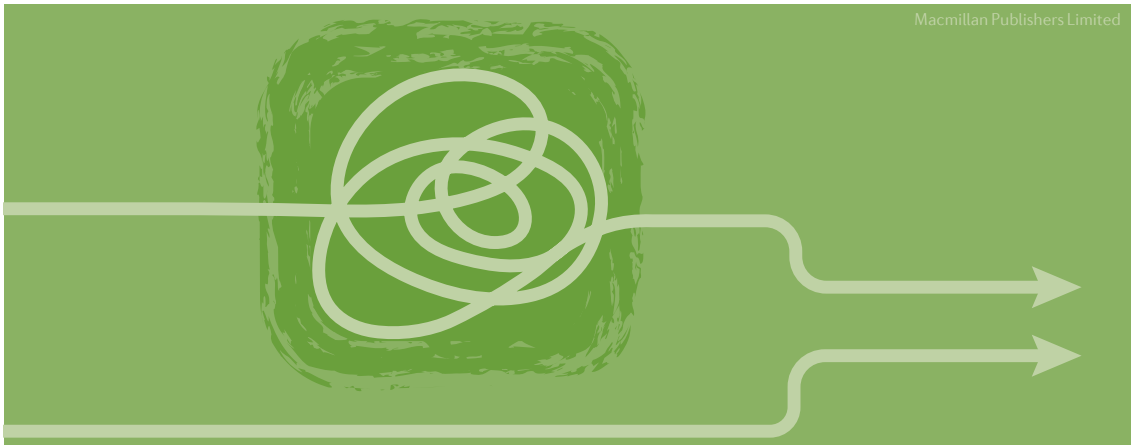
Nature Reviews Neuroscience | Published online 19 Sept 2017; doi:10.1038/nrn.2017.117



LEARNING AND MEMORY

Memories take the sub-way

Episodic memory formation and retrieval are generally thought to involve activation and reactivation, respectively, of neurons in the medial temporal lobe, which includes the entorhinal cortex (EC), CA1 and the subiculum (Sub). Of the various hippocampal subfields that have been shown to play a part in memory, the Sub is the least studied. Here, Roy *et al*. show that whereas memory formation involves a direct CA1–EC pathway, memory retrieval occurs via an indirect pathway that includes the dorsal Sub (dSub).

Previous studies have implicated CA1 and the Sub in episodic memory formation and memory retrieval, respectively. However, precisely targeted, causal evidence of a role of the dSub in memory retrieval is lacking. The authors generated a transgenic mouse line that expressed Cre recombinase under the control of fibronectin 1 (FN1), which is expressed exclusively in dSub excitatory neurons, to enable selective targeting of these neurons. Applying a combination of retrograde tracing, CLARITY and light microscopy to these mice revealed that overlapping populations of dorsal CA1 (dCA1) excitatory neurons project to layer 5 of EC (EC5) and to dSub neurons that, in turn, also project to EC5. Moreover, monosynaptic retrograde tracing experiments of dCA1 projection targets indicated that dCA1 neurons are a heterogeneous population, with some projecting to both the dSub and EC5, and others projecting solely to EC5 or the dSub.

To investigate the role of the direct and indirect dCA1–EC5 pathways in memory encoding and retrieval, the authors used a contextual fear-conditioning (CFC) paradigm in which mice were trained to associate a particular environment (behavioural context) with a footshock, and then were later tested for freezing behaviour when placed back in the same context (without footshock).

Optogenetic inhibition of dCA1→dSub or dSub→EC5 terminals during CFC training did not affect freezing behaviour, but decreased freezing when applied during the recall phase of the test. Consistent with this, optogenetic stimulation of dSub→EC5 neurons during CFC recall increased freezing in the behavioural context but not in a neutral environment that was not associated with footshock. Inhibition of pyramidal-cell terminals of the direct dCA1→EC5 projection during CFC training reduced memory formation, but did not reduce freezing behaviour when applied during the recall phase; conversely, inhibition of dCA1→dSub terminals during training did not affect behaviour, but decreased freezing when applied during recall. These findings suggest that the direct and indirect dCA1→EC5 pathways have dissociable roles in behaviour: the direct pathway is involved in the encoding of fear memory, and the indirect pathway, via the dSub, is involved in context-specific memory retrieval.

An increase in the expression of the immediate-early gene Fos can be used as a marker of neuronal activation. FOS expression in dCA1→EC5 neurons was higher during encoding than during retrieval, but showed the reverse pattern in dCA1→dSub neurons. Moreover, imaging calcium transients in dSub cells, using a genetically encoded calcium indicator, showed that a higher proportion of these cells were active during CFC recall than during training.

Overall, these data suggest that the direct dCA1→EC5 pathway and the indirect dCA1→dSub→EC5 pathway have distinct roles in memory encoding and recall, respectively.

Sian Lewis

> “the direct and indirect dCA1→EC5 pathways have dissociable roles in behaviour”

ORIGINAL ARTICLE Roy, D. S. *et al*. Distinct neural circuits for the formation and retrieval of episodic memories. *Cell* http://dx.doi.org/10.1016/j.cell.2017.07.013 (2017)