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ADDICTION

Putting relapse into context

When recovered drug addicts encounter the environment in which they used to take drugs, there is a risk that they will relapse. Bossert *et al*. now show that in rats, context-induced relapse is triggered by the activation of a subset of neurons in the ventral medial prefrontal cortex (mPFC) that seem to encode the association between environmental cues and heroin reward.

The authors trained rats housed in a particular cage (context A) to self-administer heroin. In this procedure, a lever press triggered infusion of a dose of heroin that was paired with a tone and a light. After 12 days of training, the rats were placed in a different context (context B), in which pressing the lever triggered the tone and light but no heroin delivery. Following this extinction training, the authors assessed whether the rats would 'relapse' when placed back in context A, in which lever presses now no longer triggered heroin infusion. Rats pressed the lever in context A more often than they did in context B, suggesting that they were seeking heroin.

Re-exposure to context A after extinction training induced neuronal activation (as measured by FOS immunohistochemistry) in ~6% of glutamatergic and GABAergic neurons in the dorsal and ventral mPFC. Non-selective inactivation of ventral mPFC neurons using GABA receptor agonists before relapse testing decreased the subsequent number of lever presses, whereas inactivation of dorsal mPFC neurons had no effect.

Building on the hypothesis that sparsely distributed neurons forming a neuronal ensemble encode learned associations, the authors proposed that ensembles of ventral mPFC neurons — those showing FOS immunostaining after exposure to context A — encode the association between contextual cues and heroin-induced reward. Activation of these ensembles would then trigger heroin seeking. Indeed, in *c-Fos–lacZ* transgenic rats, selective inactivation of ventral mPFC neurons showing context A-induced FOS expression — using the prodrug Daun02, which is converted to daunorubicin in FOS–LacZ-expressing neurons, leading to their long-lasting inactivation — reduced relapse.

Previous studies on cocaine relapse had suggested that the dorsal and ventral mPFC facilitate and inhibit drug seeking behaviour, respectively, but this study shows that, at least with regard to context-induced heroin seeking, the ventral mPFC has an active role in reinstatement. This suggests that the circuitry underlying context-induced relapse may differ between different forms of addiction.

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ORIGINAL RESEARCH PAPER Bossert, J. M. *et al.* Ventral medial prefrontal cortex neuronal ensembles mediate context-induced relapse to heroin. *Nature Neurosci.* 20 Feb 2011 (doi:10.1038/nn2758)