

NEUROSCIENCE

Neural implants without brain surgery

Injectable bioprobes record single-neuron activity from within blood vessels

By Brian P. Timko

Brain-machine interfaces (BMIs) enable direct electrical communication between the brain and external systems. They allow brain activity to control devices such as prostheses and computer programs, or to modulate nerve or muscle function to compensate for dysfunctional endogenous pathways. Collectively, BMIs have the potential to help individuals with paralysis or neurological disorders to regain function (1). However, recording from deep-brain regions currently requires surgery to implant probes, so less invasive methods for interfacing bioelectronic devices with neurons are required. On page 306 of this issue, Zhang *et al.* (2) present a brain-surgery-free method to probe neural function in the rat brain. They achieved this by deploying a bioelectronic recording device from an endovascular catheter, using the brain's vasculature as a natural delivery system. The technology could enable long-term, minimally invasive bioelectronic interfaces with deep-brain regions.

Conventional BMIs use detection methods such as electroencephalography and electrocorticography, which measure local field potentials from ensembles of neurons at the surface of the scalp or on the dura mater (a meningeal layer that covers the brain) (3), as well as intracortical probes that can measure single-neuron activity from deeper regions. However, intracortical probes require craniotomy and cause mechanical disruptions to the brain tissue. These probes also induce inflammation and fibrosis, which degrade device performance within weeks (4). These deleterious effects can be attributed to the large mismatch in mechanical stiffness between the implant and brain tissue. Advances in materials science have addressed this issue with biomaterials (5), including organic electronics (6), with mechanical properties tuned to match those of the human brain. In animal models, these devices integrated with brain tissues and caused minimal inflammation, even over the long term. A parallel approach is to engineer the geometry of the devices so that they are flexible and stretchable. For example, mesh bioelectronics were injected directly into a living mouse brain and obtained

stable single-neuron recordings for up to 8 months, with minimal inflammation (7).

Nevertheless, delivering devices into the brain remains a challenge. Any surgery that penetrates the blood-brain barrier poses a risk for infection, so less invasive methods to deliver devices into deep-brain regions are crucial. The vascular system is a potential delivery route because it mirrors the structure of the neuronal networks that it supports (8) and most neurons are within 10 to 20 μm of a capillary (9). The vascular network can be accessed through an incision in locations such as the jugular vein or carotid artery, which are used by neurosurgeons to implant self-expanding stents in the brain to treat conditions such as cerebral atherosclerosis (10). Stents have also been combined with electrodes (stent-electrode recording arrays) to record cortical neural activity from veins as narrow as 1.7 mm in diameter for up to 190 days (11). These BMIs enabled four patients paralyzed by lateral sclerosis to perform simple computer tasks by thought (12).

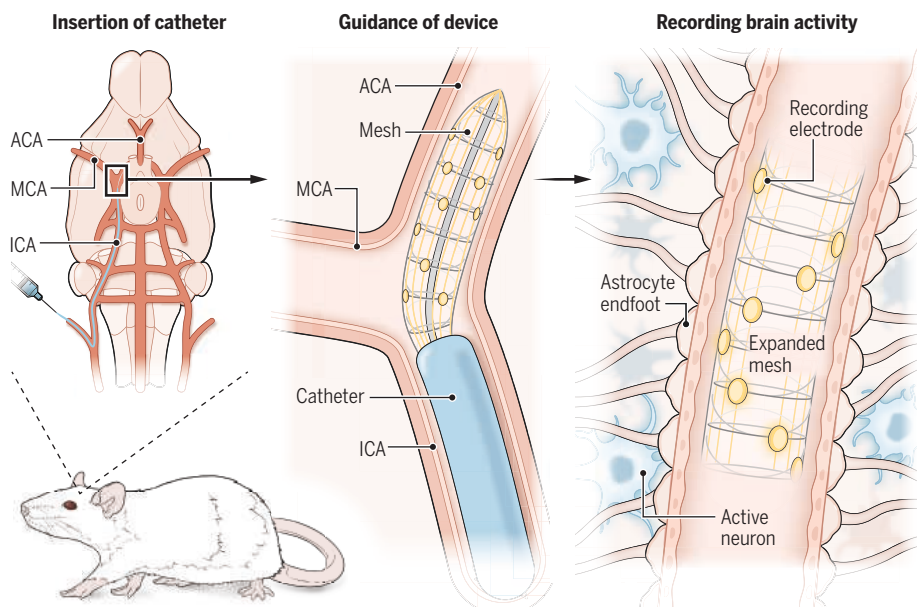
To deliver bioelectronics to regions of the brain with narrower, less accessible blood vessels, Zhang *et al.* designed a mesh-like

recording device that was much smaller and more flexible than those used previously (see the figure). This device, which contained 16 distinct recording elements, was loaded into an endovascular catheter. Using a rat model, they made an incision in the neck and guided the catheter into the internal carotid artery (ICA). When the device was expelled from the catheter, it expanded like a stent to record neuronal signals across the vascular wall. Because the device was so flexible, it could be deployed to previously inaccessible branches of the ICA with vessel diameters $<100 \mu\text{m}$. This capability enabled Zhang *et al.* to record distinct firing patterns from the middle cerebral artery (MCA) and anterior cerebral artery (ACA), which overlay the cortex and olfactory bulb, respectively. Despite the fragility of these small vessels, the implanted devices caused no substantial change to cerebral blood flow, rat behavior, or the structure of the blood-brain barrier, and did not elicit an immune response.

Because the device is so small, it was able to record not only local field potentials, as observed with the stent-electrode recording arrays, but also single-neuron activity. This

Recording of brain activity across blood vessel walls

A catheter containing the mesh recording device was inserted through an incision in the neck of a rat and guided along the internal carotid artery (ICA) to the point where it splits into the middle cerebral artery (MCA) and anterior cerebral artery (ACA). The device was then released into the MCA or the ACA and expanded to record neuronal activity across the blood vessel wall.



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ability to achieve noninvasive, single-neuron recordings is important for studies of deep-brain regions such as the medial temporal lobe where activity is not spatially clustered and therefore only identifiable at the single-neuron level. Future studies could answer long-standing questions about how memories are stored and retrieved (13).

Future BMIs could provide tailored therapies to the patient by recording and decoding their neural activity and then providing the appropriate modulatory stimuli (1). These bi-directional systems are especially relevant for advanced prosthetics, where the BMI enables both motor control and tactile feedback. Therefore, the next versions of endothelial probes should incorporate localized stimulation devices, as was demonstrated with the brain-injected meshes (7). These stimulation elements might also be used to electroporate the blood vessel wall, enabling localized drug delivery across the blood-brain barrier.

Although the probes designed by Zhang *et al.* can enter vessels such as the MCA and ACA, smaller versions could reach capillaries, which have diameters <10 μm . These smaller probes could be achieved by using nanoscale recording and stimulation elements. Nanoelectronics are also advantageous because they can be small enough to enter the cytosol, which would enable intracellular interrogations of blood vessel walls (14). The probes only have branch selectivity at the first bifurcation; future probes might contain an onboard guidance system, for example, magnetic particles that can be manipulated with an external field, allowing them to travel beyond the catheter while remaining under directional control. Such systems might obviate the need for a catheter altogether, allowing the devices to be injected through a standard needle and at other locations of the body, such as the arm. These endovascular probes might form the foundation for machine interfaces throughout the body. ■

REFERENCES AND NOTES

1. M. A. Lebedev, M. A. Nicolelis, *Physiol. Rev.* **97**, 767 (2017).
2. A. Zhang *et al.*, *Science* **381**, 306 (2023).
3. K. J. Miller *et al.*, *Neurosurg. Focus* **49**, E2 (2020).
4. B. Gunasekera *et al.*, *ACS Chem. Neurosci.* **6**, 68 (2015).
5. G. Balakrishnan *et al.*, *Adv. Mater.* **34**, e2106787 (2022).
6. J. Tropp *et al.*, *Matter* **10**, 1016/j.matt.2023.05.001 (2023).
7. T. M. Fu *et al.*, *Nat. Methods* **13**, 875 (2016).
8. A. D. Wong *et al.*, *Front. Neuroeng.* **6**, 7 (2013).
9. B. Flusty *et al.*, *Stroke* **51**, e49 (2020).
10. T. J. Oxley *et al.*, *Nat. Biotechnol.* **34**, 320 (2016).
11. P. Mitchell *et al.*, *JAMA Neurol.* **80**, 270 (2023).
12. R. Quian Quiroga, *Cell* **179**, 1015 (2019).
13. B. J. Andreone *et al.*, *Annu. Rev. Neurosci.* **38**, 25 (2015).
14. H. Acarón Ledesma *et al.*, *Nat. Nanotechnol.* **14**, 645 (2019).

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ELECTROCHEMISTRY

Electrochemical waste-heat harvesting

A combined thermal and electrochemical device enhances voltage and hydrogen production

By Boyang Yu and Jiangjiang Duan

Harvesting waste heat (e.g., solar irradiation, or from industrial processes or the human body) is crucial for carbon neutrality and sustainable development (1). Unfortunately, most waste heat is distributed near ambient temperature, making it inaccessible to conventional heat engines, which require large temperature differences (2). On the basis of redox reactions at two electrodes with different temperatures, an electrochemical device called a thermogalvanic cell can be used for continuous waste-heat harvesting, with affordable, scalable, and eco-friendly characteristics (3). Nevertheless, the limited heat-to-electricity conversion efficiency is a critical challenge for practical applications. On page 291 of this issue, Wang *et al.* (4) report a photocatalytically enhanced thermogalvanic cell that combines in situ heat-to-electricity conversion with water splitting, boosting both electricity and hydrogen production. This approach promises to improve harnessing of solar energy and other sources of waste heat.

Thermogalvanic cells have the basic configuration of two electrodes sandwiching an electrolyte, where the electrolyte contains a redox couple such as ferro/ferricyanide anions $[\text{Fe}(\text{CN})_6^{4-}/\text{Fe}(\text{CN})_6^{3-}]$ (1). To realize heat-to-electricity conversion, a heat flux input is first required to establish a temperature difference (ΔT) between the two electrodes, which can be obtained from diverse sources of waste heat. Then, the oxidation of $\text{Fe}(\text{CN})_6^{4-}$ to $\text{Fe}(\text{CN})_6^{3-}$, accompanied with more entropy, is thermodynamically favorable and injects electrons into the hot electrode, whereas the reduction reaction attracts electrons from the cold electrode, generating a thermal voltage (ΔV) (see the figure).

The thermopower of the thermogalvanic cell (S_e), quantified as $\Delta V/\Delta T$, is the key to both high cell voltage and heat-to-electricity

conversion efficiency (5). One promising way to improve S_e is to build a concentration gradient of redox ions (ΔC), which has been proven to boost efficiency of a single cell (6, 7). For example, a locally high concentration of $\text{Fe}(\text{CN})_6^{4-}$ on the hot side and $\text{Fe}(\text{CN})_6^{3-}$ on the cold side is thermodynamically favorable for a large ΔV (namely S_e). However, current strategies are only available to create single-ion concentration gradients, which limit the improvement of S_e . How to achieve a large S_e remains a challenge, owing to the lack of strategies for creating multiple-ion concentration gradients.

To this end, Wang *et al.* propose a strategy that employs photocatalysts to facilitate the conversion and accumulation of redox ions and hence the formation of their concentration gradients. In photocatalysis, photogenerated electrons with sufficient energy are excited from the valence band maximum (VBM) to the conduction band minimum (CBM), whereas holes are generated on the VBM. By matching the CBM-VBM gap and the redox potentials, the photogenerated electrons and holes can promote the reduction and oxidation reactions, respectively (8). A typical example is solar water splitting for hydrogen (H_2) production. In the study of Wang *et al.*, two types of photocatalysts were carefully chosen to couple oxygen (O_2) generation with $\text{Fe}(\text{CN})_6^{3-}$ reduction and H_2 generation with $\text{Fe}(\text{CN})_6^{4-}$ oxidation. By fixing the photocatalysts to the opposite sides of the thermogalvanic cells (see the figure), the photocatalytic $\text{Fe}(\text{CN})_6^{3-}$ reduction and $\text{Fe}(\text{CN})_6^{4-}$ oxidation lead to a locally high concentration of $\text{Fe}(\text{CN})_6^{4-}$ at the hot anode and $\text{Fe}(\text{CN})_6^{3-}$ at the cold cathode, respectively. The generation of ΔC for both $\text{Fe}(\text{CN})_6^{4-}$ and $\text{Fe}(\text{CN})_6^{3-}$ tripled S_e to 8.2 mV K^{-1} , enabling a record-high thermogalvanic performance of 8.5 mW m^{-2} K^{-2} near ambient temperature (average $\sim 33^\circ\text{C}$). Furthermore, Wang *et al.* established a universal linear relationship between S_e and the H_2 generation rate, suggesting that better photocatalysts could enable higher S_e .

The approach of Wang *et al.* provides essential design principles for photocatalytically enhanced thermogalvanic systems. Using a rational design of photocatalysts

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