NEURONAL CIRCUITS

Connecting to innate knowledge

Various strategies have evolved in animals to allow behavioural adaptation to a changing environment. Certain environmental stimuli trigger innate responses and are termed unconditioned stimuli (UCSs); they can be appetitive or aversive. By contrast, a neutral stimulus, which is neither appetitive nor aversive, can be used to trigger an innate response (that is, act as a conditioned stimulus (CS)) if presented temporally close to a UCS, such as a bell eliciting food-seeking behaviour in the classical experiments of Pavlov and his dogs. The basolateral amygdala (BLA) is known to help mediate appropriate behavioural responses to sensory stimuli, but precisely how this occurs is not well understood. In this study, Gore *et al.* use a genetic strategy to identify and manipulate specific populations of BLA neurons that represent different stimuli and show that these neuronal ensembles are involved in connecting sensory representations of UCSs to appropriate innate and learned behaviours.

The gene that encodes the photoactivatable cation channel channelrhodopsin 2 (ChR2), tagged with an mCherry reporter, was delivered by a lentivirus to BLA neurons in mice, where ChR2 expression was under the control of the *Fos* promoter. The mice were then exposed to either an aversive (footshock) or an appetitive (nicotine injection) UCS, which led to activation of neuronal ensembles specific for each UCS and to *Fos* induction that in turn drove selective expression of ChR2. The authors found that photoactivation of UCS-responsive cells of the BLA could produce valence-specific behaviours. They observed that photostimulation of footshock-responsive BLA neurons caused innate freezing behaviour and physiological responses such as decreased heart rate; stimulation of nicotine-responsive neurons produced opposite physiological responses.

Next, the authors used a modified fear-conditioning paradigm (in which a tone was used as the CS and optogenetic activation of BLA neurons in which ChR2 expression had been induced by footshock as the UCS) to show that the temporal pairing of the CS and UCS resulted in significantly more freezing than controls, indicating that aversive learning had occurred. Furthermore, pairing an olfactory stimulus — a neutral odour — to stimulation of either aversive or appetitive UCS ensembles in the BLA, led to avoidance of or attraction to the conditioned odour, respectively. Therefore, the pairing of conditioning stimuli across two sensory modalities (olfactory and auditory) with selective activation of BLA neurons was able to induce appetitive and aversive learning.

In addition to driving Pavlovian learning, UCSs can also drive operant behaviour (that is, behaviour shaped by positive or negative reinforcement). Mice showed increased nosepokes compared with control animals if the nosepokes activated a laser that stimulated neurons expressing ChR2 in appetitive UCS-activated BLA neurons, indicating that exogenous activation of nicotine-responsive BLA neurons can convey information about the valence of the stimulus and induce operant learning.

To determine the relationship between cells activated by CSs and UCSs, mice were first trained to associate a footshock stimulus with a tone. Mice were then injected with the lentivirus expressing ChR2 into the BLA, and were subsequently presented with the CS to induce expression of ChR2 in CS-responsive cells. Photoactivation of CS-responsive cells after learning caused increased freezing compared with controls, indicating that the BLA contains a representation of a CS after learning. In the next experiment, mice were first fear conditioned, and then a lentivirus was injected in which *Fos* expression drove the expression of the gene encoding the neuronal silencer halorhodopsin (NpHR). Mice were then treated with either footshock or nicotine to induce *Fos* promoter-driven NpHR expression in the relevant UCS-responsive cells. Exposure to a tone combined with photostimulation-induced silencing of footshock UCS-responsive cells attenuated freezing compared with control animals, indicating that CS-mediated behaviour required activation of the relevant UCS ensemble. Similar results were obtained with the olfactory-conditioning paradigm.

Taken together, these findings suggest that BLA cells that represent UCSs of different valences connect sensory representations of rewarding and aversive stimuli to neural circuits that generate appropriate innate responses and learned behaviour.

Sian Lewis

ORIGINAL RESEARCH PAPER Gore, F. *et al.* Neural representations of unconditioned stimuli in basolateral amygdala mediate innate and learned responses. *Cell* **162**, 134–145 (2015)

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