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Second shift

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In the amygdala, the same neurons that are active during learning are also active during memory retrieval.

It took a long time for Lois Lane to discover that Clark Kent and Superman were one and the same. Neurons also sometimes shield their dual identities. Reijmers *et al*. report that the same neurons in the amygdala are active during the learning and retrieval of associative memories in a recent article in *Science*.

In neurons, the expression of several immediate-early genes correlates with electrophysiological activity, allowing researchers to indirectly identify active neurons. The immediate-early genes *c-fos* and *Zif/Egr* briefly label active neurons. The authors aimed to differentially label neurons activated during two distinct time windows: associative learning and memory retrieval.

They designed TetTag mice expressing the LacZ reporter under the control of the tetracycline operator and the tetracycline transactivator under the control of the *c-fos* promoter. The authors fed these mice food treated with the tetracycline analog doxycycline, which suppressed LacZ expression. When they switched the mice to a doxycycline-free diet, LacZ expression remained low. Kainic acid treatment induced neuronal LacZ expression in TetTag mice on a doxycycline-free diet but not in TetTag mice fed doxycycline-treated food. Even after doxycycline was reintroduced to their diet, the LacZ tag remained stable in TetTag mice for at least 5 days, suggesting that LacZ labeled neurons activated during a doxycycline-free window.

The basolateral amygdala is important in associative memory. In fear conditioning, mice learn to associate a context with a shock. Several days later, presentation of the context retrieves the shock memory, causing mice to freeze with fear. The authors switched TetTag mice to a doxycycline-free diet and placed them in a lemon-scented cage. There, the mice received shocks immediately following the presentation of a tone. Then the authors reintroduced doxycycline to the diet. Three days later, they placed the mice back in the lemon-scented cage and played the shock-associated tones. In the amygdala, neurons activated during associative learning should be labeled by LacZ, whereas neurons activated by memory retrieval should be positive for Zif.

LacZ expression was similar in the basolateral amygdala of fear-conditioned mice, whether or not they were re-exposed to the shock context, suggesting that LacZ labeled neurons that were activated during learning. Following memory retrieval, 12% of all LacZ-positive basolateral amygdala neurons were also Zif-positive, suggesting that a subset of basolateral amygdala neurons involved in learning are reactivated during memory retrieval.

Re-exposure to the context without shock extinguishes the memory and context-associated fear. The degree of extinction varied from mouse to mouse. The number of basolateral amygdala neurons positive for both LacZ and Zif correlated with the degree of freezing to the shock context, suggesting that the number of neurons reactivated during memory retrieval correlates with the strength of the memory.

These data suggest that associative memories are formed and stored (at least temporarily) in the same neurons or neural circuits. Perhaps stimulation of these neural circuits can improve memory retrieval and new memory formation in people with brain injuries.

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1. Reijmers, L. G., Perkins, B. L., Matsuo, N. & Mayford, M. Localization of a stable neural correlate of associative memory. *Science* **317**, 1230–1233 (2007). | Article | PubMed | ISI | ChemPort |