FEAR

Flipping the switch

An acquired fear can disappear but can also quickly re-emerge in particular contexts. Two articles published in *Nature* describe three distinct types of amygdala neurons that are required for the changes in behaviour that are associated with fear learning, extinction and renewal.

In fear-conditioning paradigms, animals learn to associate a stimulus with an aversive footshock in a particular environment. If the animal is subsequently exposed to the conditioned stimulus without the footshock and in a different context the fear is eventually extinguished, but it can be refreshed if the stimulus is again presented in the conditioning context.

Lüthi and colleagues investigated, in mice, at which stages of fear learning and extinction the basal amygdala (BA) is involved. They showed that inactivating BA neurons with the $GABA_A$ (γ-aminobutyric acid type A) receptor agonist muscimol before extinction training prevented the reduction in freezing that is normally associated with extinction, whereas muscimol injections before fear-renewal training prevented the expected increase in freezing. These findings indicated that the BA might mediate the switch in freezing behaviour during fear extinction and renewal.

What could underlie this behavioural switch? The authors found that a subset of BA neurons, which they called "fear neurons", fired in response to the conditioned stimulus during and after fear conditioning but no longer did so after extinction, whereas a different subset, termed "extinction neurons", only fired in response to the stimulus after extinction.

It usually takes multiple trials for a conditioned fear to be extinguished, begging the question when in the extinction procedure the neurons change their firing behaviour. The authors found that extinction neurons changed their response one trial before fear neurons, and that both did so before the change in freezing behaviour took place, indicating that a change in the balance of activity of fear and extinction neurons might underlie the behavioural switches that are observed during fear extinction and renewal.

The authors also showed that hippocampal neurons project to fear neurons but not to extinction neurons, whereas the medial prefrontal cortex projects to extinction neurons but not to fear neurons, suggesting that the two types of neuron are part of distinct circuits.

A second paper provides further insight into the neuronal circuits that regulate fear behaviour. The BA and the lateral nucleus of the amygdala project to the central nucleus, which mediates the behavioural, hormonal and autonomic expression of fear. Some of these projections are indirect and run through inhibitory intercalated neurons. When Paré and colleagues lesioned intercalated neurons in rats after conditioning and extinction training, the rats' recall of the extinction 7 days later was impaired. Importantly, the level of freezing was negatively correlated with the number of surviving intercalated neurons, indicating that these neurons mediate the behavioural expression of extinction.

It would be interesting to know whether intercalated amygdala neurons receive projections from fear or extinction neurons in the BA. Nevertheless, these studies increase our understanding of the pathways in the amygdala that mediate fear and its extinction. The three populations of amygdala neurons identified in these studies might eventually be targeted for therapeutic interventions in people with anxiety disorders.

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ORIGINAL RESEARCH PAPERS Herry, C. *et al.* Switching on and off fear by distinct neuronal circuits. *Nature* 9 Jul 2008 (doi: 10.1038/nature07166) | Likhtik, E. *et al.* Amygdala intercalated neurons are required for expression of fear extinction. *Nature* 9 Jul 2008 (doi: 10.1038/nature07167)