

Contribution of adult-born neurons to memory consolidation during rapid eye movement sleep

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Introduction: Memory consolidation stabilizes newly acquired memories by integrating them into pre-existing memory networks, which is thought to occur via changes in synaptic strength. Sleep may influence memory consolidation by modifying synaptic strength through local neuronal oscillatory activity. Recently, we found that the activity of hippocampal adult-born neurons (ABNs) is critical for memory consolidation during sleep (Kumar et al., 2020). Here, we propose a hypothesis for how changes in ABN synaptic plasticity synchronized with neural oscillations may contribute to memory consolidation during sleep.

Synaptic plasticity during sleep: Sleep occurs in cycles of rapid eye movement (REM) and non-REM (NREM) sleep, with each sleep stage associated with characteristic synchronous neuronal activities. Slow oscillations from the cortex, spindles from the thalamus, and sharp wave-ripples (SWRs) from the hippocampus are prominent during NREM sleep, whereas theta oscillations from the hippocampus and pontine-geniculate-occipital waves are prominent during REM sleep (Diekelmann and Born, 2010). These synchronous activities may create a permissive environment for changes in synaptic strength.

Major theories, such as the synaptic homeostasis theory, posit that experience during wakefulness induces synaptic potentiation, whereas subsequent sleep globally down-scales overall synaptic strength. As a consequence, weakly connected synapses are removed while relatively strong synapses are preserved, thereby enhancing memory due to an improved signal-to-noise ratio (Diekelmann and Born, 2010). This synaptic reorganization could be mediated by SWRs and slow oscillations in NREM sleep. Indeed, silencing SWRs prevents synaptic downregulation (Norimoto et al., 2018). Moreover, in NREM sleep, synaptic downscaling occurs after presynaptic activity unless it is followed by postsynaptic activity within a specific time period (González-Rueda et al., 2018).

REM sleep may also contribute to synaptic reorganization. Newly formed spines after motor learning are predominantly pruned

during REM sleep, whereas remaining spines are strengthened (Li et al., 2017). Moreover, REM sleep promotes rapid spine elimination along with dendritic Ca^{2+} spikes after auditory fear learning (Zhou et al., 2020). These findings suggest that REM sleep is important for synaptic reorganization during memory consolidation. Indeed, in REM sleep, hippocampal neuronal activity at specific phases of the theta oscillation (i.e., phase-locked activity) plays a critical role in both the strengthening and weakening of synapses. In particular, the plasticity of perforant path synapses from the entorhinal cortex to the dentate gyrus (DG) depends on the theta phase at which input stimulation is applied (Orr et al., 2001). Indeed, memory consolidation is impaired when theta oscillation in REM sleep is blocked (Boyce et al., 2016), suggesting that neuronal activity synchronized with theta oscillation plays a critical role in synaptic plasticity during memory consolidation in REM sleep.

Role of ABNs in memory consolidation during REM sleep: The mammalian DG is unique in that it continuously generates granular neurons into adulthood. Until recently, the dynamics and roles of ABN activity during sleep were unknown. However, we showed that after contextual fear learning, the overall activity of ABNs decreases when mice are in REM sleep (Kumar et al., 2020). Remarkably, most ABNs that were sparsely active during learning reactivate during subsequent REM sleep. Furthermore, memory consolidation is impaired if the sparse activity of ABNs is silenced during REM sleep. These results provide causal evidence that the sparse activity of ABNs during REM sleep is necessary for memory consolidation, consistent with a previous finding that a sparse neuronal population in the DG reactivates during memory retrieval (Sakurai et al., 2016).

The synaptic plasticity capacity of ABNs depends on their maturational stage, with enhanced plasticity observed among 4–6-week-old ABNs (Ge et al., 2007). Correspondingly, we found that silencing the activity of 4-week-old ABNs, but not 2- or 10-week-old ABNs, during REM sleep impairs memory consolidation (Kumar et al., 2020). Moreover, random (i.e., not

phase-locked) activation of 4-week-old ABNs impairs memory, similar to a previous report (Danielson et al., 2016), suggesting that precisely timed, finely tuned ABN activity is essential for their proper function. Furthermore, silencing 4-week-old ABNs results in elongation of their spine necks, which is a sign of weakening synaptic strength and/or decoupling from presynaptic activity. By contrast, no changes in the spines of fully mature granular cells (mGCs) were observed upon their silencing during REM sleep. Considering the theta phase-dependent plasticity mechanism in the DG (Orr et al., 2001), our findings suggest that finely-tuned, theta phase-locked ABN activity contributes to memory consolidation during REM sleep.

A hypothesis for ABN-mediated memory consolidation in REM sleep: As a stable contextual fear memory trace can be encoded by mGCs in the DG, theta phase-locked ABN activity could promote memory consolidation by interacting with mGCs. Indeed, ABNs inhibit mGC activity via direct monosynaptic connections when a small number of ABNs are activated through inputs relevant to contextual information (Luna et al., 2019). We hypothesize that the DG contains both theta phase-locked and non-phase-locked ABNs (**Figure 1A**). Learning induces the formation of new spines on 4-week-old ABN dendrites via enhanced synaptic plasticity. This may increase non-phase-locked ABN activity, triggering global spine elimination and reducing overall ABN activity in REM sleep after learning (Kumar et al., 2020). However, theta phase-locked activity stabilizes spines in a subset of ABNs that remain sparsely active in REM sleep (**Figure 1B**). This sparse ABN activity inhibits mGC activity in a theta phase-specific manner, allowing connected mGCs to activate at the reciprocal theta phase (**Figure 1C**). This concurrent theta phase-locked activity of mGCs modifies their synaptic plasticity (Orr et al., 2001), allowing them to establish a memory trace (**Figure 1D**). This hypothesis is consistent with a previous observation that the theta phase preference of hippocampal neuron activity during REM sleep changes after context learning (Mizuseki et al., 2011).

Testing this hypothesis would require the examination of ABN activity in relation to theta oscillation. This could be achieved using two approaches: (1) determining the effect of manipulating ABN activity at a specific theta phase during memory consolidation and/or (2) verifying whether ABNs fire at a particular theta phase. Regarding the first approach, combining optogenetics with a closed-loop feedback system might allow for

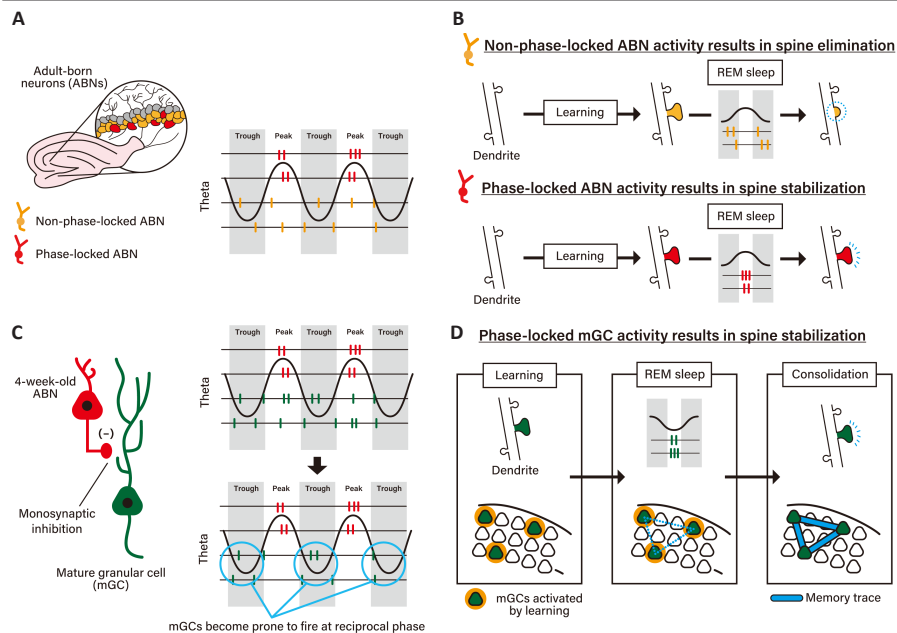


Figure 1 | ABNs may influence mGC theta phase-locked activity during memory consolidation in REM sleep. (A) Theta phase-locked ABNs and non-phase-locked ABNs in the hippocampus. (B) Theta phase-locked activity stabilizes ABN spines, whereas non-phase-locked activity eliminates ABN spines. (C) Phase-locked ABN activity may inhibit mGC activity in a theta phase-specific manner, thereby coordinating the activity of mGCs at the reciprocal phase. (D) Phase-locked mGC activity may induce modifications in synaptic strength that establish a memory trace. ABN: Adult-born neurons; mGC: mature granular cell.

phase-specific manipulation. Regarding the second approach, as genetically encoded Ca^{2+} sensors cannot achieve the time resolution necessary to directly assess theta phase-locked neural activity, a method capable of examining ABN activity with higher temporal resolution is required. Moreover, as memory-encoding ABNs could exhibit specific activity patterns, it would be necessary to stimulate ABNs by mimicking their naturally occurring activity pattern *in vivo*, which might be possible using a patterned light stimulation technique (Marshel et al., 2019).

Conclusion: The sparse, theta phase-locked activity of ABNs could produce changes in their synaptic strength and promote fear memory consolidation by influencing mGC activity. Future research on the mechanism by which ABN synaptic plasticity contributes to memory consolidation would pave the way toward developing new therapeutic strategies for memory disorders.

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References

Boyce R, Glasgow SD, Williams S, Adamantidis A (2016) Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. *Science* 352:812-816.

Danielson NB, Kaifosh P, Zaremba JD, Lovett-Barron M, Tsai J, Denny CA, Balough EM, Goldberg AR, Drew LJ, Hen R, Losonczy A, Kheirbek MA (2016) Distinct contribution of adult-born hippocampal granule cells to context encoding. *Neuron* 90:101-112.

Diekelmann S, Born J (2010) The memory function of sleep. *Nat Rev Neurosci* 11:114-126.

Ge S, Yang CH, Hsu KS, Ming GL, Song H (2007) A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. *Neuron* 54:559-566.

González-Rueda A, Pedrosa V, Feord RC, Clopath C, Paulsen O (2018) Activity-dependent downscaling of subthreshold synaptic inputs during slow-wave-sleep-like activity in vivo. *Neuron* 97:1244-1252.

Kumar D, Koyanagi I, Carrier-Ruiz A, Vergara P, Srinivasan S, Sugaya Y, Kasuya M, Yu TS, Vogt KE, Muratani M, Ohnishi T, Singh S, Teixeira CM, Chérasse Y, Naoi T, Wang SH, Nondhalee P, Osman BAH, Kaneko N, Sawamoto K, et al. (2020) Sparse activity of hippocampal adult-born neurons during REM sleep is necessary for memory consolidation. *Neuron* 107:552-565.

Li W, Ma L, Yang G, Gan WB (2017) REM sleep selectively prunes and maintains new synapses in development and learning. *Nat Neurosci* 20:427-437.

Luna VM, Anacker C, Burghardt NS, Khandaker H, Andreu V, Millette A, Leary P, Ravenelle R, Jimenez JC, Mastrodonato A, Denny CA, Fenton AA, Scharfman HE, Hen R (2019) Adult-born hippocampal neurons bidirectionally modulate entorhinal inputs into the dentate gyrus. *Science* 364:578-583.

Marshel JH, Kim YS, Machado TA, Quirin S, Benson B, Kadmon J, Raja C, Chibukhchyan A, Ramakrishnan C, Inoue M, Shane JC, McKnight DJ, Yoshizawa S, Kato HE, Ganguli S, Deisseroth K (2019) Cortical layer-specific critical dynamics triggering perception. *Science* 365:eaaw5202.

Mizuseki K, Diba K, Pastalkova E, Buzsáki G (2011) Hippocampal CA1 pyramidal cells form functionally distinct sublayers. *Nat Neurosci* 14:1174-1181.

Norimoto H, Makino K, Gao M, Shikano Y, Okamoto K, Ishikawa T, Sasaki T, Hioki H, Fujisawa S, Ikegaya Y (2018) Hippocampal ripples down-regulate synapses. *Science* 359:1524-1527.

Orr G, Rao G, Houston FP, McNaughton BL, Barnes CA (2001) Hippocampal synaptic plasticity is modulated by theta rhythm in the fascia dentata of adult and aged freely behaving rats. *Hippocampus* 11:647-654.

Sakurai K, Zhao S, Takatoh J, Rodriguez E, Lu J, Leavitt AD, Fu M, Han BX, Wang F (2016) Capturing and manipulating activated neuronal ensembles with CANE delineates a hypothalamic social-fear circuit. *Neuron* 92:739-753.

Zhou Y, Lai CSW, Bai Y, Li W, Zhao R, Yang G, Frank MG, Gan WB (2020) REM sleep promotes experience-dependent dendritic spine elimination in the mouse cortex. *Nat Commun* 11:4819.

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