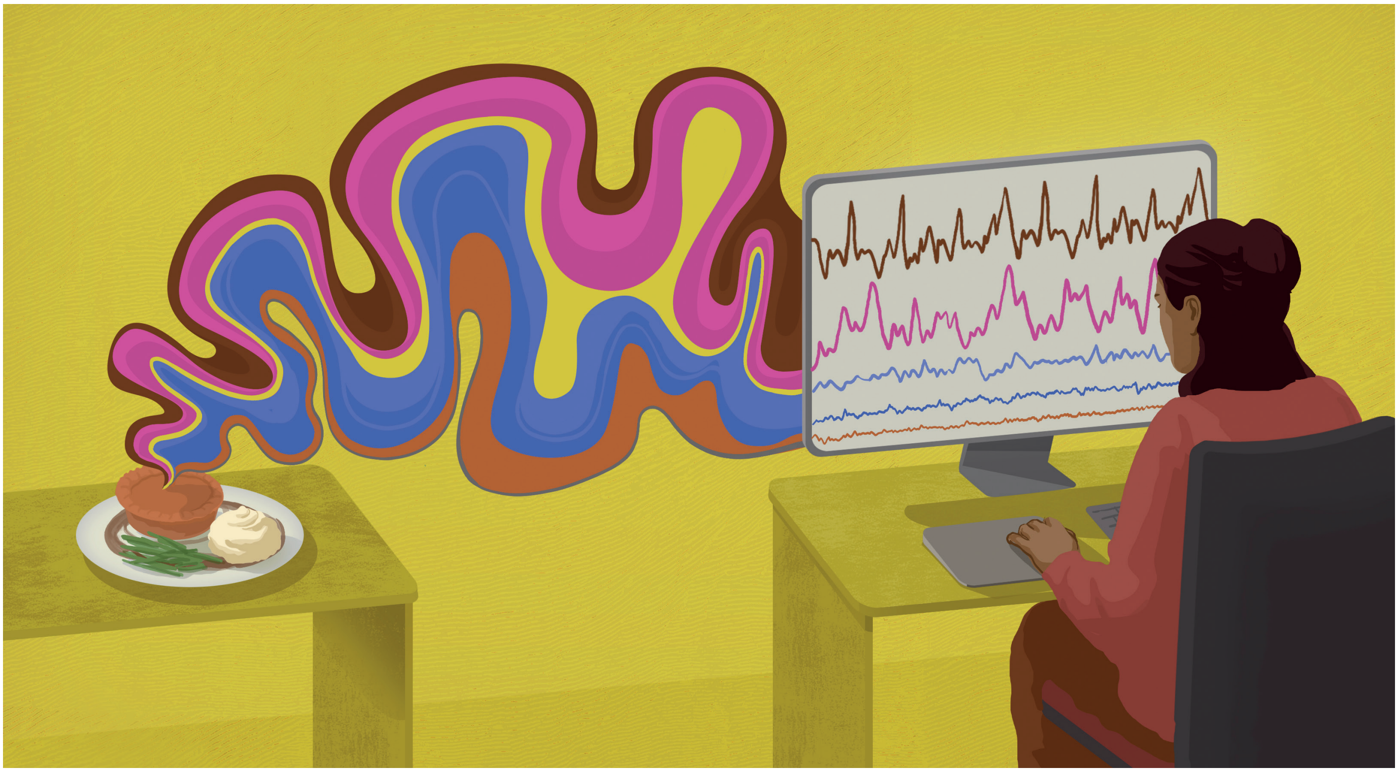

ILLUSTRATION BY SAM FALCONER

Smell by wire

An electronic olfactory implant that could help to restore a person's sense of smell is in the early stages of development. By Simon Makin

One of the many aspects of the COVID-19 pandemic that has taken the world by surprise is the vast swathes of people who lost their sense of smell. For most people who get COVID-19, the loss of smell is brief, but some do not regain their sense of smell for 6 months or longer[1]. "There's going to be a whole cohort of individuals who aren't going to recover, looking for some help," says Richard Costanzo, a physiologist at Virginia Commonwealth University (VCU) in Richmond.

Losing the ability to smell – a condition called anosmia – is more detrimental than many people think. Aromas provide flavour, and therefore affect eating behaviour. What's more, people who are unable to smell their environment have a greater risk of not being able to detect gas leaks, fires and spoiled food. Some become depressed. And even before the pandemic, anosmia was surprisingly common, affecting around 5% of people by one estimate[2]. "Viruses have been knocking out the sense of smell for a long time," Costanza says. But they are not the only cause: olfactory dysfunction can also be the result of head trauma, and a consequence of age.

Currently there are few treatment options available. A technique called olfactory training can help in some cases, and a number of approaches to repairing damaged olfactory tissues are being explored (see page S7). However, a small but growing group of scientists is pursuing another avenue: olfactory implants that restore smell by bypassing the peripheral olfactory system and electrically stimulating the brain.

Research is in the early stages, but there is a patent[3], a prototype and a handful of preliminary studies. Demonstrating safety is most researchers' primary concern, but efforts are also under way to assess the feasibility of stimulating more central brain regions. Although clinical use is currently some time off, interest in the idea seems to be growing. "Thanks to COVID, this has become an area of more interest to investors," says Daniel Coelho, a cochlear-implant surgeon at VCU. "The size of the market has grown exponentially, unfortunately." A 2021 study of 2,581 people with COVID-19 at 18 European hospitals found that olfactory dysfunction persisted for 2 months in nearly 1 in 6 people, and almost 1 in 20 had still not recovered after 6 months[1].

The first sense

Compared with other senses, the olfactory system is poorly understood. Odorant molecules that waft into our nose come into contact with the olfactory epithelium at the top of the nasal cavity, where they bind to receptors on sensory neurons. These neurons fire signals up the olfactory nerve, to an outer brain region called the olfactory bulb. This arrangement is unique among our senses, says Costanzo. "It's the only case where a neuron is exposed to the outside world and has an axon that connects directly to the central nervous system. It's very primitive."

From the olfactory bulb, signals are conveyed to the brain's primary olfactory cortex – a group of several brain regions that includes the amygdala, piriform cortex and entorhinal cortex. This direct wiring into multiple regions, including parts of the limbic system that are involved in memory and emotion, is thought to give smell its ability to vividly evoke memories (see page S2).

Many questions remain about how smell inputs are processed. Each sensory neuron in the nose expresses just one olfactory receptor, of a pool of around 400. However, each receptor can accept several odorants, and every odorant can bind to several receptors. This arrangement enables people to differentiate a huge number of odours — in the tens of thousands at least, and perhaps orders of magnitude more — but the complex combinatorial code that maps molecules to scents is largely unknown.

Proof of principle

The notion of using an electronic device to restore sensory function is not new: cochlear implants have for decades been used to provide some hearing to many people with severe deafness. Electrical signals transmitted to electrodes implanted in the cochlea stimulate the bottom of the auditory nerve, which transmits the signals to the brain. Although initially intended for people with profound deafness, these implants are increasingly given to people with a greater level of residual hearing. Outcomes of the implant vary widely, but a 2020 review found that, on average, word perception improved from 8% to 54% in the implanted ear[4]. This does not restore natural hearing, but can significantly improve some recipients' quality of life.

Costanzo and Coelho have long thought that something analogous ought to be possible for olfaction. "There's no reason to think applying the same tried-and-true principles of brain stimulation won't work," Coehlo says. In 2016, they filed a patent[3] for a system that comprises a chemical sensor, processor and transmitter and an internal part comprising a receiver and an implantable electrode array. They also produced a prototype, built into a pair of glasses, and two proof-of-principle studies. The first, published in 2016, demonstrated that odours produce characteristic spatial patterns of activity in healthy rats' olfactory bulbs, and that electrically stimulating various areas of the olfactory bulb similarly evoked different patterns of neural activity[5]. The second study, in 2018, repeated the electrical stimulation in rats with severed olfactory nerves, to make it more relevant to treating anosmia[6].

The studies add to evidence for how the olfactory system is organized. "In the auditory system, we know it's based on frequencies. In the chemical sensing system, we don't know what the fundamental element is," says Costanzo. "But we know there's a spatial map." The topography of this map is more complex than in the cochlea — but this is not necessarily a barrier. "Where banana activates the olfactory bulb is not really important," says rhinologist Eric Holbrook at Harvard Medical School in Boston, Massachusetts. "As long as you learn by random stimulation where that is, and you're able to reproduce it."

Holbrook was a postdoc in Costanzo's lab, and still collaborates with the VCU team. In a study published in 2018, he and his colleagues placed electrodes at three positions on the bone adjacent to the olfactory bulb, in people who had undergone a type of sinus surgery that makes the bulb more accessible. The researchers then stimulated the electrodes and asked the participants what they could smell[7]. Three of the five participants said they could smell something, although they struggled to identify what. "Onion-like was one response," says Holbrook.

The group is now collaborating with Mark Richardson, a neurosurgeon and researcher at Massachusetts General Hospital in Boston, to probe deeper into the olfactory brain to understand how smells are organized in the cortex. Stimulating the brain more centrally could be helpful if the damage that is interfering with a person's sense of smell extends beyond the periphery, to the olfactory bulb or beyond. They are collecting data on which areas of the brain activate when a person detects an odour, using people with seizure disorders who have already had electrodes implanted in their brains to monitor electrical activity.

Other researchers are also pursuing olfactory implants. ROSE (restoring odorant detection and recognition in smell deficits), an EU-funded project involving seven institutions in five European countries, launched in September 2021. "The aim is to develop proof-of-principle miniaturized odour sensors and stimulation arrays that will be evaluated in patients," says Moustafa Bensafi, a neuroscientist at the French national research agency CNRS in Lyon, who is coordinating the project. Neuroscientist Thomas Hummel at the Technical University of Dresden in Germany is also involved in the project, and together with his colleagues in Greece will test various electrode placements on the underside of the olfactory bulb. They are also looking at deeper brain stimulation in people with epilepsy. "When we stimulated one patient, close to the piriform cortex, they perceived spinach," says Hummel. "That was a very happy day."

Making a difference

An important question for any prospective therapy is whether there is sufficient demand. In 2019, Hummel and his colleagues surveyed the attitudes of 61 people with olfactory dysfunction[8]. Of the group, more than half of whom had essentially no sense of smell, 34% said that they would consider an olfactory implant, even knowing it involved invasive surgery. The greater their olfactory impairment, the more likely they were to consider the intervention. This suggests there could be demand for the technology, but it might depend on the degree to which natural sensation can be restored. "The question is whether these implants could be really helpful in daily life," says Hummel.

When cochlear implants were introduced in the 1960s, little was known about how to stimulate the auditory system, and just hearing a buzz was thrilling, Coelho says. "Now that would be considered a terrible outcome." Olfactory implants might start out in a similar way, as relatively minor aids, and become more capable over time. "That first implant will give us so much information to then figure out what to do next," says Holbrook.

This could happen in the not-too-distant future. "It could be three to five years or so," says Hummel. "The tools are basically there." Costanzo is similarly optimistic. "Electronic noses are getting better and better," he says. "We have a prototype that can identify four or five odours, but in five years that's going to be so much better."

The most immediate hurdle is assuring patients, physicians and regulators that an implant would be safe. "How can we stimulate the brain the safest way for the patient?" says Costanzo. "We have some ideas, but we're not there yet."

Some researchers are investigating. A study published in April by a team in France assessed a potential surgical technique for feasibility and risk[9]. The researchers conducted the procedure on cadavers, using dyes to look for cerebrospinal fluid leaks, which occurred in every case. The other, perhaps greater risk, is infection. "The nose is not a clean area," says Costanzo. "But these challenges are all doable."

Ultimately, the boost in profile that COVID-19 has given this condition might prove to be the spur that researchers needed. "People are listening more when you talk about olfaction," says Hummel. "They know what it means when you lose it." There aren't many upsides to what the world has been through over the past two years, but perhaps better treatment options for people with olfactory loss will be one.

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