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Previews

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Route selection with a cognitive map

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In this issue of *Neuron*, Widloski and Foster (2022) show that, in a complex maze with changing barrier configurations, rat hippocampal neurons maintain their location-specific firing but learn to generate activity sequences representing possible routes to rewards, that respect the locations of barriers, and to rapidly adapt to barrier reconfiguration.

This morning I took off on my bike for my usual ride to campus, about 3 miles away. It's a no-brainer for me. I've followed the same route hundreds of times, and I don't think at all about the route. I know every pothole and place where I have to be cautious. My behavior along the route is pretty automatic and likely orchestrated by my striatum (Packard and McGaugh, 1996). So, my mind (cortex) is relatively free to focus on what I'll be writing for this *Neuron* preview. But this morning, there's a glitch. When I get to the second possible branchpoint in my route, there is tree trimming going on, and the road and sidewalk are blocked. My thoughts are instantly interrupted, and I experience a bit of frustration. But no worries, I know a detour that's a bit longer and requires some route decision making. I switch courses, but now my thoughts about what to write are put on the back burner because I have to think about which branches in my new, relatively unfamiliar route to take. Maybe I'll go up the hill and negotiate the social sciences building complexes or maybe I'll keep to the road a bit longer and ride through the bike path. I get on the bike path, but it's late, and there are students all over it, making progress slow, so I decide to cut across the park and go up the hill. I have a good sense of direction, and at any point on this extended detour, I could have pointed pretty accurately in the direction of my office. But at no time does my brain plot a course through the potential obstacles. At each decision point, I'm planning a tortuous route that will eventually get me where I'm going without having to ride through walls or crowds of undergrads deafened by their earpods.

What was my brain actually doing during this seemingly trivial process? Neuroscientists have pondered this issue since at least the time of Tolman, who in 1948 studied the abilities of rats to make similar, flexible, and educated route choices. Our current understanding is still sketchy, but has been aided by several crucial discoveries in the last 50+ years, mostly in laboratory rodents. First was the discovery by O'Keefe and others that, throughout the hippocampal formation, the principal neurons generate a sparsely coded neural correlate of the animal's location—so-called "place cells." The second was the discovery that hippocampal cells have particular dynamics (the so-called theta-phase precession) that, in theory, would facilitate the asymmetric coupling (Skaggs et al., 1996) of place cells activated along a route in a manned similar to what D.O. Hebb, in 1949, called a "phase sequence." This would allow the potential reactivation of previously experienced routes because cells earlier in the route would tend to activate those later in the route. A prediction of such an effect is that the "place fields" of each cell would expand backward toward the fields of earlier cells because they are now being activated by them and not just by the location-specific inputs. This prediction has been verified (Mehta et al., 1997), as has the internal reactivation of experienced sequences of place cell firing, during sleep or pauses in behavior (Skaggs and McNaughton, 1996; Johnson and Redish, 2007). The latter studies, however, were carried out in animals running relatively simple spatial sequences, without much decision making required. In an elegant experimental paradigm and a technical *tour de force*, Widloski and Foster (2022), in this issue of *Neuron*, recorded simultaneously from a large number of CA1 neurons in rats. They show that the rat brain rapidly learns to generate and explore possible paths to goals in a maze with reconfigurable, "jailbar" style barriers, which the animals could see and smell through, but not cross. In each session, the rat must learn a new route to a goal, constrained by the reconfigurable barriers. The brain rapidly learned to generate fictive trajectories, expressed in sequences of place cell firing in the hippocampal CA1 region, that respected the new barrier configuration. The replay sequences were much more closely aligned to the future trajectory compared to the past trajectory of the animal across all sessions. Despite a large number of conflicting barrier configurations used, the replays rapidly adapted to the new configuration with 87% of the sessions showing high barrier conformity. Barrier impermeability remained intact when looking at all population activity during immobile periods and not just replay.

Throughout the daily learning process, hippocampal place cells generally did not reconfigure their firing locations, thus maintaining a stable coordinate framework for the overall environment; however, a more subtle effect known as "rate remapping" (Leutgeb et al., 2005) appeared to correlate with the rearrangements. Cells adjusted their within-field firing rates (up or down) in a repeatable manner as the barriers were rearranged between new and previous configurations. This process is thought to be essential in order for the hippocampus to "index" (see McNaughton, 2010, for review) cortical representations of the features present at a given location during different experiences (in this case the barriers) and hence, presumably, to calculate the

appropriate trajectory. Interestingly, the stable cell population (mean fraction of stable cells per session = 58%) alone was shown to be sufficient to support replay going around the barriers. The unstable cells, on the other hand, encoded for local environment features, firing to a barrier-specific configuration in a repeating manner. Despite largely stable place cell firing, the rapidly adapting replay content might facilitate exploring alternative routes, forming shortcuts, and novel route planning. Another possibility is that the variability in replay content could allow for flexible storage of memories at different levels of detail, enabling better generalizations.

The hippocampus itself is unnecessary to follow familiar routes and has no direct output that could control the actual behavior. Presumably, fictive hippocampal trajectories that end at a representation of the goal location must trigger the motor system to follow the corresponding route. The details of exactly how such triggering occurs and the hippocampal interaction with extra-hippocampal circuits (in either cortex or striatum) remain for future studies. Another question for future work is exactly how the appropriate hippocampal trajectories are initiated. Is it a result of random selection of recently encoded trajectories? Do successful behavioral trajectories bias the plasticity of the neural trajectories leading to success? Where do the hippocampal trajectories actually arise: in hippocampal CA3 (which has the theoretically necessary, recurrent connectivity that CA1 lacks) or maybe they are externally driven from the neocortex? How do the representations of new configurations suppress the old, no longer consistent ones? Are the latter erased or merely suppressed by some inhibitory circuit rearrangement? What is the role of the striatum, which likely eventually takes over the task (Packard and McGaugh, 1996)? We know, for example, that cortical activity sequences can replay in a manner that is (sometimes) correlated with hippocampal sequences (Rothschild et al., 2017), that high-level neocortex can also exhibit reactivation of remote reward sites after failure to obtain the best reward somewhere else (Mashhoori et al., 2018), and that there is some coordination of reactivation between hippocampus and at least parts of the striatum. An important scientific discovery usually opens a host of new questions, and the paper by Widloski and Foster (2022) is no exception. From the perspective of someone who began his studies of hippocampus in an era where cells were recorded one cell at a time, the advances we are seeing today are stunning, and the pace of technological advance promises much more to come. Moreover, the kinds of discoveries illustrated by the current Widloski and Foster results will undoubtedly strongly influence the advance of machine learning systems.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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