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LEARNING AND MEMORY

Influences from above on memory

Memory retrieval in the hippocampus is thought to be influenced by top-down inputs from the prefrontal cortex (PFC); however, such inputs have not yet been identified. Now, Deisseroth and colleagues identify neurons that project from the dorsal anterior cingulate cortex (dACC) to the CA1 and CA3 regions of the hippocampus (dACC–CA projections) in mice and show that these neurons regulate the retrieval of contextual fear memories.

To examine the connectivity between the cortex and hippocampus, the authors injected a rabies-virus-based retrograde tracer into the latter. Through this approach, they identified neurons not only in various brain regions that are known to send inputs to the hippocampus but also in the PFC, mainly the dACC. Optogenetic activation of the dACC neurons induced excitatory postsynaptic currents in CA1 and CA3 cells that were consistent with the dACC–CA connections being monosynaptic.

To assess the roles of these projections in memory, the authors first fear conditioned mice to express freezing (a fear response) in a particular context (context A). The next day, they placed these animals in a novel context (context B) and found that, through optogenetic activation of the dACC–CA projections, they could induce freezing behaviour in conditioned but not unconditioned mice. Moreover, this light-driven freezing response was diminished by fear-extinction training and could be re-established by reinstating fear conditioning. Furthermore, optogenetic inhibition of dACC–CA projections in fear-conditioned mice that were placed in context A led to a decrease in freezing behaviour. Together, these findings show that the activity of dACC–CA projections is both necessary and sufficient to retrieve fear memories in recently conditioned mice.

The authors next examined fear-memory retrieval at a network level in the hippocampus. To do so, they imaged hippocampal neuron calcium responses (using two-photon microscopy) in head-restrained mice that ran on a ball to navigate virtual tracks. These mice underwent fear conditioning (through application of aversive air puffs), which led to suppression of licking behaviour (the fear response) when the animals were placed in the fear context (a particular virtual track).

Analysis of calcium responses in CA2–CA3 that were imaged over the course of fear conditioning revealed that, for each of the contexts, there was a small group of neurons that showed increasingly correlated activity with learning. After conditioning, there were more of these so-called highly correlated (HC) neurons associated with the fear context (FC-HC neurons) than there were associated with the neutral context (NC-HC neurons). Moreover, during tests of memory retrieval, the activity of HC neurons seemed to occur towards the beginning of bouts of synchronous activity across the wider neuronal population. This suggests that HC neurons may recruit other neurons during memory retrieval.

In this experimental set-up, optogenetic stimulation of dACC–CA inputs in fear-conditioned mice that were placed in the neutral context caused a reduction in licking behaviour, confirming the importance of these projections in retrieving recently encoded fear memories. Importantly, this fear-memory-retrieval behavioural response was associated with a markedly increased recruitment of FC-HC neurons by the dACC–CA projection.

Overall, this study describes a top-down pathway through which the PFC regulates the retrieval of recent fear memories. Specifically, neurons projecting from the dACC to the hippocampus preferentially recruit HC neurons that are associated with the encoded fear memory and that, in turn, can recruit other pyramidal cells in the hippocampal network.

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> “optogenetic stimulation of dACC–CA inputs in fear-conditioned mice that were placed in the neutral context caused a reduction in licking behaviour”

ORIGINAL RESEARCH PAPER
Rajasethupathy, P. *et al.* Projections from neocortex mediate top-down control of memory retrieval. *Nature* http://dx.doi.org/10.1038/nature15389 (2015)

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