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LEARNING AND MEMORY

Artificial activation of a memory trace

How memories are represented at the neuronal level is a central question in neuroscience. It is thought that a learning experience is encoded by a population of neurons, forming a memory trace or engram. Two papers, published in *Science* and *Nature*, now show that distinct memories have distinct memory traces in the hippocampus, and that a memory trace can be artificially activated to induce fear behaviour.

The two studies applied similar approaches to target neurons that were activated by a learning experience. Liu *et al.* made use of transgenic mice in which channelrhodopsin 2 (ChR2) could be expressed specifically in activated dentate gyrus (DG) granule cells by putting it under the control of the *c-fos* promoter. Garner *et al.* used mice that expressed a DREADD (designer receptor exclusively activated by designer drug) known as hM3Dq in activated (c-Fos-expressing) neurons. Activation of ChR2 by light or of hM3Dq by clozapine-*N*-oxide (CNO) causes cells that express these receptors to fire. Using these approaches, the authors could artificially reactivate neurons associated with a specific memory. The expression of ChR2 or hM3Dq could be prevented by feeding the animals doxycyclin (Dox), allowing the authors to temporally restrict the expression of these receptors.

> “the fear memory for context B could be artificially induced in context A”

IMAGE SOURCE

Liu *et al.* allowed a group of Dox-fed mice to habituate to a neutral context (context A) and measured their baseline freezing levels. The mice were then taken off Dox to open a window for activity-dependent labelling with ChR2 and subsequently underwent fear conditioning in another context (context B). After conditioning, the authors gave the animals Dox (to prevent further ChR2 expression) and, on the following day, tested their freezing levels in the original, non-fearful context A. Freezing levels were initially low but, crucially, they greatly increased when the authors light-activated ChR2-expressing cells — that is, cells associated with context B — suggesting that the fear memory for context B could be artificially induced in context A. The authors further showed that light-induced reactivation of a memory trace for a non-fearful environment did not increase freezing levels in a different context, even in mice that had undergone fear conditioning in a third context. This suggests that different neurons encode different memories and, indeed, immunohistochemistry showed that ChR2-positive neurons associated with one context were different from c-Fos-labelled neurons associated with another context. Together, these findings suggest that reactivation of neurons that encode a fear memory is sufficient to induce recall of that memory.

Garner *et al.* used a different study design. They exposed mice to a non-fearful context (context A). The next day, the animals received both Dox (to prevent further hM3Dq expression) and CNO (to activate hM3Dq-expressing neurons) and underwent fear conditioning in context B. Thus, the neurons that encoded context A were active while the mice learnt to associate context B with a footshock. The following day, the authors tested freezing levels in context B in the absence and presence of CNO. Interestingly, only the mice that received CNO during testing showed high levels of freezing. This suggests that during fear conditioning, the memory trace for context A had become part of the trace for context B and was therefore required for the full expression of the fear memory of context B. By contrast, in mice that did not receive CNO during fear conditioning in context B, CNO treatment during memory testing in context B reduced freezing levels, suggesting that reactivation of a non-relevant memory trace impairs the retrieval of a different memory.

By directly activating distinct ensembles of cells, these studies have shown that it is possible to artificially induce recall of a fear memory and have thereby provided further insight into the cellular basis of memory.

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ORIGINAL RESEARCH PAPERS Liu, X. *et al.* Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature* 22 Mar 2012 (doi:10.1038/nature11028) | Garner, A. R. *et al.* Generation of a synthetic memory trace. *Science* **335**, 1513–1516 (2012)