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Hippocampal sequences link past, present, and future

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Abstract

Disrupting the reactivation of hippocampal neurons during sleep impairs memory consolidation in rats. However, the functional importance of reactivation during awake states is unknown. An experiment in which awake reactivation was disrupted suggests that this phenomenon could adaptively guide behavior by linking previous learning with the current state of the world.

Pyramidal neurons in the rat hippocampus are tuned to space; deviations from this primary spatial tuning provide experimental access to cognitive neural processes [1]. During attentive behaviors, place cells form a veridical representation of the subject's location in the environment. In less attentive states, however, cells cease to represent current location; instead, during population bursts of spiking called sharp-wave ripples (SWRs), neurons express temporally-compressed representations of spatial trajectories. These spiking sequences were first noted in rats sleeping after task performance, and were accordingly characterized as ‘replay’ or ‘reactivation’ [2]. However, similar representations occur during moments of waking quiescence [2,3,4].

Theoretical work suggested that repetition of behavioral firing patterns during SWRs could be important for memory consolidation [2]. Recently, direct support for this idea emerged when disrupting SWRs during post-behavior sleep was shown to result in learning deficits [5,6]. However, the role of awake SWRs remains unclear. If sleep reactivation supports consolidation, does awake reactivation perform a similar function, processing information ‘in real time’, as experience accumulates?

Recent work by Jadhav and colleagues [7] tackled awake reactivation directly, by interrupting SWRs as subjects learned a hippocampus-dependent behavior. Rats were rewarded for visiting the three arms of a W-shaped maze in a sequence. Inbound trials began from either of the outer arms – the correct response was to go to the center arm. Outbound trials began in the center arm and required subjects to visit the outer arm opposite from whence they last came. Thus, inbound trials always led to a single goal, but outbound trials

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alternated between two goals. The two trial types of the task imposed different memory demands: whereas inbound trials could be solved via a straightforward place-reward association, outbound trials were more challenging, as sensory cues were insufficient to indicate the rewarded location. Instead, the alternation rule meant that subjects had to remember their recent performance history in order to determine the correct choice.

While rats learned the task, Jadhav and colleagues [7] disrupted SWRs by electrical stimulation of the ventral hippocampal commissure. Activating ventral commissure fibers inhibits spiking in the CA1 hippocampal region long enough to prevent reactivation during SWRs without disrupting place cell activity outside of the SWR.

Although both task components are sensitive to hippocampal lesions, Jadhav and colleagues [7] found that blocking awake reactivation differentially affected inbound and outbound trials. Rats subjected to SWR disruption performed inbound trials normally, but were impaired on the more cognitively-intensive outbound cases.

This dissociation under SWR disruption suggests that inbound and outbound trials access the hippocampus for different reasons. Intact place cell activity and post-run reactivation support inbound trials in the absence of awake SWRs, but this is not the case for outbound trials. Requiring subjects to integrate their location, recent past behavior, and a reward contingency seems to depend on awake SWRs. Importantly, the authors showed that SWR disruption mildly degraded outbound trial performance even if subjects learned the task before stimulation began, rendering it unlikely that awake SWR blockade impaired behavior by interrupting consolidation alone. Instead, the authors argue that awake reactivation functions as a spatial working memory, bringing representations of past sequences into the present context [8]. Together, these findings show that the function of awake and sleep reactivation are dissociable for at least some behaviors.

As with most good experiments, the work of Jadhav and colleagues [7] raises as many questions as it answers. As the authors show, disruption of awake SWRs allows for a more finely-grained assessment of how the hippocampus is involved in behavior. Instead of asking whether the hippocampus is necessary for a given task, future work can answer questions about the particular information the hippocampus contributes to task performance. This study also opens the door to examining how downstream structures utilize hippocampal output. For instance, hippocampal activity influences neurons in reward-processing regions well-suited to linking a value signal with representations called up in spatial working memory. Disrupting SWRs while recording activity in hippocampal output targets could help dissect the interaction between remembered spatial trajectories, value, and behavior.

Perhaps the most daunting unanswered question concerns the content of reactivation sequences. The authors' working memory hypothesis predicts that awake reactivation content should subserve immediate behavioral needs. Before initiating an outbound trial, for instance, a replay of the previous inbound path would include a representation of where that journey began, which could be used to infer the correct destination in the current trial [8].

More generally, it should be possible to construct tasks that bias the content of reactivation sequences by virtue of their memory demands. Interestingly, however, replay content can be

quite ‘divorced’ from ongoing behavior. On a similar task, it was shown that trajectories leading to an inactivated reward site were persistently represented in reactivation sequences, despite the lack of actual behavior directed to that location [9]. Other work has demonstrated that awake replays can represent entirely different environments than the one in which the rat currently resides [3,4]. The behavioral utility of these nonlocal representations remains unclear.

Current data suggest that the connection between sequence content and function is complicated. To better understand replay content, the ‘holy grail’ of reactivation manipulations would involve blocking sequences representing particular regions of space. For instance, eliminating sequences beginning at a reward site and proceeding to the animal's current position would directly test their involvement in solving the credit assignment problem of reinforcement learning [10]. Similarly, eliminating sequences directed towards a goal location could reveal whether such activity has a role in planning future actions toward that site. The ability to induce sequences in the hippocampal network would allow for many fascinating experiments.

Could forcing the hippocampus to represent a never-experienced trajectory implant a behaviorally-accessible spatial memory? Unfortunately, controlling replay content in a manner that mimics normal physiology currently lies beyond current technology. Nevertheless, as causal techniques in neuroscience become increasingly sophisticated, today's unanswerable questions shift incrementally from the domain of science fiction towards the pages of *Science* magazine.

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