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Flies Sleep on it, or Fuhgeddaboutit!

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Abstract

Many studies in diverse organisms, including humans, have demonstrated a fundamental role for sleep in the formation of memories. A new study by Berry et al. (2015) indicates that in fruit flies, sleep accomplishes this in part by preventing an active process of forgetting.

Preview

“Our birth is but a sleep and a forgetting”

William Wordsworth, from Ode: Intimations of Immortality

Anyone who has crammed for an exam will tell you that memorizing takes considerable effort, while forgetting happens all too easily. In actuality, forgetting is a regulated mechanism in the brain for discarding useless information in favor of storing more salient memories. Recent work in *Drosophila* has emphasized that the forgetting of memories formed during aversive olfactory conditioning is an active process of the brain, with molecular and neuronal substrates that are distinct from the processes that regulate memory formation (Berry et al., 2014). In this issue of *Cell*, Berry et al (2015) extend these observations to show that sleep disables a key “forgetting circuit” in the *Drosophila* brain, normally active during arousal, resulting in better memory retention.

While the neural mechanisms underlying memory formation are not well understood, significant evidence supports a role of sleep in this process (Stickgold 2005). During sleep in mammals, memories become stabilized through a process of systems-level consolidation; synchronized brain activity during non-REM sleep transfers memories from their initial storage location in the hippocampus to more permanent storage sites in the neocortex. For this process to occur efficiently, consolidation must be prioritized by a memory’s salience, with irrelevant information that is not consolidated eventually

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forgotten (Wilhelm et al., 2011; Stickgold and Walker, 2013). An analogous consolidation process occurs in *Drosophila*-- specific neurons in the mushroom bodies are required for the acquisition of an odor memory, but this memory is later transferred to anatomically distinct long-term storage sites (Waddell, 2010). Furthermore, sleep modulates the retention of fly odor memories, suggesting that the sleep-dependence of memory consolidation likely has ancient evolutionary origins (Ganguly-Fitzgerald, 2006; Donlea et al., 2011).

In this issue, Berry and colleagues revisit the role for sleep in *Drosophila* and propose that sleep supports memory function by disrupting active forgetting. The authors previously identified a subset of dopaminergic neurons (DANs) that innervate the mushroom body, promote forgetting when stimulated, and inhibit forgetting when silenced (Berry et al., 2014). To better understand how these DAN forgetting neurons are modulated by the fly's experience, the authors first simultaneously monitored the fly's locomotion on an air-suspended ball and DAN calcium activity using a genetically encoded calcium indicator (GCaMP^{3.0}). Because the DANs innervate distinct regions of the mushroom body, they were able to distinguish the activity of each DAN. They found that one specific DAN (which they refer to as MV1) showed correlated activity with the fly's locomotion, based on sharp transitions in the calcium signal that matched transitions between active and inactive behaviors. Importantly, these DANs did not drive locomotor activity and are likely downstream from the neural circuit controlling locomotion, as neither genetically-targeted, temperature-controlled inhibition nor activation of these neurons had an appreciable effect on locomotor activity.

Because the critical MV1 forgetting neuron was activated by the fly's waking experience, Berry and colleagues hypothesized that the DANs—and therefore forgetting-- might be inhibited by sleep. In *Drosophila*, sleep-like states are defined as periods of quiescence that are associated with increased arousal thresholds to sensory stimuli and homeostatic regulation (e.g. increased sleep need following periods of deprivation) (Hendricks et al., 2000). Using both a pharmacological and genetically-targeted induction of sleep, Berry and colleagues observed that, indeed, activity of the MV1 forgetting neuron was inhibited when sleep was increased. Furthermore, the same genetic and pharmacological induction of sleep immediately following an odor-avoidance learning task improved the retention of olfactory memories several hours later. Amazingly, this memory retention effect of sleep required the sleep-induced silencing of DANs, as stimulation of DAN activity during post-learning sleep eroded memory formation. In contrast, mechanically arousing the flies post-learning eroded memory formation, an

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effect that could be blocked by simultaneously inhibiting DAN activity during the post-learning arousal. In other words, manipulation of DAN activity during sleep or arousal can decouple sleep and arousal states from their effects on memory retention and forgetting, respectively.

Together, these data suggests a simple model that links sleep's memory effects onto a single critical circuit: forgetting is induced by DAN activity, which can then be inhibited by sleep or enhanced by arousal (Figure 1). This model is conceptually in-line with models from behavioral psychology that posit that sleep facilitates memory by blocking interfering stimuli experienced during waking (Mednick et al., 2011). In the case of *Drosophila*, those interfering stimuli would enhance the activity of the forgetting neurons. Importantly, such a model need not be exclusive—active memory formation is likely to be working simultaneously, perhaps in competition with, active forgetting mechanisms, with both processes dependent on the animal's behavioral state.

These exciting findings open the door to several immediate questions. First, what is responsible for activating DANs, locomotion itself or the sensory stimulation and higher arousal levels accompanying locomotion? Second, DAN forgetting activity is also silenced during short bouts of locomotor quiescence that are unlikely to be bona fide sleep. Is the reduction in DAN-mediated forgetting a more general phenomenon associated with decreased activity, such as during quiet wakefulness and anesthesia? And finally, do flies forget indiscriminately, or can forgetting be biased towards irrelevant information? For example, are flies more likely to sleep after especially salient experiences to prevent forgetting?

The exact relationship between memory and sleep is still very much a mystery. Barry and colleagues have taken a significant step forwards toward understanding this relationship by identifying how the fly's behavioral state modulates the activity of a single critical circuit involved in memory loss. This new twist on current sleep-memory models serves as an excellent mechanistic starting point to frame future research in *Drosophila*, but also possibly mammalian, learning and memory.

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Figure 1. Flies that have learned to associate electric shocks with a neutral odor will subsequently remember to avoid the odor. The erosion of this memory is actively regulated by a dopamine circuit (DAN) in the fly brain. During arousal, DAN activity is high and enhances forgetting. During sleep, DAN activity is low and forgetting is decreased.

