

Who moved my cheese (again)?

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A study shows that spatial learning is accompanied by the reorganization of place fields of hippocampal CA1 neurons, and that this reorganization is subsequently reactivated in an NMDA-dependent manner for memory consolidation.

Our understanding of the link between space and memory dates back at least to classical times and the ancient Greek and Roman mnemonic ‘method of loci’. To pinpoint the biological basis of this link, research has focused on the hippocampus, the brain area where these functions seemingly come together. However, establishing the neural connection between them has been challenging, with experiments providing individual pieces of what has turned out to be an intricate jigsaw puzzle. The study by Dupret and colleagues¹ in this issue now pieces together several chunks of this puzzle in one set of experiments, revealing an intriguing but complex picture of how spatial memory is formed.

The first piece of the space-memory puzzle was the discovery that the hippocampus seems central to this link. This was followed shortly thereafter by the finding that neurons recorded from hippocampal areas CA3 and CA1 show patches of spatially localized activity called ‘place fields’, hence the name ‘place cells’ for these neurons. These findings led to the influential ‘cognitive map’ hypothesis, suggesting that the hippocampus constructs a map-like representation of space². The next piece of the puzzle was the discovery that hippocampal synapses show a high degree of plasticity, a property long thought to underlie memory³, and that this plasticity is largely dependent on the associative activation requirements of NMDA receptors (NMDARs), which are possessed by place cells in abundance. Crucially, blockade of NMDARs blocks not only synaptic plasticity but also spatial memory⁴.

More puzzle pieces continued to turn up. Several experiments showed an apparent role for the hippocampus in post-learning consolidation of memories⁵, whereas electrophysiological studies found that patterns of hippocampal activity expressed during awake exploration—for example, sequences of place cell activation as the rat traversed the

environment—recur during subsequent periods of quiescence or sleep⁶. These bursts of reactivation occur during electroencephalographic events known as ‘sharp-wave/ripples’ (SWRs; they occur every few seconds in an immobile animal) and are thought to represent episodes in which the hippocampus compresses newly learned information and then broadcasts it out into the neocortex for subsequent long-term storage, and perhaps even for assembly into new, predictive constructions⁷.

Collectively, these puzzle pieces add up to an intriguing story in which the hippocampus creates a spatial map using associative NMDAR-dependent synaptic plasticity and then sends it to the neocortex to be stored. Until now, however, these elements of the story had not been tested within a single study. Dupret and colleagues¹ have now attempted just this in a complex and challenging experiment in which rats learned several sets of spatial locations—a new set for each day—and then rested while the newly acquired memories were processed ‘offline’ in the presence or absence of NMDAR blockade. The findings support the story, but not in an entirely straightforward way.

Dupret *et al.*¹ used the ‘cheeseboard’ task, in which rats exit from a start box to retrieve food from three unmarked holes—selected at random each day from a large array distributed across a circular arena—before returning to the start (Fig. 1). On each day during a ‘pre-probe’ trial, the rats first freely explored the unbaited arena, showing a preference for visiting the previous day’s reward locations. After resting, the rats were placed on the arena again for a period of learning, during which they acquired knowledge about a new set of three rewarded locations. After learning, the rats experienced another rest period, followed by one more ‘post-probe’ trial during which they were allowed to explore the again unbaited arena. Throughout the experiment, single-neuron activity and local field potentials were recorded for later analysis. As a control, the rewarded locations were signposted in some learning trials to provide visual cues to the goal location, thus reducing the need for spatial processing and memory. Sometimes, after the first pre-probe

trial, the rats received an injection of the drug CPP, which blocks NMDARs.

Rats succeeded in learning the new reward locations on each day, and this memory persisted at least until the next day. Intriguingly, some of the place fields became more clustered near the reward locations after learning, a pattern that persisted within each experimental day. This clustering happened only for CA1 and not for CA3 neurons, suggesting a functional difference between these two areas and also ruling out inhomogeneous-sampling artifacts as a spurious cause of the clustering. In the control task, the rats did not learn the locations of the signposted locations, and nor did this place field clustering occur. Thus, the fields clustered around areas where the rats had needed to attend to, and/or memorize, surrounding spatial cues. Notably, the amount of clustering correlated with memory performance in the learning session and also with performance in the following, post-probe recall session. Thus, the hippocampal CA1 place code showed plasticity that correlated, in both strength and time scale, with memory performance.

The authors also show that blockade of NMDARs before learning did not affect either learning or place field clustering during a given session. However, when tested in the post-probe trial two hours later, the rats seemed to have forgotten that day’s rewarded locations, and the place field clustering had also abated. This finding is consistent with previous reports that NMDAR blockade does not affect learning but does affect consolidation of the new pattern⁸. To examine memory consolidation further, Dupret *et al.*¹ then looked at what happened during the SWR events either during the learning trial or during the rest phases between. They differentiated between SWRs emitted during exploration (eSWRs), during awake immobility (iSWRs) or during slow-wave sleep (sSWRs). The number of eSWRs emitted at goal locations correlated with memory performance in undrugged rats but not during NMDAR blockade, whereas iSWRs never correlated with performance. When comparing cells with place fields at goal locations with those having fields in the start box, the firing rates of the ‘goal-centric’ cells were

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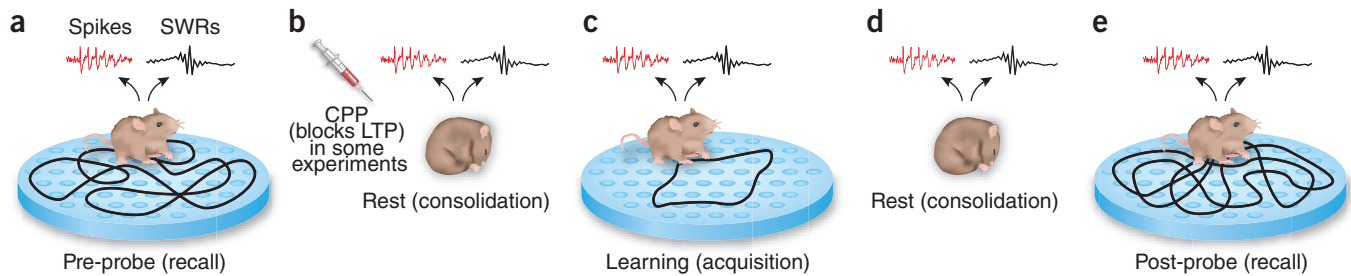


Figure 1 Electrophysiological recording during the stages of memory retrieval, new acquisition and new recall interspersed with rest periods. **(a)** In the first ('pre-probe') session of the day, rats would freely explore the cheeseboard arena, spending most time near the holes that had been baited with food on the previous day. Recordings of single neurons called place cells, and of local field potential activity, were made throughout the trial. Place cell spikes (red traces) tended to cluster near the previous day's reward locations. The local field potential showed periodic bursts of sharp-wave ripples (SWRs; black traces) during exploration (eSWRs) or pausing (iSWRs). **(b)** During a rest period immediately afterwards, activity of single neurons and sleep-related SWRs (sSWRs) were recorded. **(c)** Rats then explored the arena again, learning the new locations of the baited holes. Across the course of this session, place fields of CA1 (but not CA3) neurons tended to move toward the rewarded locations. **(d)** sSWRs in the rest period after learning showed activation of cells with fields near the reward locations. **(e)** In the 'post-probe' session, place fields persisted in their new configuration unless the rats had undergone CPP-induced NMDAR blockade.

higher during eSWRs, an effect that disappeared with NMDAR blockade. The synchrony of CA1 activity during eSWRs also correlated with memory performance. Taken together, these findings are consistent with the hypothesis that the network reactivation during eSWRs contributed to memory consolidation.

Finally, Dupret *et al.*¹ investigated sSWRs in the intervening rest periods. Cells that fired together during the learning trials (because their place fields overlapped) also tended to fire together during sSWR events. This effect was stronger for fields near the goal than for fields in the start box, but not if NMDARs were blocked. In the latter case, the firing patterns from the beginning of learning, rather than from the end, were more strongly reactivated. Thus, it seems that NMDARs are needed to stabilize the new memory traces. Patterns of activity that are reactivated during sSWRs tend to reflect patterns near one of the newly learned goal locations. Again, the amount of reactivation goal-related firing during sSWR periods correlates with memory performance.

What do these findings mean for the cognitive map, plasticity-memory and reactivation-consolidation hypotheses? The clustering of CA1 fields with learning resembles previous findings of accumulation of place fields near goals^{9–11}. However, the amount of shift induced within each place field was small, and the temporal dynamic of the shift, which was slow and linear during the whole learning phase, contrasts with that of the very fast learning shown by the rats. Thus, why might these changes in fields occur, and what (if anything) could be their functional significance?

Because the field shift in the Dupret *et al.*¹ study did not occur with either the cued locations or the start box, it seems not to be a simple response to reward. Both field shift and learning occurred under conditions in which the rats were attending closely to spatial cues. One potential explanation for the results is that this attention increases the sensory drive from these cues onto the place cells to an extent that would be proportional to distance from the goal(s). Such enhanced sensory drive might then strengthen synaptic links with the place cells and bias their fields toward goal location(s) while at the same time facilitating memory formation. Regardless of the cause, interventional studies will be needed to determine whether this clustering functions to adaptively enhance the representation of significant places.

What about the plasticity-learning hypothesis? Blocking NMDARs did not affect either the learning or the place field shift, but it did affect consolidation of both, consistent with previous studies suggesting a role for NMDARs in stabilizing place fields⁸ and memories¹². The lack of effect on initial learning might be because the apparatus as a whole was not novel; previous research suggests a role for NMDARs in initial map formation but not in map updating¹³. Interestingly, the effect coincided with a lack of inhibition of interfering memories, which, in the presence of NMDAR blockade, were actually strengthened. Perhaps NMDARs are needed to suppress obsolete information?

Finally, what about the reactivation-consolidation hypothesis? Dupret *et al.*¹ observed correlations between learning and both the network synchronization during eSWRs and reactivation of goal

representations during sSWRs, findings that tie in well with the more direct evidence for a causal role of SWRs in hippocampal learning^{14,15}. However, the observation of reactivation in some SWR states and not others (exploration but not immobility) suggests that the physiological basis of hippocampal-neocortical 'broadcasting' is, at the very least, complex. Nevertheless, the study by Dupret *et al.*¹ provides convincing evidence that the cognitive map is plastic, and that this plasticity resembles the properties of spatial memory in several important respects. The next step will be to show a causal link by means of experiments in which such plasticity is locally modulated, perhaps optogenetically.

COMPETING INTERESTS STATEMENT

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at <http://www.nature.com/natureneuroscience/>.

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