Nature Reviews Neuroscience | AOP, published online 5 April 2013; doi:10.1038/nrn3487

LEARNING AND MEMORY

Remembrance of things similar...

J.Vallis/NPG

What did you have for breakfast today? And what did you watch on TV last night? These questions are deceptively difficult, because they require your brain to distinguish between many almost identical memories (of other breakfasts and other evenings) and to identify the right one. This process is known as 'pattern separation'. A new study uses an elegant technique to clarify how the dentate gyrus contributes to pattern separation by activating distinct populations of granule cells in response to similar events.

Deng *et al.* used 'TetTag' transgenic mice to identify neurons that were activated by different experiences. Such mice are treated with doxycycline to inhibit the expression of a doxycycline-sensitive transgene; when doxycycline treatment is withdrawn, activation of a neuron will cause it to permanently express the tau-*lacZ* marker. The mice can then be placed back on doxycycline treatment and exposed to a specific experience before their brains are removed and examined; neurons that are activated by the latter experience can also be identified by looking for the expression of immediate-early genes. This allows researchers to compare the activation of neurons at two defined time points in the same animals.

Deng *et al.* exposed mice that were not receiving doxycycline to one of two unfamiliar cages; neurons activated by such exposure were tagged with tau-*lacZ* expression. They then reinstated doxycycline treatment and placed the mice back in one of the cages (which some of the mice had seen in the earlier part of the protocol) before studying tau-*lacZ* and immediate-early gene expression in the brains of the mice.

In the hippocampal CA1 region, which is important for memory, neurons that were activated by the first exposure to a cage (that is, during learning) were more likely to be reactivated by subsequent exposure to the same cage (recall) than by the other cage. However, in the dentate gyrus, the neurons that were activated during learning were no more or less likely to be activated during recall of the same cage than other neurons. Furthermore, when the mice were placed in a different cage from the learning episode, neurons that were active during learning were less likely to be activated than other neurons, suggesting that different stimuli specifically activate distinct populations of dentate neurons. This was true even when the two cages being compared were very similar but not identical, which indicates that this selective activation could contribute to pattern separation.

Further work should help to clarify how the dentate gyrus and CA1 work with other hippocampal regions to generate, store and recall memories, and how pattern separation is integrated with these processes.

Rachel Jones

ORIGINAL RESEARCH PAPER Deng, W., Mayford, M. & Gage, F. H. Selection of distinct populations of dentate granule cells in response to inputs as a mechanism for pattern separation in mice. *eLife* **2**, e00312 (2013)

> "the dentate gyrus contributes to pattern separation by activating distinct populations of granule cells in response to similar events"