When memories get complex, sleep comes to their rescue

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Humans can form rich, detailed, and vivid memories of events that they experience. These episodic memories involve multiple interconnected elements including people, places, objects, and emotions, bound together by a narrative structure, and residing in a specific context. However, research on episodic memories has often used contrived and tightly controlled tasks to experimentally examine how these memories are encoded, processed, and retrieved. Tasks operationalizing episodic memory in humans include retrieving features of visual stimuli presented on screen or recalling words from a learned list. Although this stripped-down approach has its merits, it fails to address a key feature of episodic memories – the inter-relations among their elements.

Studies exploring sleep's benefits to episodic memory have also largely evaded the complexity of the interconnected networks that make up real-life memories. During sleep, the neural substrates supporting memories are reactivated, leading to memory consolidation. The best-understood example of this process has been the temporally structured "replay" of firing patterns by ensembles of hippocampal place cells during sleep (and resting wakefulness) in rodents (1). Despite its mechanistic appeal, the memories reactivated through hippocampal replay are a simplistic model for human episodic memories. Nevertheless, most consolidation studies done in humans also consider sleep's effects on single, isolated memories (2).

In this issue of PNAS, Lutz et al. (3) test how sleep impacts memories that are tightly interwoven together. Their stimuli consisted of sets of four words: a location (e.g., pool), an animal (e.g., mouse), a food item (e.g., bread), and an object (e.g., bag). After learning the words in pairs, participants either slept or remained awake overnight in the lab. Among the studied sets, some pairwise links were more tightly interlinked (e.g., pool ↔ mouse ↔ bread ↔ pool), whereas some links broke this closed loop, creating a weaker association that is not embedded in the cohesive memory network (e.g., bread ↔ bag; Figure 1, left). For memories that were part of the tightly knit triad, sleep had no effect on retrieval. Strikingly, however, sleep rescued memory for the weaker association (Figure 1, right). Furthermore, it strengthened the cohesiveness of the set as a whole: it bolstered links between word pairs never observed together before (e.g., mouse ↔ bag) and increased the likelihood of jointly remembering the different elements of a set (i.e., the probability of retrieving one word given that another was retrieved). These beneficial effects of sleep were correlated with the density and amplitude of fast sleep spindles, which are 12-15 Hz waxing and waning waveforms observed using EEG and have been linked with memory consolidation (4).

These findings complement a growing literature addressing how sleep interacts with complex features of episodic memories (5). For example, studies have shown that sleep facilitates the extraction of gist from a set of semantically interrelated words (6) and promotes inference regarding how memories are related among themselves (7). These findings, complemented by those made by Lutz et al. (3), support the idea that sleep not only improves memories but restructures connections among them, effectively modifying their cognitive organization and possibly the neural infrastructure supporting them (8). Other studies have investigated the scope of memory reactivation during sleep and the consequences of co-reactivation of multiple memories (9, 10). Two-stage models of memory (8, 11) suggest that interleaved reactivation during sleep gradually molds neural circuits supporting memory, and this slow process is key for avoiding catastrophic interference between memories. Simultaneous co-reactivation of multiple memories may therefore have harmful effects on each memory's fidelity (10, 12, 13). When memories aren't at risk of interfering with one another, however, joint reactivation may benefit multiple memory elements (9, 14, 15, see discussion in 5). Lutz et al. (3) provide another example of memory reactivation of complex memories that evades the risks of catastrophic interference: their sets are made of networks of interconnected concepts that may not compete or conflict among themselves.

Lutz et al.'s (3) results inform yet another emerging theme in the literature on sleep's effects on memory: sleep seems to have a special role in rescuing weak memories from oblivion. Multiple studies have demonstrated that the benefits of sleep are stronger for weakly encoded memories than for strongly encoded ones (16–19). It is not entirely clear why sleep would prioritize weaker memories and what determines which weak memories will be rescued and which not. One possibility is that the compensatory effects of sleep are nonessential when memories are over-trained or boosted through multiple testing opportunities (10, 20). Although it is possible that stronger memories may simply have limited room to benefit from sleep, these memories seem to show limited improvements even when they are far from their effective ceiling. Lutz et al. (3) show that memory for strongly learned words (i.e., those that are part of the cohesive memory triad) deteriorates after the delay in both sleep and wakefulness. Memory for the weakly learned words, however, only deteriorates in the wake group. These results are hard to reconcile with claims about ceiling effects; sleep could potentially have maintained the stronger memories at their higher levels, but instead, it prioritized the rescue of the weaker ones.

Human sleep is notoriously hard to explore using scientific tools: participant introspection during sleep is limited, and methodological constraints make mechanistic investigation challenging. Nevertheless, our understanding of sleep’s relationship with memory has substantially advanced over the past decades. With increasingly naturalistic designs, we are starting to reveal sleep’s role in consolidating memories in real-life settings. Future research into this question can build on technological and methodological advances that have revolutionized research on memory and perception using dynamic stimuli such as movies, stories, and music (21, 22). The findings published by Lutz et al. (3) provide a valuable step toward truly understanding how sleep benefits rich and complex episodic memories.

Figure 1: Task design and main results for Lutz et al. (3). Participants learned sets of four words from four distinct categories (left). Three words were tightly interlinked among themselves (Location-Animal-Food), and the fourth was directly linked with one of the four (Food-Object). Participants either slept or spent the night awake. The sleep group showed improved incorporation of the distal word relative to the wake group (right). This effect was correlated with the occurrence and amplitude of sleep spindles (middle).

References

1. W. E. Skaggs, B. L. McNaughton, Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science (New York, N.Y.)* **271**, 1870–3 (1996).

2. B. Rasch, J. Born, About sleep's role in memory. *Physiological Reviews* **93**, 681–766 (2013).

3. N. D. Lutz, E. Martínez-Albert, H. Friedrich, J. Born, L. Besedovsky, Sleep shapes the associative structure underlying pattern completion in multielement event memory. *Proceedings of the National Academy of Sciences* (2024).

4. J. W. Antony, M. Schonauer, B. P. Staresina, S. A. Cairney, Sleep Spindles and Memory Reprocessing. *Trends in Neurosciences* **42**, 1–3 (2019).

5. J. W. Antony, E. Schechtman, Reap while you sleep: Consolidation of memories differs by how they were sown. *Hippocampus* (2023) https:/doi.org/10.1002/hipo.23526.

6. M. H. C. Mak, A. O'Hagan, A. J. Horner, M. G. Gaskell, A registered report testing the effect of sleep on Deese-Roediger-McDermott false memory: greater lure and veridical recall but fewer intrusions after sleep. *Royal Society Open Science* **10**, 220595 (2023).

7. J. M. Ellenbogen, P. T. Hu, J. D. Payne, D. Titone, M. P. Walker, Human relational memory requires time and sleep. *Proceedings of the National Academy of Sciences of the United States of America* **104**, 7723–8 (2007).

8. J. L. McClelland, B. L. McNaughton, R. C. O'Reilly, Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychological review* **102**, 419–457 (1995).

9. E. Schechtman, *et al.*, Multiple memories can be simultaneously reactivated during sleep as effectively as a single memory. *Communications Biology* **4**, 25 (2021).

10. B. H. Joensen, *et al.*, Targeted memory reactivation during sleep can induce forgetting of overlapping memories. *Learn Mem* **29**, 401–411 (2022).

11. G. Buzsáki, Two-stage model of memory trace formation: a role for "noisy" brain states. *Neuroscience* **31**, 551–570 (1989).

12. J. P. Oyarzun, J. Moris, D. Luque, R. de Diego-Balaguer, L. Fuentemilla, Targeted Memory Reactivation during Sleep Adaptively Promotes the Strengthening or Weakening of Overlapping Memories. *The Journal of Neuroscience* **37**, 7748–7758 (2017).

13. E. M. Siefert, *et al.*, Memory reactivation during sleep does not act holistically on object memory. 2023.12.14.571683 (2023).

14. E. Schechtman, J. Heilberg, K. A. Paller, Context matters: changes in memory over a period of sleep are driven by encoding context. *Learn Mem* **30**, 36–42 (2023).

15. E. Schechtman, J. Heilberg, K. A. Paller, Memory consolidation during sleep involves context reinstatement in humans. *Cell Rep* **42**, 112331 (2023).

16. E. A. McDevitt, K. A. Duggan, S. C. Mednick, REM sleep rescues learning from interference. *Neurobiol Learn Mem* **122**, 51–62 (2015).

17. D. Denis, *et al.*, The roles of item exposure and visualization success in the consolidation of memories across wake and sleep. *Learning & memory (Cold Spring Harbor, N.Y.)* **27**, 451–456 (2020).

18. M. Petzka, I. Charest, G. M. Balanos, B. P. Staresina, Does sleep-dependent consolidation favour weak memories? *Cortex* **134**, 65–75 (2021).

19. E. Schechtman, *et al.*, Sleep reactivation did not boost suppression-induced forgetting. *Scientific reports* **11**, 1383–1383 (2021).

20. J. W. Antony, K. A. Paller, Retrieval and sleep both counteract the forgetting of spatial information. *Learn Mem* **25**, 258–263 (2018).

21. S. A. Nastase, A. Goldstein, U. Hasson, Keep it real: rethinking the primacy of experimental control in cognitive neuroscience. *NeuroImage* **222**, 117254 (2020).

22. M. Ramot, *et al.*, Emergence of Sensory Patterns during Sleep Highlights Differential Dynamics of REM and Non-REM Sleep Stages. *J. Neurosci.* **33**, 14715–14728 (2013).