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LEARNING AND MEMORY

You only learn once

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The ability to form memories of one-time experiences, such as a visit to a new place, is crucial. The CA3 region of the hippocampus has been suggested to be important in directing rapid long-term potentiation following single experiences, but the source of novelty-signalling inputs to CA3 is unclear. In a new study in mice, Tonegawa and colleagues demonstrate that projections from the locus coeruleus (LC) to CA3 enable the formation of memories for novel environmental contexts.

Previous studies have revealed that LC activity changes in response to novel stimuli, suggesting that it could signal novelty to the hippocampus. In the new study, the authors used virus-mediated labelling and retrograde tracers to confirm that LC neurons send projections to CA3. Then, they optogenetically inhibited neurons expressing noradrenaline transporter (NET), which mostly reside in the LC, while mice explored a novel environment. The next day, the mice were placed back into the same environment. Whereas control, non-LC-inhibited mice explored the environment less on day 2 than on day 1, reflecting context recall, mice in which the LC was inhibited on day 1 did not show a reduction in exploration of the same environment on day 2. Thus, LC activity is necessary for encoding a single experience of a novel environmental context.

The LC releases both noradrenaline and dopamine. Here, the authors showed that intrahippocampal injection of a dopamine 1 receptor-specific antagonist, but not a β-adrenergic receptor antagonist, impaired the encoding of the novel environment. Together with observations that there are very few projections from the dopaminergic ventral tegmental area to CA3, these results indicate that dopamine released from LC projections in the hippocampus might be important for encoding a novel context.

To examine whether silencing the LC affects the formation of cellular ensembles representing the memories of novel experiences — that is, memory 'engrams' — the authors used an activity-dependent genetic labelling approach to identify CA3 neurons that were active during the first session in a novel context and (with a different label) CA3 neurons that were active during the second session. The reactivation of putative memory engrams during the second session was assessed by analysing ensembles of neurons that were doubly labelled. Compared with control mice, mice in which the LC was silenced during the first session showed impaired reactivation of CA3 ensembles. Thus, inhibition of the LC during exposure to a novel context may disrupt the formation of a stable engram relating to that context.

Forming memories of new contexts depends on the mapping of the novel space by spatially tuned hippocampal place cells that are subsequently reactivated upon returning to the same place. The authors used calcium imaging to assess the place fields of CA3 place cells in mice as the animals explored a novel context A on day 1 (A1), the same context A again on day 2 (A2) and another novel context, B, on day 3. In control mice, individual CA3 place cells showed similar spatial tuning across the A1 and A2 sessions (that is, their place fields remained the same) and showed remapping in context B. Chemogenetic suppression of the LC during A1 resulted in the formation of different place fields in A1, A2 and B. Therefore, LC activity is required for the encoding of a spatial map of novel contexts by CA3 place cells.

Together, these results suggest that, when mice explore a new context, LC neurons projecting to CA3 enable the formation of a memory engram and a lasting spatial map of the novel environment, possibly through release of dopamine.

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ORIGINAL ARTICLE Wagatsuma, A. *et al.* Locus coeruleus input to hippocampal CA3 drives single-trial learning of a novel context. *Proc. Natl Acad. Sci. USA* **115**, E310–E316 (2017)