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LEARNING AND MEMORY

A memorable double act

> "pharmacological inactivation of the dorsal hippocampus ... had no effect on retrieval induced by light stimulation of the RSC ensemble."

The functional relationship between the hippocampus and the cortex in memory formation and retrieval is not completely understood. A major question is whether the hippocampus is necessary for the reactivation of cortical representations during memory retrieval. Two new studies now provide further insights into this issue.

In the first study, Wiltgen and colleagues used transgenic mice in which a green fluorescent protein (GFP) was expressed under control of the *c-fos* promoter (to restrict GFP labelling to activated cells) and a tetracycline response element (to halt GFP expression temporarily by feeding the mice doxycycline (Dox)). The authors exposed the mice to a fear conditioning procedure after removing Dox from the diet, so that neurons activated during conditioning were labelled with GFP. In addition, the light-activated proton pump ArchT was expressed in GFP-labelled CA1 neurons, so that these cells — which form the hippocampal 'memory trace' of the experience — could later be silenced.

During a retrieval test 2 days after conditioning, the authors silenced this memory trace in some of the mice by delivering green light to the hippocampus. This substantially reduced retrieval (measured as the amount of time spent freezing in the conditioning context) compared with mice in which the CA1 memory trace was not silenced, whereas silencing of CA1 neurons that were not active during conditioning had no effect. This confirms previous findings that retrieval of a recent memory requires the reactivation of the original CA1 ensemble.

Next, the authors identified the projections of the CA1 ensemble to several cortical regions, including the retrosplenial cortex (RSC). Silencing the CA1 trace during retrieval selectively reduced activation (measured by c-fos expression) of cortical cells that expressed GFP (that is, neurons that were activated during fear conditioning). GFP-labelled cells in the central nucleus of the amygdala, which receives input from the cortical regions and from CA1, also showed reduced activation upon silencing of the CA1 ensemble. These findings suggest that activation of a CA1 memory trace triggers reactivation of the cortical representation of the memory.

In the other study, Mayford and colleagues used transgenic mice in which the fluorescent protein tdTomato and the channelrhodopsin variant ChEF were expressed under control of both the *c-fos* promoter and a tetracycline response element. The authors showed that fear conditioning in a novel cage after Dox removal increased the number of ChEF–tdTomato-tagged neurons in the RSC compared with the control (home cage) condition, as did exposure to the novel cage alone. Moreover, light delivery to the RSC could trigger retrieval (that is, freezing) outside the conditioning context. This effect was observed not only when RSC neurons were tagged with ChEF–tdTomato during fear conditioning but also when RSC neurons were tagged during exposure to the conditioning context before the conditioning procedure itself. This indicates that an RSC ensemble can form a representation of a context that can subsequently be incorporated into a new fear memory.

The authors showed that *c-fos* mRNA levels in several amygdala nuclei and the entorhinal cortex (which are downstream of the RSC) after artificial reactivation of a fear-context-associated RSC ensemble were similar to those after a normal retrieval test. By contrast, pharmacological inactivation of the dorsal hippocampus reduced freezing in a retrieval test but had no effect on retrieval induced by light stimulation of the RSC ensemble.

Together, these studies show that, during normal (stimulus-driven) retrieval, the hippocampus is required for the reactivation of cortical activity patterns that occurred during encoding but that artificial reactivation of the representation in the RSC is sufficient to drive recall.

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ORIGINAL RESEARCH PAPERS Tanaka, K. Z. *et al.* Cortical representations are reinstated by the hippocampus during memory retrieval. *Neuron* http://dx.doi.org/10.1016/j.neuron.2014.09.037 (2014) | Cowansage, K. K. *et al.* Direct reactivation of a coherent neocortical memory of context. *Neuron* http://dx.doi.org/10.1016/j.neuron.2014.09.022 (2014)