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New neurons never sleep

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Young neurons tickle memory during REM sleep

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Abstract

Memory formation is a dynamic process and sleep is part of it. Consolidation of memories relies on finely orchestrated brain activities occurring during the post-learning sleep period. In this issue of *Neuron*, Kumar and colleagues provide evidence that the activity of adult-born hippocampal neurons, during REM sleep, is critical for the consolidation of episodic memory.

Sleep is thought to be critical for the consolidation of encoded events, a process wherein temporary and labile encoded representations form stable and long-lasting memories. The sleeping brain generates oscillatory patterns of activity that allow information processing. In mammals, sleep occurs in cycles of rapid-eye-movement (REM) sleep and non-REM sleep, two states that are highly different based their electrophysiologic characteristics, their neurobiology and their functions. Non-REM sleep is characterized by high amplitude slow-waves (0-4Hz) rhythm and the presence of sharp-wave-ripples while an oscillatory activity of 6-8 Hz called theta rhythm is predominant during REM sleep. Theta oscillation is observed in local field potential recordings from cortical structures including the hippocampus. Accumulating evidence indicate that REM sleep plays a key role in memory consolidation, and reducing hippocampal theta rhythms during REM sleep results in the impairment of hippocampo-dependent memories (Boyce et al., 2016). It indicates that theta oscillation may provide a favorable state for shaping memory. However, the underlying mechanisms and cell populations involved remain to be discovered.

In the 60's, Altman and Chorover (1963) revealed for the first time the existence of newly born neurons in the adult brain, a unique form of brain plasticity. Since this pioneering work, a wealth of evidence has accumulated indicating that neurons generated in the dentate gyrus throughout adulthood are

causally involved in several hippocampal functions and that they support the expression of elaborated cognitive functions including the formation of episodic memories. Between 4 and 7 weeks of age in mouse, these adult-born neurons go through a critical period characterized by a low activation threshold and a high excitability, allowing them to respond to even weak inputs (Marin-Burgin et al., 2012). Owing to these particular characteristics, the maturing new neurons are expected to play a critical role in sensory and memory processes.

In this issue of *Neuron*, Kumar and colleagues (2020) deployed a sophisticated combination of transgenic and imaging strategies to overcome the scarcity and sparse activity of new neurons, with the aim of investigating their contribution to memory consolidation during sleep. They used calcium neural imaging in freely moving mice equipped with a miniaturized microendoscope to examine new neurons' activity. By crossing two transgenic lines of mice, they generated offspring in which they managed to record the activity of young adult-born granule neurons no older than 4 weeks, *i.e.* their critical time period, by probing calcium events. Consistent with a previous report (Danielson et al., 2016), Kumar and colleagues first observed that adult-born granule neurons of untrained mice exhibit a sparse activity during wakefulness which further slows down during sleep periods. Then, the authors subjected mice to contextual fear conditioning, a protocol eliciting a simple form of learning, in order to explore the activity of adult-born hippocampal neurons during memory consolidation after learning. Within this task, mice have to learn the association between a new environmental context and the delivery of electric foot shocks, this learning involving the hippocampus. When exposed to this context again, the animals display freezing, a typical fear behavior, routinely used as a proxy to score memory. A single trial of aversive conditioning is sufficient for learning, which conveniently allows to distinguish the acquisition from the consolidation phase of memory. Moreover, this procedure generates a robust and long-lasting memory whose kinetic is well described (Izquierdo et al., 2016). The authors report that the activity of adult-born hippocampal neurons is significantly reduced during the periods of REM sleep, in mice that later expressed a strong fear memory in comparison to control animals with a weak memory. Interestingly, this effect is only observed during REM sleep, which suggests a state-dependent phenomenon. These findings raise a number of questions including why does the very sparse activity of adult-born neurons during REM sleep matter so much to memory consolidation ? What are the underlying biological mechanisms ?

In search of a comprehensive and dynamic picture of adult-born neuron's activity across the entire memory process, the authors took up the challenge of monitoring the activity of individual adult-born neurons throughout the learning, consolidation and retrieval phases of associative fear memory. Interestingly, a majority of the adult-born neurons that were active during learning also participated

to subsequent activity recorded during REM sleep episodes of memory consolidation. How were these neurons selected during the learning task and how were they subsequently identified to be reactivated during memory consolidation, has yet to be deciphered. Work by Trouche et al (2009) proposed that the new neurons active during the learning phase could be tagged to promote their preferential recruitment when a similar experience is encountered, suggesting reactivation during retrieval. Further work shall determine whether the reactivation of the same neuronal assembly during REM sleep consolidation relies on such neuronal tagging and what the nature of this tag is. However, in Kumar et al, young neurons remained inactive during memory retrieval. Given that the adult-born neurons contribute to learning and consolidation but not to memory retrieval, it is tempting to speculate that they do not conserve memory, but rather participate in building a downstream neuronal network in charge of storing memory.

To establish the causal contribution of new neuron activity during REM sleep to memory consolidation, Kumar and colleagues used optogenetic tools to silence adult-born neurons during REM sleep. They found that theta oscillation at the surface of the skull above the hippocampus or, directly in the dentate gyrus was not modified. New neurons are few and their activity is sparse. The authors estimated that they managed to silence 467 events over the 6hrs of experimental recording. Such activity is relatively reduced compared to the global activity that can be recorded in the dentate gyrus during REM sleep, possibly explaining the lack of effects on theta oscillations. The monitoring of calcium events confirmed that the neurons were activated but it provided no information regarding the actual pattern of neuronal activity, due to a limited temporal resolution and sensitivity of the technology. The timing of neuronal activity, with respect to local theta oscillation, is critical for the modulation of synaptic strength (Orr et al., 2001) but the firing mode of the new neurons is not yet known. Do they fire at the peak, the dip, the ascendant or descendant phase of theta oscillation? The timing of their firing relative to the theta oscillation is probably critical to their effectiveness in promoting memory retention. Challenging experiments will thus be required in the near future to answer these questions and further understand why young neurons and theta rhythm are conducive to memory stabilization.

Memory formation involves synaptic changes both on mature and immature hippocampal neurons. For instance, learning of contextual fear accelerates the formation of dendritic spines on adult-born neurons, while memory consolidation strengthens their spine connectivity (Petsophonsakul et al., 2017). Here, Kumar et al show that although sparse, the activity of new neurons during REM sleep controls the expression of genes typically involved in synaptic plasticity. The authors therefore investigated whether the new neurons active during REM sleep underwent structural changes.

Silencing adult-born neurons during REM sleep-dependent memory consolidation had no impact on the increase in their spine density triggered by learning but led to the production of elongated spine necks. It was reported that upon synaptic stimulation, long-necked spines can rapidly be mobilized and their neck shorten to increase synaptic strength (Araya et al., 2014). This mechanism may be triggered during REM sleep to specifically strengthen and stabilize synapses of the immature new neurons that are recruited upon learning.

Last, the authors provide the ultimate argument that adult-born neurons, of a critical age and with an activity finely-tuned to REM sleep contribute to memory consolidation. Indeed, adult-born neurons were silenced at any time but REM sleep, at different maturation stages (2, 4 and 10 weeks of age) or activated at random frequency during the REM sleep post-training period. It was only when the silencing or the random activation of young adult-born neurons (4 weeks-old) occurred during REM sleep, that fear memory was impaired. These data demonstrate that the contribution of adult-born neurons to memory consolidation happens only when the brain is in a specific state (REM sleep), their activity is tune to theta oscillations and while they display low activation threshold and high excitability. Future experiments should unravel how REM sleep provides an appropriate context for adult-born neurons to deliver information allowing the embedding of a memory trace in downstream circuits although their activity, as currently recorded by calcium imaging, is sparse.

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