Active and effective replay: systems consolidation reconsidered again

James W. Antony and Anna C. Schapiro

In their recent Opinion article (A contextual binding theory of episodic memory: systems consolidation reconsidered. *Nat. Rev. Neurosci.* **20**, 364–375 (2019))[1], Yonelinas et al. propose that findings often taken as evidence for standard systems consolidation theory (SSCT) can be reinterpreted in a contextual binding (CB) framework. We agree that context is critical for explaining many memory phenomena and that SSCT, as defined, is probably incorrect. We do not advocate for the ideas that all memories become hippocampally independent, that the ones that do come to rely on neocortex retain the same quality or that the hippocampus does not undergo further learning with replay. Thus, on many counts, we are in agreement. However, we do think that during sleep and offline waking periods, hippocampal–neocortical interactions promote active transformation of memories resulting in increased neocortical engagement, which can usefully be called 'systems consolidation', and that some key empirical findings in this area are not predicted by the CB framework.

The CB account posits that replay (in wake or sleep) reflects context-related residual activity, which should tend to diminish with changes in spatial and temporal context (absent any retrieval driving context reinstatement). But replay seems to be more persistent and adaptive than this, as it can occur as frequently for a remote spatial context as for the current environment[2]; has been observed 10 hours after exposure to a novel environment, with stronger activity during sleep than wake periods[3]; and, critically, can occur more for infrequently experienced[4], gradually learned[5] and weakly encoded[6] information. These findings may not be strictly inconsistent with CB, but they are not motivated by it; additional mechanisms would be needed to explain why context is more strongly reinstated in these situations, especially during sleep.

We think there is strong evidence that sleep benefits memory beyond the reduction of contextual interference, and that this active process drives systems consolidation (as defined above). If sleep primarily benefits hippocampus-dependent memory by reducing interference or through local consolidation processes, specific active cortical events and hippocampal–cortical interactions during sleep should not be robustly and causally related to later memory. However, cortical replay coincides with hippocampal replay[7] and high-frequency replay-associated bursts called ripples[8], and this coupling is associated with later memory[9]. Hippocampal and neocortical ripples coincide and their coupling increases with learning[10], and disrupting the coupling between hippocampal ripples and cortical sleep spindles impairs memory retention[11]. In addition, optimal replay relies on the potential for spindles to occur[12], and artificially boosting individual slow oscillations increases spindle power and improves memory[13]. These processes seem to promote systems consolidation: timing optogenetic stimulations of the neocortex precisely to hippocampal ripples enhances endogenous hippocampal–neocortical coupling and alters neocortical neuronal spiking patterns that support behaviour[14].

Yonelinas et al. argue that replay primarily reflects prior memory formation rather than driving subsequent memory transformation. However, they acknowledge that post-encoding hippocampal activity may cause local cellular consolidation or re-encoding that could sometimes "lead to the formation of strong neocortical semantic representations that could support decontextualized memory for remote events". This latter mechanism fits well into our conceptualization of systems consolidation; we contend that this is a feature, rather than a side effect, of replay. Although more work is needed for full confidence in this contention — such as experiments that carefully track and manipulate the influence of the hippocampus on cortical representations[15] — we think the evidence already points to replay having a critical and active role in driving consolidation across memory systems.

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1. Yonelinas, A. P. et al. A contextual binding theory of episodic memory: systems consolidation reconsidered. *Nat. Rev. Neurosci.* **20**, 364–375 (2019).
2. Karlsson, M. P. & Frank, L. M. Awake replay of remote experiences in the hippocampus. *Nat. Neurosci.* **12**, 913–918 (2009).
3. Giri, B. et al. Hippocampal reactivation extends for several hours following novel experience. *J. Neurosci.* **39**, 866–875 (2019).
4. Gupta, A. S. et al. Hippocampal replay is not a simple function of experience. *Neuron* **65**, 695–705 (2010).
5. van de Ven, G. M. et al. Hippocampal offline reactivation consolidates recently formed cell assembly patterns during sharp wave-ripples. *Neuron* **92**, 968–974 (2016).
6. Schapiro, A. C. et al. Human hippocampal replay during rest prioritizes weakly learned information and predicts memory performance. *Nat. Commun.* **9**, 3920 (2018).
7. Ji, D. & Wilson, M. A. Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nat. Neurosci.* **10**, 100–107 (2007).
8. Wilber, A. A. et al. Laminar organization of encoding and memory reactivation in the parietal cortex. *Neuron* **95**, 1406–1419 (2017).
9. Zhang, H., Fell, J. & Axmacher, N. Electrophysiological mechanisms of human memory consolidation. *Nat. Commun.* **9**, 4103 (2018).
10. Khodagholy, D., Gelinas, J. N. & Buzsáki, G. Learning-enhanced coupling between ripple oscillations in association cortices and hippocampus. *Science* **358**, 369–372 (2017).
11. Xia, F. et al. Parvalbumin-positive interneurons mediate neocortical-hippocampal interactions that are necessary for memory consolidation. *eLife* **6**, e27868 (2017).
12. Antony, J. W. et al. Sleep spindle refractoriness segregates periods of memory reactivation. *Curr. Biol.* **28**, 1736–1743 (2018).
13. Ngo, H. V. et al. Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. *Neuron* **78**, 545–553 (2013).
14. Maingret, N. et al. Hippocampo-cortical coupling mediates memory consolidation during sleep. *Nat. Neurosci.* **19**, 959–964 (2016).
15. Mao, D. et al. Hippocampus-dependent emergence of spatial sequence coding in retrosplenial cortex. *Proc. Natl Acad. Sci. USA* **115**, 8015–8018 (2018).

Competing interests
The authors declare no competing interests.