

Letter

Sculpting Remote
Memory: Enduring
Hippocampal Traces
and vmPFC
Reconstructive
ProcessesMorris Moscovitch¹ and
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Barry and Maguire's (hereafter B&M) recent take in *TICS* on the role of the hippocampus in remote memory retrieval, that it has a (scene) constructive role, rather than being part of the long-lasting representation of rich and detailed episodic memories, is both thoughtful and provocative [1]. They make two main claims: (i) the underlying cellular physiology of the hippocampus, including the existence of lifelong neurogenesis in the dentate gyrus, creates an unstable basis for remote or permanent memory; and (ii) existing data from behavioral and neuroimaging studies, in animals and humans, can be explained without assuming that the hippocampus remains a critical part of the representation of remote memories.

Space does not permit us to address these claims in detail, but our reading of the literature suggests that the hippocampus can retain information about some specific events that occurred long ago, in contrast to B&M's position. To start, although there is, as B&M claim, considerable drift in which hippocampal place cells represent an environment over time, along with considerable synaptic turnover, it appears that these instabilities do not prevent the network as a whole from stably representing an environment for at least a month [2,3]. In B&M's view, lifelong neurogenesis implies an unstable substrate for memories in dentate gyrus since recently formed cells interfere with previous memory traces,

leading to memory deficits [4]. However, optogenetic studies show that traces can survive in the hippocampus, be reactivated, and lead to memory expression in behavior for some time after learning, even if they are typically 'suppressed' by neurogenesis [5] (Guskjolen and Frankland, Reinstatement of forgotten memories via environmental reminders, Personal Communication, January 27, 2019). Studies on reconsolidation provide further evidence of long-lasting, although sometimes inaccessible, hippocampal traces. When context fear memories were reactivated, the recovered memories, and the cues/reminders that elicit them, were specific to the original context rather than generalized to other, schematically similar, contexts [6]. Optogenetic suppression of these cells, even at very long delays after acquisition, leads to memory loss, attesting to the longevity and viability of these hippocampal traces (see [7]). Cellular mechanisms have been demonstrated in the hippocampus that could support such selective long-term retention [8]. Thus, while causing interference that can lead to forgetting of many remote memories, neurogenesis simultaneously acts to stabilize and protect the remaining memories from interference and degradation. In our view, neurogenesis and reconsolidation are processes that sculpt memories by pruning vulnerable memories while updating and strengthening old ones. In sum, there is little evidence to support the view that the flux observed in hippocampus renders it incapable of forming and sustaining long-lasting representations.

With respect to the neuropsychological data, B&M argue that all episodic memories decay over time, leaving behind only gist and the contributions that episodes make to pre-existing schemas. Insofar as episodic details are recalled, they must be reconstructed, with ventromedial prefrontal cortex (vmPFC)-based schemas providing the impetus. Two predictions follow: remote memories will

be inaccurate, and recall will be led by the vmPFC and posterior neocortex, with the hippocampus following both.

Although many memories are forgotten, accuracy and even precision can be maintained if participants are free to report only those memories about which they are certain ([9] and references therein). What changes with time is the grain of reported memories, in that older memories being coarser and gist-like. Even at very long intervals, some fine-grained memories remain.

With respect to the second prediction, it has been shown that given the proper proximal and/or direct cue, the (anterior) hippocampus leads the vmPFC in constructing future scenarios from prior episodic knowledge, and not the other way around as B&M propose for all scene (re) construction [10]. Similarly, frequency oscillations between the hippocampus and precuneus during autobiographical memory retrieval indicates that the hippocampus leads the way [11].

In sum, we question B&M's separation of constructive from retentive (storage) processes of the hippocampus, at least with respect to remote memories. By contrast, we argue that both occur: the selective retention and retrieval of detailed, remote memories can be supported by long-lasting hippocampal traces operating in conjunction with reconstructive processes guided by schematic, vmPFC representations. How these distinct representations interact in any particular recollection, and how they influence each other over longer durations remain questions for future research, which is likely to be stirred by B&M's provocative proposal. Our own view is that neurogenesis and reconsolidation, as well as other memory-altering processes, such as sleep, playing out in both vmPFC and hippocampal formation, sculpt remote memories by strengthening some, transforming and updating others, and eliminating the rest.

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Letter

Consolidating the Case for Transient Hippocampal Memory Traces

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Moscovitch and Nadel 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 1 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 (1 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.

Moscovitch and Nadel also consider their view 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 Moscovitch and Nadel offer no new insights into this concern.

Reconsolidation is considered by Moscovitch and Nadel 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.

Moscovitch and Nadel 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 (4-week-old) memories [6]. Once again, we discussed this particular study [2] and noted that specific memory traces were not targeted.

Moscovitch and Nadel 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 (1-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.