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PSYCHIATRIC DISORDERS

A motivating microcircuit

> reduced activity of the mPFC–DRN pathway may have a role in the inertia and amotivational state associated with depression

The prefrontal cortex (PFC) has a crucial role in regulating our actions. However, PFC dysfunction can have different, sometimes even opposite, behavioural effects — such as increased impulsivity and reduced motivation — which probably depend on the circuits of which the affected PFC neurons are a part. Warden *et al.* now show that in rats, PFC projections to the dorsal raphe nucleus (DRN) specifically induce active rather than passive behavioural responses in a forced swim test (FST).

J.Vallis/NPG

In this test, rats or mice are placed in a cylinder filled with water. After a period of vigorous activity (presumably in an attempt to escape), animals adopt an immobile, floating behaviour; this latter, passive behaviour has been interpreted as 'despair' but also as a strategy for conserving energy. Thus, both types of behaviour could be adaptive, and the authors assessed how medial PFC (mPFC) neurons control which of the two responses is selected.

The authors developed a method that allowed them to simultaneously record locomotor behaviour and activity of individual neurons in the mPFC before and during a 15-min FST. Rats were mostly immobile before the FST. Most neurons (81%) showed a change in activity from pre-FST to FST, and 44% of recorded neurons showed different activity in the mobile versus immobile phases of the FST. However, mPFC neuron activity did not simply correlate with motor activity. Some neurons showed greater activity during mobile FST phases compared with immobile FST phases or the (mainly immobile) pre-FST period, whereas other neurons showed the opposite pattern. Still other neurons were more active in the pre-FST than the FST period but, during the FST, were more active in the mobile phase than in the immobile phase. For neurons showing higher activity during the mobile versus immobile FST phase, neuron activity preceded the onset of motor activity.

In accordance with this varied activity profile of mPFC neurons, optogenetic activation of all excitatory mPFC neurons in 2-min epochs had no net effect on activity in the FST. But what about stimulating a distinct population of mPFC neurons?

The authors focused on mPFC neurons that target the DRN, the source of most serotonergic projections in the brain. They optogenetically stimulated the axons of the channelrhodopsin-2-expressing mPFC neurons that project to the DRN by illuminating the DRN rather than the mPFC. This caused a rapid and profound increase in mobility in the FST that ceased when the light was switched off. Importantly, this stimulation did not alter activity in an open field, indicating that the effect was not due to a general increase in locomotor activity. By contrast, direct optogenetic stimulation of DRN neurons increased both mobility in the FST and general locomotor activity. This suggests that an mPFC–DRN pathway specifically controls action selection in a challenging environment.

Considering that antidepressant treatment can increase mobility in the FST in rodents, these findings indicate that reduced activity of the mPFC–DRN pathway may have a role in the inertia and amotivational state associated with depression.

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ORIGINAL RESEARCH PAPER Warden, M. R. *et al.* A prefrontal cortex–brainstem neuronal projection that controls response to behavioural challenge. *Nature* 18 Nov 2012 (doi:10.1038/nature11617)

FURTHER READING Tye, K. M. & Deisseroth, K. Optogenetic investigation of neural circuits underlying brain disease in animals. *Nature Rev. Neurosci.* **13**, 251–266 (2012)