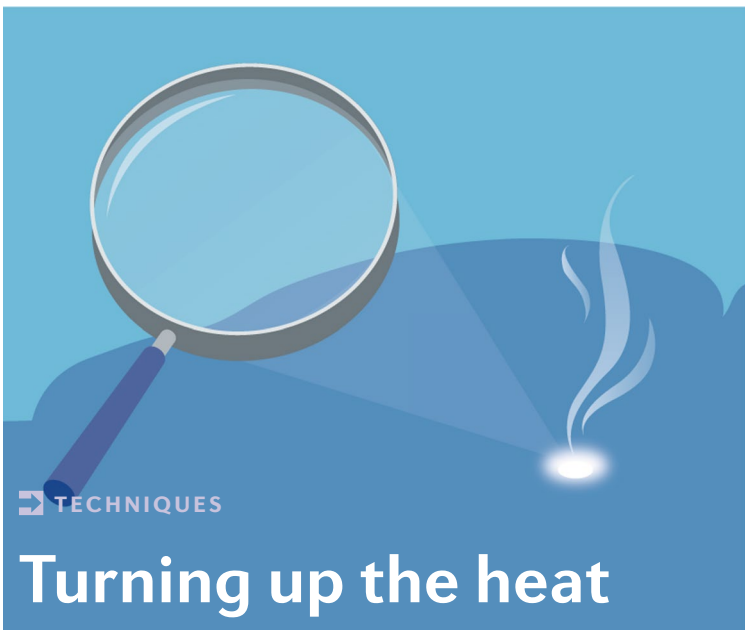

Credit: Springer Nature Limited

Turning up the heat

> They found that light delivered through an optical fibre to this brain region supressed the spiking activity of medium spiny neurons

Optogenetics involves the use of light-activated ion channels termed opsins to control the activity of defined populations of neurons. A key assumption when using this approach is that the light stimulus used to activate the opsins has no other effects. However, previous studies have indicated that sustained light delivery to brain tissues can cause heating of 0.2–2°C. As many neuronal circuit processes are temperature dependent, could light itself affect neuronal activity via the generation of heat? In a new study in *Nature Neuroscience*, Owen, Liu and Kreitzer found that light delivery to the dorsal striatum was sufficient to inhibit neural activity and affect behaviour, and that the effects of such stimulation were associated with tissue heating.

The authors recorded single units in the dorsal striatum of awake, head-fixed, wild-type mice (that is, mice that were not engineered to express opsins or fluorophores). They found that light delivered through an optical fibre to this brain region supressed the spiking activity of medium spiny neurons (MSNs), the principal neurons of this brain region.

A similar drop in firing rate was noted in whole-cell recordings during light delivery to MSNs in acute brain slices from wild-type mice — ruling out the possibility that the suppression in spiking is the result of sensory responses to light detection at the back of the retina. Notably, in both of these experiments, low-power light delivery (3 mW) led to a modest drop in firing rate, whereas high-power light delivery (15 mW) suppressed firing rate more markedly.

The authors next examined how the light stimuli elicited their effects by examining whether they heated the targeted brain tissue. They replaced the recording electrode with a thermocouple probe and found that, in vivo, light delivery led to a transient rise in temperature of up to 2 °C, with the time course for the change in temperature closely matching that for the suppression of MSN firing. These findings suggest that light delivery alters MSN activity by locally heating brain tissue.

To examine this possibility, the authors recorded from acute brain slices in which they inserted a small copper tube containing water of varying temperature to warm or cool the tissue. Whole-cell recordings in MSNs voltage-clamped at −50 mV in which a potassium-based internal solution was used revealed that warming the tissue elicited an outward current, with a markedly linear relationship between temperature and current magnitude being observed.

Further recordings in which the authors used holding potentials from −140 mV to −50 mV demonstrated that the light-induced current reversed at −93 mV, suggesting that it was a potassium conductance. In line with this, including caesium in the recording solution or application of barium chloride (which inhibits certain potassium channels) blocked or reduced, respectively, the light-activated current. Thus, in MSNs, light-induced heating of brain tissue activates an inwardly rectifying potassium channel that leads to suppression of firing.

Finally, the authors assessed whether the light-induced effects on MSN activity could alter behaviour. They unilaterally delivered light into the dorsal striatum of wild-type mice, which biased the mice's rotational behaviour in the direction of the illuminated hemisphere. Thus, light-driven suppression of MSN firing can affect behavioural outcomes.

Together, these findings indicate that light-induced changes in temperature may affect neuronal activity and influence behaviour. As a result of their findings, the researchers suggest minimization of light power and duration in optogenetic studies, and the inclusion of control experiments that account for potential off-target effects of light delivery.

Isobel Leake

ORIGINAL ARTICLE Owen, S. F. et al. Thermal constraints on in vivo optogenetic manipulations. *Nat. Neurosci.* **22**, 1061–1065 (2019)