuffled template.

Another concern is the issue of event independence. Statistical methods generally assume that each event being compared is independent. We assume that each neuron generates its activity independently of the other neurons. However, some previous studies have treated all spikes generated by a neuron (rather than just the first spike) as independent events. This is problematic because place cells typically fire in bursts, generating non-independent events.

Finally, it is important to note that the strongest evidence supporting de-novo preplay, has only found approximately 7% of trajectory events preplaying a single trajectory [6]. Thus the number of preplay events observed in these studies is more frequent than chance levels, but not by much. And therefore "statistical clarity" is more important than ever, to either properly dismiss or support the view that the hippocampus maps out the future *de novo*.

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