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LEARNING AND MEMORY

Once upon a recent time

According to the memory allocation hypothesis, when a group of hippocampal neurons encode a memory, they become temporarily more excitable and, during this time, have an increased likelihood of being involved in the encoding of a subsequent memory. Such a mechanism may mean that the recall of one memory can increase the chance of recall of other temporally close memories. A new study in *Nature* provides evidence in mice to support this hypothesis and indicates that the processes involved may be disrupted with ageing.

Contextual memories are encoded by neurons distributed throughout the hippocampus. Here, the authors used a head-mounted miniature fluorescence microscope to record calcium transients in CA1 neurons of mice exploring different novel contexts: A, B and C. Mice explored context A 7 days before C, and explored context B 5 hours before C. Analysis of the groups of neurons activated in each context revealed that the number of neurons active in both contexts B and C was higher than in both contexts A and C; that is, there was more 'overlap' between the sets of neurons encoding temporally close contexts.

To investigate the behavioural relevance of this increased overlap, the authors placed the mice in contexts A, B and C as before, and then 2 days later placed the mice in context C and delivered a footshock. Another 2 days later, the mice exhibited freezing — a sign of fear memory — in both contexts C and B, but not in the temporally more distant context A, suggesting that the memories of contexts B and C were somehow linked.

The authors hypothesized that the memory of a particular context could be enhanced by exposure to another context 5 hours earlier. Mice were placed in the first context 5 hours before a second one that was subsequently associated with a footshock. When placed again in the second (shock-associated) context, the mice that had explored the first context 5 hours before the second showed more freezing — indicating stronger fear memory — compared with controls.

CA1 neuron excitability decreases with age, so the authors predicted that the linking of temporally close memories might also decline with age. Indeed, in older mice (aged 14–18 months), there was no difference in the overlap of the groups of neurons encoding memories spaced 5 hours or 7 days apart. Moreover, unlike the younger mice, the older mice showed no transfer of fear memory of C (shocked context) to B, and showed no enhancement of the memory of a second context that was preceded by a first novel context.

To test whether enhancing CA1 neuronal excitability might rescue the deficit in linking memories in the older mice, the authors used a lentivirus to express the clozapine-*N*-oxide (CNO)-activated excitatory receptor hM3Dq in a sparse set of CA1 neurons. Mice were injected with either saline or CNO immediately before exploring the first context, and all mice were treated with CNO immediately before being placed in the second context. After 2 days, the animals were placed in the second context again and given a footshock, and another 2 days later the amount of freezing behaviour — indicating transfer of the fear memory — in the first (non-shocked) context was assessed. Mice treated with CNO before exposure to the first and second contexts exhibited more freezing behaviour than did mice treated with CNO only before encoding of the second context, suggesting that the linking of the first and second contexts had been improved by promoting excitability of the same set of neurons.

Together, these results support the memory allocation hypothesis, and also indicate that diminished neuronal excitability of groups of hippocampal neurons may mediate the deficits in memory linking seen in older mice.

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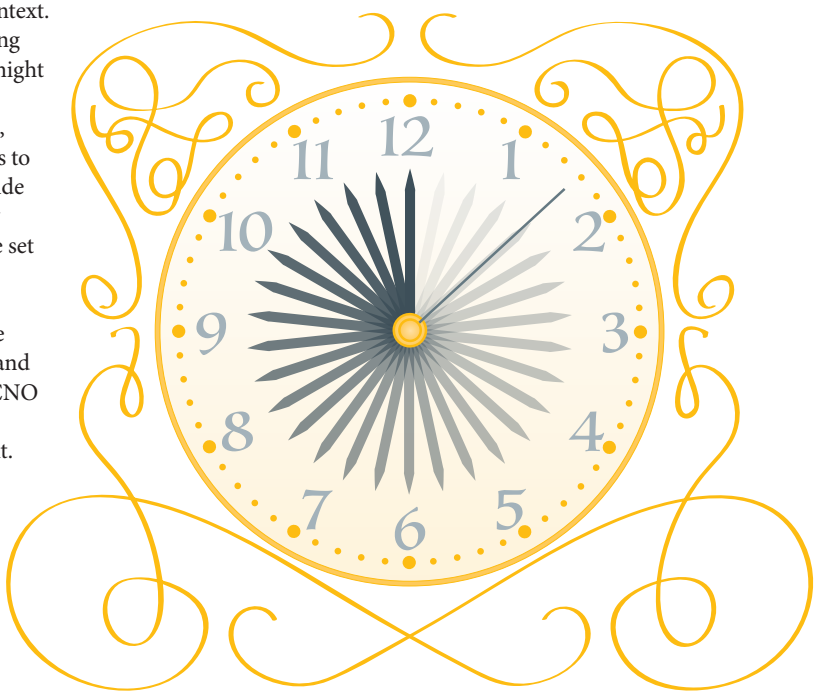
> "there was more 'overlap' between the sets of neurons encoding temporally close contexts"

ORIGINAL ARTICLE Cai, D. J. *et al.* A shared neural ensemble links distinct contextual memories encoded close in time. *Nature* http://dx.doi.org/10.1038/nature17955 (2016)
FURTHER READING Rogerson, T. *et al.* Synaptic tagging during memory allocation. *Nat. Rev. Neurosci.* **15**, 157–169 (2014)



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