incorporate delays that allow photons in different time bins to interfere at a specific position (Fig. 1). This means that a large network of beam splitters can be replaced by a single beam splitter, which is coupled to fibre loops that must be long enough to accommodate all the required delays. In practice, Madsen and co-workers' set-up incorporated three beam splitters connected by fibre loops.

Second, Borealis can be readily reconfigured. Previous experiments typically relied on static networks, in which each component is fixed once fabricated[6,7]. This feature trades programmability of the device for ease of implementation and scaling. Although some programmable devices have been demonstrated[7,8], none has been as comprehensively configurable as Borealis, the optical elements of which can all be readily programmed. In other words, the reflectivity of a beam splitter can be tuned in real time. This is made possible by the binned encoding scheme: because the device uses a system of only three beam splitters, it is possible to change their parameters between the arrival of photons in one time interval and the next.

Finally, a major concern is how to certify that the output data are correct. In contrast to other tasks (such as factoring) for which it is easy to check an answer, the complexity of quantum-advantage demonstrations often seems to prevent verification that an operation is even approximately correct. To circumvent this, statistical tests can be used to rule out alternative answers, but they cannot fully determine an output. This introduces a problem known as spoofing, in which classical algorithms that do not faithfully reproduce a quantum output can mimic it well enough to pass these statistical tests.

Madsen *et al.* ran a comprehensive set of tests on the output of Borealis, and showed that it could not be spoofed, even by algorithms that were tailored to spoof previous experiments on Gaussian boson sampling. This provides some evidence that the experiment is robust to spoofing, but it might not be the end of the story — one such algorithm was developed after publication of the experiments it spoofed[6,7], and was tailored for the task[9]. Algorithms that better mimic the output of Borealis will no doubt also arise, which will in turn lead to more-sophisticated statistical tests to rule them out.

Quantum advantage is not a well-defined threshold, based on a single figure of merit. And as experiments develop, so, too, will techniques to simulate them — we can expect record-setting quantum devices and classical algorithms in the near future to take turns in challenging each other for the top spot. Madsen and colleagues' work is a leap forward for quantum physics in this race. It also solves technological challenges that might put us ahead in the longer race towards viable quantum computers, and that are likely to prove useful for other aspects of quantum information processing.

Daniel Jost Brod is at the Physics Institute, Federal Fluminense University, Niterói, Rio de Janeiro 24210-346, Brazil.
e-mail: daniejostbrod@id.uff.br

1. Madsen, L. S. *et al. Nature* **606**, 75–81 (2022).
2. Arute, F. *et al. Nature* **574**, 505–510 (2019).
3. Wu, Y. *et al. Phys. Rev. Lett.* **127**, 180501 (2021).
4. Hamilton, C. S. *et al. Phys. Rev. Lett.* **119**, 170501 (2017).
5. Deshpande, A. *et al. Sci. Adv.* **8**, eabi7894 (2022).
6. Zhong, H.-S. *et al. Science* **370**, 1460–1463 (2020).
7. Zhong, H.-S. *et al. Phys. Rev. Lett.* **127**, 180502 (2021).
8. Taballione, C. *et al.* Preprint at https://arxiv.org/abs/2203.01801 (2022).
9. Villalonga, B. *et al.* Preprint at https://arxiv.org/abs/2109.11525 (2021).

The author declares no competing interests.

Neuroscience

Nerve regrowth can be painful

Suna L. Cranfill & Wenqin Luo

Neuronal fibres have been tracked as they regrow into the skin following nerve injury in mice. The analysis reveals that mis-wiring of pain-sensing fibres generates hypersensitivity to touch in skin associated with the injury. **See p.137**

Pain provides an essential warning of impending tissue damage, protecting us from worse injuries. But when our nervous systems are damaged, this transient warning can turn into a persistent and debilitating pain[1]. The mechanisms that underlie this neuropathic pain are incompletely understood, leading to inadequate treatment options. Gangadharan *et al.*[2] report on page 137 their ten-month analysis of mice recovering from nerve damage.

"The authors' work adds to a growing appreciation of the complex link between pain and nerve regeneration."

The authors describe a surprising link between neuropathic pain and reinnervation.

Research on nerve damage in rodents often involves the spared nerve injury (SNI) model. The sciatic nerve sends three branches down the hindlegs of rodents — in the SNI model, two of these branches are severed. This leads to loss of nerves in the regions of the skin supplied by the severed branches (the denervated side), but not of those in the skin innervated by the spared nerve[3]. Within a few days of the injury, the skin innervated by the spared nerve develops a condition called mechanical allodynia, in which normally innocuous stimuli, such as gentle touch, are perceived as painful. This hypersensitivity to touch can persist for months.

Most studies involving the SNI model have focused on this pain in the spared territory. By contrast, Gangadharan *et al.* focused on the denervated side, studying neural regrowth for up to 42 weeks after SNI in mice, by means of a non-invasive imaging technique. They used genetic engineering to label two types of sensory neuron — tactile fibres, which are sensitive to light touch, and nociceptors, which are sensitive to strong mechanical forces and other noxious stimuli. As a result, the fibres expressed fluorescent proteins, enabling their growth to be tracked under a microscope. The group also assessed the animals' behavioural responses to mechanical stimuli throughout the 42-week period.

Nociceptors, but not tactile fibres, began reinnervating the denervated territory around eight weeks after SNI. This correlated with a regained response to strong mechanical forces such as robust prodding. As nociceptor reinnervation progressed, however, the mice began to show hypersensitivity to gentle forces. Cutting the spared nerve eliminated these nociceptor fibres, indicating that they were sprouting from the spared nerve. Gangadharan *et al.* showed that nociceptors are responsible for mechanical allodynia in the reinnervated territory after SNI, but not for that in the spared territory. This is a previously undescribed type of SNI-induced mechanical allodynia, which the authors termed reinnervation-induced neuropathic pain.

© 2022 Springer Nature Limited. All rights reserved.

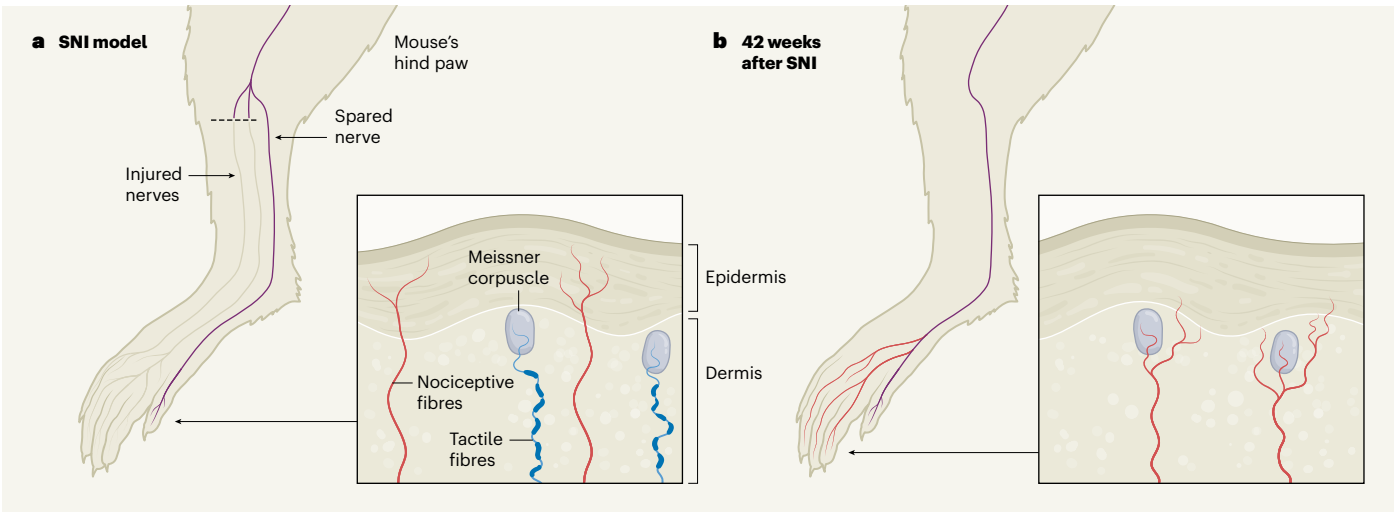

Figure 1 | Tracking nerve regrowth after injury. a, In the spared nerve injury (SNI) model, two nerve branches that supply one side of a mouse's hind paw are severed, and one nerve branch supplying the other side is spared. Gangadharan *et al.*[2] tracked the growth of two types of neuronal fibre – tactile and nociceptive – derived from the spared nerve in hindlimb skin that is associated with injury. In the skin of the spared side, tactile fibres innervate structures called Meissner corpuscles in the dermis layer, whereas nociceptive fibres terminate as free nerve endings in the epidermis. **b**, Tracking the nerves for 42 weeks after SNI, the authors found that nociceptive fibres regrew into the denervated skin, and terminated at the junction of the dermis and epidermis, with some of them innervating Meissner corpuscles. This altered the properties of the sprouting nociceptors in such a way that the fibres were activated by gentle touch, triggering pain (not shown).

Nociceptors typically respond to strong mechanical forces – how do they acquire the ability to respond to gentle forces in the denervated territory? Gangadharan and colleagues found a possible explanation in the fact that sprouting nociceptive fibres terminate in an unusual way in the denervated skin. Normally, most nociceptors terminate as free nerve endings in the outermost layer of skin (the epidermis). By contrast, tactile fibres innervate specialized structures called mechanosensory end organs, which mediate the detection and transduction of gentle forces, and reside in the dermis, the deeper layer of skin[4] (Fig. 1a). The authors showed that sprouting nociceptive fibres in the denervated region terminate at the junction between the dermis and epidermis, where many of them innervate a type of mechanosensory end organ called the Meissner corpuscle[5] (Fig. 1b).

The authors analysed the reinnervated Meissner corpuscles using high-resolution electron microscopy, and found that the nociceptors were positioned in such a way that they could be stimulated by gentle mechanical stimuli. Electrophysiological recordings from sprouting nociceptors confirmed that they do indeed have a lower threshold for mechanical stimulation in the reinnervated region than do nociceptors in the spared side.

This is the first clear evidence of nociceptive fibres mis-targeting mechanosensory end organs during reinnervation, and of this previously undescribed type of mechanical allodynia in neuropathic pain. However, questions remain. Tactile fibres are typically covered in a fatty insulating sheath called myelin, whereas most nociceptors are unmyelinated[1]. A small percentage of Meissner corpuscles normally contain unmyelinated fibres, but whether they are tactile or nociceptive is unclear[6,7]. Could these unmyelinated Meissner corpuscle-innervating fibres in the spared branch be the main source of corpuscle reinnervation in the injured region? Or do sprouting nociceptors that form typical free nerve endings in the epidermis of the spared region exhibit abnormal corpuscle innervation? In other words, are some unmyelinated fibres intrinsically primed to target Meissner corpuscles, or do denervated Meissner corpuscles promote mis-targeting?

These questions could be addressed by single-cell labelling of sprouting nociceptors or further molecular and genetic characterization of Meissner corpuscle-reinnervating fibres. It would also be interesting to examine whether sprouting nociceptors innervate other mechanosensory end organs, such as Merkel cells in the paw skin. Unlike Meissner corpuscles, Merkel cells in the paw are normally not innervated by unmyelinated fibres – studying them could therefore help to differentiate between the potential mechanisms of Meissner corpuscle innervation by unmyelinated fibres. From the perspective of nerve regeneration, an interesting question is why spared nociceptive but not tactile fibres are capable of sprouting.

Pain circuits in the dorsal spinal cord and brain, which process crosstalk between tactile and nociceptive fibres[1], should also be investigated as possible contributors to reinnervation-induced neuropathic pain. For example, because tactile pathways typically inhibit transmission of nociceptive signals in the spinal cord[8,9], a change in the relative numbers of tactile and nociceptive fibres in the denervated side might generate a nociceptive circuit that is subject to less inhibition than such a circuit in the spared side.

Gangadharan and colleagues' work adds to a growing appreciation of the complex link between pain and nerve regeneration. Pain protects the reinnervating regions from further injury, but persistent neuropathic pain from mis-wiring of reinnervated fibres is an unwanted outcome. It is to be hoped that work such as this will eventually lead to strategies that enable peripheral nerve regeneration and reinnervation without neuropathic pain.

Suna L. Cranfill and **Wenqin Luo** are in the Department of Neuroscience, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.
e-mails: sunali@vet.upenn.edu; luow@pennmedicine.upenn.edu

1. Basbaum, A. I., Bautista, D. M., Scherrer, G. & Julius, D. *Cell* **139**, 267–284 (2009).
2. Gangadharan, V. *et al. Nature* **606**, 137–145 (2022).
3. Decosterd, I. & Woolf, C. J. *Pain* **87**, 149–158 (2000).
4. Moehring, F., Halder, P., Seal, R. P. & Stucky, C. L. *Neuron* **100**, 349–360 (2018).
5. Fleming, M. S. & Luo, W. *Front. Biol.* **8**, 408–420 (2013).
6. Paré, M., Elde, R., Mazurkiewicz, J. E., Smith, A. M. & Rice, F. L. *J. Neurosci.* **21**, 7236–7246 (2001).
7. Ishida-Yamamoto, A., Senba, E. & Tohyama, M. *Brain Res.* **453**, 362–366 (1988).
8. Foster, E. *et al. Neuron* **85**, 1289–1304 (2015).
9. Arcourt, A. *et al. Neuron* **93**, 179–193 (2017).

The authors declare no competing interests.
This article was published online on 25 May 2022.

© 2022 Springer Nature Limited. All rights reserved.