Soft sensor tracks the neurochemical messengers dopamine and serotonin

Neurotransmitters have key roles in regulating the nervous system. To better understand these processes, researchers need tools to analyse neurotransmitter signalling in the organs of living animals. We have invented NeuroString, a soft sensor for monoamine neurotransmitters, which can be fitted to the brain or gut of animals without disturbing the organ's natural functions.

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The problem

Researchers have made great progress in neurotransmitter sensing by using genetically engineered fluorescent probes[1]. Bioelectronic neural interfaces have also been used to study wild-type animals and even humans, but these devices have mainly focused on the electrophysiology of the nervous system[2,3]. However, the bioelectronic tools for studying neurochemistry are limited. They tend to be rigid and brittle, and can lead to undesired stimulation of the target tissue or inflammatory responses, making them poorly suited to monitoring soft tissues.

Scientists need soft bioelectronic interfaces that can monitor the natural spatio-temporal dynamics of neurotransmitters in both the central and peripheral nervous systems, without interfering with the physiology of soft and moving organs such as the brain and the gut. These tools could ultimately enable the development of next-generation brain–machine interfaces and medical therapies that modulate neurotransmitter activity.

The solution

Our sensor uses a technique called fast-scan cyclic voltammetry[4]. This involves rapidly raising and lowering the voltage applied to a probe to repeatedly oxidize and reduce the target neurotransmitters, generating a neurotransmitter-specific current.
We selected graphene as our electrode material because it acts as a catalyst for the oxidation of monoamine neurotransmitters such as dopamine and serotonin. It also has excellent electrical properties, good biocompatibility and can withstand bending, stretching and twisting.

Using a process called laser carbonization, we created a network of graphene nanofibres decorated with transition-metal nanoparticles. These nanoparticles can bind to neurotransmitters and improve electron transfer, making the sensor suitable for sensitively and selectively analysing neurochemistry. We then embedded the network in an elastomer matrix to make it soft and highly stretchable, while preserving the unique electrochemical properties of the nanomaterials (Fig. 1a). The graphene nanofibres maintained an interconnected 3D conductive network even when they were deformed in the matrix.

We used this sensor, which we call NeuroString, for long-term, stable and simultaneous sensing of dopamine and serotonin levels in the mouse brain. It performed well in the brain and generated a minimal inflammatory response in a series of experiments using optogenetic stimulation, pharmacological stimulation (Fig. 1b) and behavioural assays. We then tested the sensor in the gastrointestinal tract, where its stretchability and softness conforms well to the intestinal tissue without disturbing peristaltic movement or stimulating undesired serotonin release. The device provided continuous and high-fidelity monitoring of serotonin released in the gut lumen in both a rodent model of irritable bowel syndrome and a large-animal model.

NeuroString's elastic features make it suitable for simultaneously monitoring neurotransmitter signalling in both nervous systems, and potentially addresses current technical limitations in studying the dynamics of the gut's chemistry and interactions with microorganisms.

The implications

Our soft and conformable bioelectronic interface can probe the complex and versatile chemical signalling in organs, going beyond electrophysiological recording methods. It is simple and minimally invasive, and provides opportunities to study gut physiology and to diagnose irritable bowel syndrome. NeuroString has the potential to reveal the dynamics of neurotransmitters, as well as their roles in communication between the brain and the gut and its microbiome. This work could lead to the development of diagnosis methods for people with psychiatric disorders, along with new treatment methods through gastrointestinal interventions.

NeuroString is not as sensitive or selective as the latest genetically encoded fluorescent probes — a limitation inherent to the voltammetry method. But bioelectronic electrochemical sensors such as NeuroString could be particularly useful in humans, because these devices do not require any genetic modification of the host[5].

In future, we hope to improve the sensor's spatial resolution using micro- or nanofabrication. We could also improve its selectivity and functionality by incorporating different probes, and eventually integrating it with wireless hardware. This should enable the validation of its long-term performance in the brain and gut of larger animals.

It might even be possible to link the sensor to a system for modulating the concentration of targeted neurotransmitters. This implanted, closed-loop system could be used to reprogram a person's brain chemistry in real time.

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EXPERT OPINION

"The stretchable nanocomposite material and soft bioelectronic device proposed in this manuscript are promising solutions for dopamine and serotonin sensing. The device seamlessly interfaces with continuously moving organs and provides chronically stable and multiplexed neurochemical sensing in the brain and gut. Impressively, the authors have performed thorough demonstrations of the proposed device *in vivo*."

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FIGURE

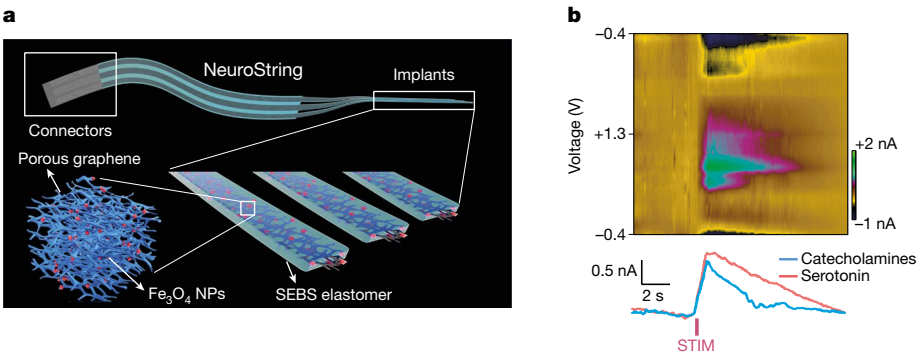

Figure 1 | NeuroString can be used to monitor neurotransmitters in the brain and gut. a, NeuroString is a soft, sensitive and selective neurochemical sensor that is made from nanoscale graphene–iron oxide nanoparticle networks encased in an elastomer matrix. NPs, nanoparticles; SEBS, styrene-ethylene-butylene-styrene. **b**, When a changing voltage is applied to a NeuroString sensor implanted in a mouse brain, it induces currents (top panel) that can be used to calculate the concentrations of catecholamines (such as dopamine) and serotonin that are released before and after the brain receives electrical stimulation (STIM) after pharmacological treatment (bottom panel). nA, nanoampere; s, second; V, volt.

BEHIND THE PAPER

When engineers develop new tools, early prototypes are often fairly primitive. Yet many biologists understandably prefer to use well-developed instruments to study specific problems in biology. This is a huge challenge for interdisciplinary research, because all parties need to compromise and learn to work within the constraints of an emerging technology. When we initially started this project in 2017, it took me several months to find a collaborator who would be willing to invest time and resources on a nascent research tool. After communicating with more than ten biologists across California, I eventually met a neuroscientist — X. Chen at Stanford University — who was excited about our concept. We later secured funding from the Stanford Bio-X Interdisciplinary Initiatives Seed Grants Program to complete the initial proof of concept. I am glad that my mentor Z. Bao, and our collaborators, provided the freedom and patience needed for this interdisciplinary work.

J.L.

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FROM THE EDITOR

Flexible electronic platforms show great promise for biosensing applications, as exemplified by this work. Not only have the authors been able to engineer a biocompatible sensor capable of the simultaneous (and selective) detection of the neurotransmitters dopamine and seratonin, the resulting devices are so soft that they don't cause tissue damage or interfere with organ function when used *in vivo*. This is an impressive combination of properties that should lend itself to whole-body, real-time biochemical sensing.

Editorial Team, *Nature*