Consolidating the case for transient hippocampal memory traces

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Moscovitch and Nadel (M&N) maintain that remote memory traces endure in the hippocampus [1], despite a wealth of evidence demonstrating rapid structural and functional turnover [2]. They outline the key studies that support their view. However, we consider this evidence inconclusive and often contradictory.

A study tracking hippocampal markers of plasticity in mice across repeated environmental exposures was provided as evidence of a month-long stable representation [3]. In fact, a stark decrease in neural pattern similarity between day one and day 31 was observed, with few cells active during initial exposure reappearing at the latest time-point. This decrease in representational similarity as a function of temporal distance was evident at every intervening time-point. Even with more temporally-adjacent environmental exposures, only a small proportion of all imaged cells (20%) consistently reappeared. We do not consider this a stable neural representation over time.

An electrophysiological investigation in mice was also cited as demonstrating the stability of hippocampal representations. This study reported increased synaptic transmission in the hippocampus after successful retrieval of a location in a place-avoidance task at recent (one day) and remote (30 day) time-points [4]. However, given the requirement to retrieve this memory in the original environment at both time-points prior to recordings, it remains unclear whether increased synaptic transmission at the remote time-point was attributable to persistent structural changes or reconsolidation processes.

M&N also consider their viewpoint reinforced by a study which attempted to recover long-lost memories through optogenetic stimulation [5]. However, we find the invoking of this paper puzzling, having given its findings thoughtful consideration [2]. We expressed reservations about the interpretation of memories as being “recovered” because they did not persist following artificial stimulation, yet M&N offer no new insights into this concern.

Reconsolidation is considered by M&N as evidence of enduring hippocampal traces. For example, following contextual fear conditioning, re-exposure to a specific environment at a remote time-point renders the memory vulnerable to hippocampal lesions. Their interpretation is that the reminder reactivates dormant, inaccessible hippocampal traces. However, our alternative view, the reconstruction of a specific memory in the hippocampus with the new trace being vulnerable to disruption, explains the data equally well.

M&N also claim that the optogenetic suppression of specific hippocampal traces at very long delays disrupts memory retrieval. We do not know to what study they are referring, as they merely cite a general review article in support. Therein, a single study involved optogenetic silencing of hippocampal cells during remote (four-week-old) memories [6]. Once again, we discussed this particular study [2], and noted that specific memory traces were not targeted.

M&N maintain that selective long-term stabilisation of traces within the hippocampus relies on specific cellular mechanisms, citing [7]. More accurately, this study pertained to cellular mechanisms underlying the forgetting of recent (one-week-old) memories, a natural process of AMPA receptor endocytosis. Regarding long-term retention, there are cellular mechanisms which maintain AMPA receptor expression soon after learning, contributing to memory persistence [8]. We argue this stabilisation is temporary and facilitates systems-level consolidation, as these changes are unlikely to endure permanently in the hippocampus, given the well-documented physiological flux. We also disagree with M&N's proposal that neurogenesis acts to stabilise and protect some remote memories, given evidence that it preserves hippocampal capacity for new learning by erasing older memories [9].

M&N also challenge two other predictions of our proposal. They argue that remote memory is not inaccurate. In support of this, they refer to a study which assessed the change in accuracy of participants' recall over the course of one week [10]. We do not consider a one-week-old memory to be remote, and even across this brief period a marginal drop in accuracy was, in fact, reported.

They also challenge the prediction that the vmPFC drives hippocampal activity during scene construction, referring to an fMRI investigation of future thinking [11]. However, a recent MEG study has demonstrated, with a high degree of temporal precision, that the vmPFC leads the hippocampus and drives its activity during scene construction [12]. We acknowledge that during the elaboration phase of autobiographical memory retrieval the hippocampus modulates activity in the precuneus [13]. However, further work is needed to characterise the network interactions governing memory retrieval during the crucial earliest phase of construction, which is when we predict the vmPFC will lead.

Finally, we did not suggest, as M&N claim, that all episodic memories decay over time leaving behind only gist. We maintain that rich, detailed remote episodic memories reconstructed via vmPFC-neocortical-hippocampal interactions can produce a full sense of re-experiencing.

In summary, we argue that the hippocampus is critical for retrieving rich remote episodic memories in perpetuity, but this does not imply its role is one of storage. Letting go of the notion of an enduring hippocampal memory trace will, we believe, provide a more productive way forward for memory research. We thank M&N for participating in this debate, and hope that our perspective continues to provoke discussion and, importantly, motivate experiments that will definitively establish the precise role of the hippocampus and vmPFC in remote memory retrieval.

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