Nature Reviews Neuroscience | https://doi.org/10.1038/s41583-019-0256-8 | Published online: 10 December 2019

ADDICTION

Foreseeing compulsion

> “animals … later classified as compulsive drinkers were less deterred by the pre-binge quinine punishment”

Only a minority of people who drink alcohol will develop an alcohol use disorder. However, the neural basis of the individual differences that might predispose some people, and not others, to become addicted to alcohol is not clear. Writing in *Science*, Siciliano et al. show that mice develop different drinking phenotypes, and that compulsive drinking — that is, drinking despite punishment — can be predicted by functional differences in a medial prefrontal cortex (mPFC)–dorsal periaqueductal gray (dPAG) circuit.

The authors developed a longitudinal alcohol-exposure paradigm. Before the task, mice were trained to associate an auditory tone with a sugar reward. Then, on days 1–3 of the task, the tone was instead paired with alcohol delivery, and subsequently alcohol plus the bitter-tasting quinine (the latter serving as an aversive stimulus, or punishment) on days 4–5. From day 6 to day 19, collectively called the ‘binge period’, the mice had free access to water and alcohol. After the binge period, the auditory tone was again paired with delivery of alcohol on days 20–22 and then alcohol plus quinine on days 23–26.

The authors used measures of alcohol consumption by individual mice after the binge period to classify each animal into one of three phenotypes: low drinkers, which consumed low levels of alcohol with or without punishment; high drinkers, which consumed high amounts of unadulterated alcohol but lower levels of alcohol combined with quinine; and compulsive drinkers, which consumed high levels of alcohol even when it was combined with quinine.

Next, the authors retrospectively analysed each mouse’s pre-binge behaviour, to determine whether behavioural differences could predict the development of the different phenotypes after the binge period. Differences in the consumption of unadulterated alcohol before or during the binge did not predict post-binge phenotype. However, compared with eventual low drinkers, animals that were later classified as compulsive drinkers were less deterred by the pre-binge quinine punishment.

Credit: Savushkin/Getty

Previous work has shown that a mPFC–dPAG circuit encodes aversive events. Here, Siciliano et al. reasoned that a functional deficit in this circuit might disrupt aversive processing in the animals that would go on to develop compulsive drinking. Strikingly, imaged calcium responses of dPAG-projecting mPFC cells during the initial alcohol-only exposure could predict which animals would become compulsive drinkers: on day 1, a greater proportion of these neurons showed drinking-associated inhibitory responses in the eventual compulsive drinkers than in the low drinkers. Thus, differences in the neural dynamics of this circuit on day 1 could predict the drinking phenotype many days later.

Last, the authors optogenetically manipulated the activity of mPFC–dPAG neurons in various behavioural assays. Optogenetically inhibiting these neurons as mice drank alcohol mixed with quinine made the animals less deterred by the aversive taste of quinine. Similarly, optogenetic inhibition of these cells also increased animals’ latency to withdraw their tails from hot water. However, photoinhibition of the mPFC–dPAG projection was not reinforcing, suggesting this manipulation decreases sensitivity to aversive stimuli. Consistent with this notion, optogenetic stimulation of mPFC–dPAG neurons during alcohol-drinking bouts served as a punishment, leading to long-lasting reductions in alcohol drinking.

Together, these results imply that functional differences in the mPFC–dPAG circuit may disrupt aversive processing and predispose mice to develop compulsive drinking behaviour.

Natasha Bray

ORIGINAL ARTICLE Siciliano, C. A. et al. A cortical-brainstem circuit predicts and governs compulsive alcohol drinking. *Science* **366**, 1008–1012 (2019)