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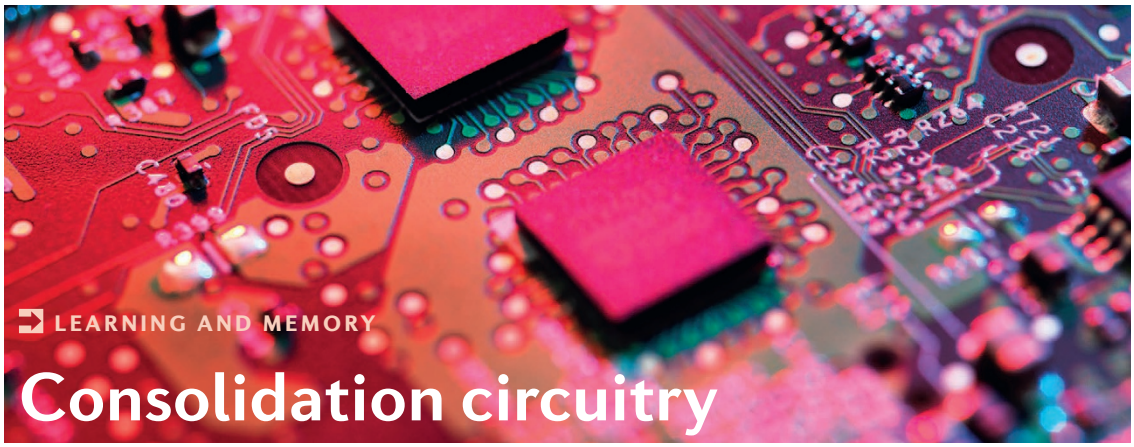

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Consolidation circuitry

Episodic memories are thought to form initially in the hippocampus and to be later transferred to the cortex for long-term storage (as so-called remote memories), but this process of memory consolidation is poorly understood. Tonegawa and colleagues now show that memory engram cells associated with remote memories are generated in the prefrontal cortex (PFC) early during learning in a contextual fear conditioning paradigm and that this process depends on hippocampus–entorhinal cortex and basolateral amygdala (BLA) inputs.

The authors first explored the circuits involved in memory consolidation in mice. Through use of a retrograde tracer, they identified projections from layer 5a (L5a) cells in the medial entorhinal cortex (MEC) to the frontal cortex and to the BLA — regions implicated in fear memory formation. Optogenetic inhibition of MEC L5a terminals specifically in the PFC during day 1 of contextual fear conditioning did not affect fear memory recall at day 2 or 8 but impaired memory recall at day 15, suggesting that MEC L5a–PFC projections have a role in the formation of long-term contextual fear memories early in the learning process.

Memory engram cells are neurons that are activated during learning and reactivated during memory recall that is cued by the original stimulus. Here, contextual fear conditioning activated neurons in the PFC, as revealed by FOS expression, and optogenetic activation of these previously activated PFC neurons induced freezing in mice, suggesting that these neurons are engram cells. These neurons received input from MEC L5a cells, and inhibition of MEC L5a cells during contextual fear conditioning training prevented any PFC activation-induced freezing responses, supporting the assertion that MEC L5a–PFC projections function in remote memory formation.

> “contextual fear conditioning activated neurons in the PFC … and optogenetic activation of these previously activated PFC neurons induced freezing in mice”

PFC neurons that were activated on day 1 of contextual fear conditioning could be reactivated when mice were exposed to the conditioned context at day 12 but not at day 2, and optogenetic inhibition of these cells only at the later time disrupted memory retrieval. This provides further evidence that contextual fear conditioning generates PFC engram cells during learning and suggests that these cells are necessary for remote memory retrieval. Optogenetic inhibition of BLA–PFC projections during contextual fear conditioning impaired PFC engram cell generation and remote memory formation, indicating that BLA inputs are also necessary for remote memory formation in the PFC.

The authors next examined whether dentate gyrus (hippocampal) engram cells are involved in PFC engram cell functional maturation, by engineering the former to express tetanus toxin light chain (TeTX) following their activation during contextual fear conditioning such that their output was inhibited. TeTX-mediated inhibition impaired context-induced PFC engram cell reactivation 12 days after conditioning, suggesting that dentate gyrus engram cells have a role in the functional maturation of PFC engram cells. The dentate gyrus engram cells themselves could be reactivated when mice were placed in the fear-conditioned context on day 2 after conditioning but not at day 13, indicating that these hippocampal cells become functionally silent with time.

Finally, the authors further examined the role of the BLA in fear memory formation. Optogenetic inhibition of MEC–BLA projections during contextual fear conditioning impaired memory formation. Moreover, the application of such inhibition on day 2 after conditioning impaired memory retrieval, but inhibition applied on day 12 after conditioning had no effect on retrieval, suggesting that MEC–BLA projections are important in the recall of recent memories. By contrast, optogenetic inhibition of PFC–BLA projections during retrieval impaired recent but not remote memory recall, indicating that these projections are important for remote memories and that BLA engram cells are maintained after conditioning.

Together, these data suggest that the PFC engram cells necessary for remote memory form at an early point in learning but that they are initially immature, and that the process of long-term memory consolidation is dependent on maturation of these PFC engram cells and involves interactions between the PFC, the hippocampal–entorhinal cortex and the BLA.

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