Nature Reviews Neuroscience | AOP, published online 12 February 2014; doi:10.1038/nrn3698

FEAR

Balancing memories

Memories of fearful events can disappear through a process known as extinction, in which a separate 'extinction memory' is created. The formation of both fear memories and extinction memories involves the basal amygdala (BA), the hippocampus and the medial prefrontal cortex (mPFC). A new study now shows that the balance of activity between 'fear neurons' and 'extinction neurons' in the BA, which project to the prelimbic (PL) and infralimbic (IL) portions of the mPFC, respectively, determines whether a fear memory is extinguished.

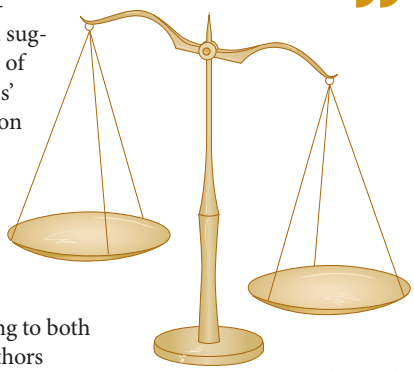
Senn *et al.* exposed one group of mice to fear conditioning (FC mice) and two other groups to fear conditioning followed by 2 days of effective extinction training (Ext mice) or by 2 days of training that did not result in extinction (no-Ext mice). Control mice were exposed only to the conditioned stimulus. Two hours after the final session, FOS expression was increased in the BA of FC mice and, to a lesser extent, in the BA of Ext mice and no-Ext mice compared with control mice.

Retrograde tracing studies showed that in all three groups of mice, the increased FOS expression occurred in BA neurons that project to the mPFC, raising the question of what the activation of BA–mPFC neurons reflects. The authors hypothesized that distinct subpopulations of mPFC-projecting BA neurons mediate fear conditioning and extinction, respectively. Indeed, retrograde tracing revealed that fear conditioning induced FOS expression mainly in BA neurons projecting to the PL mPFC (BA–PL neurons), whereas fear extinction was associated with FOS expression only in BA neurons projecting to the IL mPFC (BA–IL neurons).

To further investigate the role of the two projections in fear conditioning and extinction, the authors expressed channelrhodopsin 2 and halorhodopsin selectively in BA–PL neurons or BA–IL neurons in mice. Single-unit recordings showed that a proportion of optogenetically defined BA–PL neurons specifically responded to a conditioned stimulus but never to an extinguished stimulus, whereas a proportion of optogenetically defined BA–IL neurons specifically activated in response to an extinguished stimulus but never to a conditioned stimulus. This confirmed the FOS-expression data and suggested the existence of BA–PL 'fear neurons' and BA–IL 'extinction neurons'.

The mice then underwent fear conditioning to two different tones, followed by extinction training to both tones. When the authors optogenetically activated BA–IL neurons during extinction training to tone 1 and inhibited them during extinction to tone 2, they found that extinction of tone 1 was better than extinction of tone 2. The same procedure in BA–PL neurons had the opposite effect. These findings suggest that the balance of activity in the two BA subpopulations might determine whether an extinction memory is formed.

> When the authors optogenetically activated BA–IL neurons during extinction training to tone 1 and inhibited them during extinction to tone 2, they found that extinction of tone 1 was better than extinction of tone 2



L. Crow/NPG

The two subpopulations of BA neurons also showed distinct changes in firing properties in response to fear conditioning and extinction: BA–IL neurons from Ext mice (*in vitro*) and functionally identified 'extinction neurons' (*in vivo*) showed increased burst firing in response to an extinguished stimulus, whereas BA–PL neurons from no-Ext mice (*in vitro*) and 'fear neurons' (*in vivo*) increased their burst firing in response to a conditioned stimulus.

These findings show that the BA contains populations of 'fear neurons' and 'extinction neurons' that each project to a specific mPFC subregion, and suggest that fear extinction training induces a shift in the balance of activity between these two populations.

Leonie Welberg

ORIGINAL RESEARCH PAPER Senn, V. *et al.* Long-range connectivity defines behavioral specificity of amygdala neurons. *Neuron* **81**, 428–437 (2014)