Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
As of 1 July 2022, there have been 545,226,550 confirmed cases of COVID-19 reported to the World Health Organisation as well as 6,334,728 deaths linked to the disease. In the current third year of the pandemic, these numbers are set to increase further, as the virus continues to spread in many countries, often unhindered by significant public health interventions beyond the well-established vaccinations, and therefore also continues to evolve.

Although the vaccinations are currently successful in keeping serious complications and fatal cases at manageable levels, long-term problems generally captured under the umbrella term long COVID are estimated to affect between 20 and 50% of cases. This means that a significant patient population of more than 100 million people globally will likely continue to experience debilitating effects of the infection for months or even years to come. Public health experts have pointed to the as yet unquantifiable cost of long COVID as a reason to uphold measures like mask mandates rather than relying on vaccinations alone.

One of the acute symptoms of COVID-19 that may persist in the long term is the loss of smell. Early on during the pandemic, anosmia was identified as a frequently observed symptom, sometimes even the only one that patients with a positive test result noticed. More recent versions of the virus, such as the early versions of the omicron variant, seem to be less likely to affect smell, with fewer than 25% of people reporting anosmia. One in 20 of those who lose their sense of smell as a result of COVID-19 have not recovered it within six months.

Extrapolated to half a billion cases, these numbers add up to a significant problem in terms of quality of life lost for millions. Therefore, researchers are called upon to find remedies, and they can base their research on a large cohort of anosmia patients with a well-known causation history.

A sensory loss

Culturally, modern societies are primed to pay less attention to smell than to our other senses, a disregard typically reflected in our languages. In contrast to hunter-gatherer societies, European languages don’t have specific words for smells like we have for colours and have to resort to comparisons instead (Curr. Biol. (2015) 25, R173–R176). Recent analyses of odorant receptors have suggested, however, that we can normally distinguish many millions of different smells, even if we can’t describe them (Curr. Biol. (2019) 29, R663–R665). This is made possible by combinatorial use of the ~400 types of active receptors that make up a healthy sense of smell.

To many, the importance of smell only becomes dramatically clear when they lose it, as the loss will affect their wellbeing and quality of life in multiple ways, ranging from the enjoyment of food and drink to social interactions and mental health. It can also become a safety issue in the context of gas leaks, fires, or spoilt food.

Before COVID-19, olfactory dysfunction was an underappreciated although not uncommon disorder estimated to affect between 5 and 15% of the general population. It is often attributed to ageing, sometimes to specific causes like viral infections, head trauma, or chronic rhinosinusitis, but in many cases it occurs without any obvious reason. Therefore, it was a challenge to systematically investigate causation mechanisms and search for a cure.

As some patients recovered their sense of smell spontaneously, it was also difficult to tell whether a given recovery was attributable to any treatment tried.

The most widely tried treatment option so far is olfactory training, which essentially relies on systematic exposure to a small number of strong odours. The idea is that the olfactory neurons can re-learn to make the right connections.

**Nasal issues:** The COVID-19 pandemic has caused widespread loss of smell and thereby led to a renewed scientific interest in anosmia research. (Photo: Mark C. Olsen/New Jersey National Guard.)
The related post-viral problem of parosmia, a distorted sense of smell, is being discussed along similar lines, as it may be due to the repair mechanisms of the olfactory system setting up wrong connections. Although parosmia can often feel a heavier burden than the total lack of smell, experts see it as a more hopeful situation because sensory communications are happening and may be corrected.

The first studies of olfactory dysfunction in COVID-19 patients and animal models suggest that the SARS-CoV-2 virus doesn’t hit olfactory neurons directly. These neurons are lacking the ACE2 receptor and the TMPRSS2 protease, which the virus uses for cell entry. Instead, SARS-CoV-2 enters other cell types in the olfactory epithelium, including sustentacular cells, which wrap around sensory neurons and are believed to provide structural and metabolic support for the neurons, as well as basal cells, which act as stem cells that can regenerate the tissue when it has been damaged, as the group of Sandeep Datta at Harvard Medical School, USA, has shown (Sci. Adv. (2020) 6, eabc5801).

Mariana Zazhytska from Columbia University, New York, USA, and colleagues now demonstrate in human patients and in hamster models that infection of other cells in the olfactory epithelium causes widespread downregulation of odorant receptors and their signalling genes in olfactory neurons (Cell (2022) 185, 1052–1064. e12). Furthermore, the spatial compartmentalisation of receptor genes is disrupted, a change that affects the expression of the receptors and may persist on the timescale of months.

The findings offer a molecular explanation of how the virus can manipulate olfactory neurons, even though the virus doesn’t have a pathway of entering them. The authors argue that this may have wider implications beyond olfaction in explaining symptoms in other organs affected and resolving the apparent contradiction between the small number of cell types the virus can enter and the wide range of disruption it causes in the body.

However, other unrelated factors may also be playing a part in post-viral anosmia and parosmia. In a study currently available as a preprint, John Finlay at Duke University in Durham, USA, and colleagues have implicated inflammatory infiltration in the gene expression changes that ultimately cause olfactory dysfunction (bioRxiv (2022) https://doi.org/10.1101/2022.04.17.488474).

Systemic inflammation disrupting gene expression in the olfactory system was also observed in hamsters in a study by Justin Frere from New York University, USA, and colleagues (Sci. Transl. Med. (2022) https://doi.org/10.1126/scitranslmed.abq3059). These authors suggest that the hamster model may become useful for developing new therapies against anosmia, parosmia, and other manifestations of long COVID.

Finding therapies
Aria Jafari from the University of Washington at Seattle and Eric Holborn at Harvard Medical School, both USA, have reviewed the available therapies in the light of the situation brought about by the COVID-19 pandemic (Curr. Allergy Asthma Rep. (2022) 22, 21–28). They emphasise that the only cases for which a proven medical therapy exists are those caused by rhinosinusitis, a simultaneous infection of nasal mucosa and the sinuses, which are treated with localised or systemic application of corticosteroids. Where the cause of the smell dysfunction is unknown, clinicians may also try steroids for a limited time to see if they have an effect.

For other causes, including post-viral anosmia, olfactory training is currently the most widely used treatment. This method was first introduced by Thomas Hummel at the University of Dresden, Germany, in 2009. His original protocol involved sniffing four different odours (rose, eucalyptus, clove and lemon) twice daily for three months. The non-invasive nature and easy applicability of the intervention has likely contributed to its rapidly growing popularity. Since then, other researchers have expanded and modified the protocol and also reported benefits.

Several recent neuroimaging studies reviewed by Jafari and Holborn have demonstrated specific improvements in the functional architecture of the olfactory system after three months of training, hinting at solid mechanistic explanations for its success.

Where these methods fail, some new ideas are now offering hope. Jafari and Holborn review recent studies on the use of N-acetyl cysteine for its protective effects after acute injury to olfactory neurons, as well as the application of the patient’s own platelet-rich plasma (PRP) to help restoration of olfactory neurons, which is subject to an ongoing clinical trial. In other contexts, PRP has been used to stimulate tissue regeneration.

Holbrook’s group at Harvard has also trialled the use of electrical stimulation of olfactory neurons and obtained promising initial results that warrant further investigation.

A whole new nose
Taking the idea of electronic stimulation further, some researchers are already hoping to develop the olfactory equivalent of the cochlear implant, an electronic nose that feeds sensory information directly to the brain. Richard Costanzo and Daniel Coelho at Virginia Commonwealth University (VCU) in Richmond, USA, have already filed a patent for such a system, developed a prototype, and conducted preliminary studies in rats (Int. Forum Allergy Rhinol. (2018) 8, 922–927).

In September 2021, Moustafi Bensafi from the CNRS at Lyon, France, and colleagues from other European countries including Thomas Hummel, launched a European effort called ROSE (restoring odorant detection and recognition in smell deficits). The project aims to assemble a “digital olfaction module”, which “will enable people with loss of smell to perceive their olfactory environment.”

Teaching an electronic nose which smell is which is a task that can nowadays be left to artificial intelligence and deep learning algorithms. Following the discovery that dogs can smell COVID-19 infections in humans, the group of Noam Sobel at the Weizmann Institute in Rehovot, Israel, has developed an
The lights and shadows of consciousness

Jonathan Birch* and Andrew Crump

Being You: A New Science of Consciousness
Anil Seth
(Faber & Faber, London; 2021)
ISBN: 978-0-571-33770-5

As George Eliot observed, it is a watershed moment when we realise that other people have "an equivalent centre of self, whence the lights and shadows must always fall with a certain difference". In a sense, these other "centres of self" will always elude us. Other people may tell us what they are feeling, and we may try to empathise, but we can never fully project our own perspective into theirs, or theirs into ours.

Then again, Eliot did not have a VR headset. In a memorable passage in Being You, neuroscientist Anil Seth describes experiencing a 'virtual body swap'. You stand next to a partner, both of you wearing headsets displaying a live video feed and both wearing eye-level cameras with the feeds swapped. You appear in your own visual field. You walk up to yourself and shake hands. You start to feel as though the visually distant hand is your hand and the visually closest hand is your hand. In one variant, you look at your new body in the mirror, then give your old body a hug.

This ingenious setup represents the promise, and perhaps also the pitfalls, of contemporary consciousness science. Being You is an engaging and accessible tour through the field's boldest theories, most creative experiments and most surprising findings. You could give the book to a smart teenager and get them asking questions that they will be thinking about for the rest of their lives. It excites, inspires and seems certain to draw new people into consciousness science.

Part of what makes Being You such a good entry point is the lack of dogmatic tub-thumping for any particular theory. Consciousness science contains dizzying disagreements about the correct theory: the spectrum ranges from views in which consciousness is an illusion to views in which it pervades the universe, with many varieties of intermediate position. All such theories have speculative elements, and current evidence does not decide between them. Being You is honest about this unfortunate situation but makes a convincing case that we don't need consensus on a grand theory to begin stitching together a patchwork of relevant evidence.

To do this, Seth advocates a strategy he calls tackling 'the real problem'. This term is a retort to fellow VR enthusiast David Chalmers, who in the 1990s distinguished 'easy problems' of consciousness from the 'hard problem'. The 'easy problems' are those of explaining the various functional capacities related to consciousness, such as our capacities to report what we are seeing, draw on sensory information in planning and reasoning, exert top-down control over our actions, and so on (it's a long list). The 'hard problem' is explaining why any of this information processing leads to conscious experiences. As Chalmers puts it, "why doesn't all this information-processing go on 'in the dark', free of any inner feel? [...] Why should physical processing give rise to a rich inner life at all?". Our difficulty in getting any grip on the hard problem is why such wildly different theories proliferate.

For Seth, there is a valuable research programme that targets neither the hard problem (directly) nor the easy problems. His insight is instead to ask, what levers of control can we find, both inside and outside the brain, that allow us to manipulate the content and character of a person's subjective experience? Hallucinogenic drugs are an obvious example, but they are rather crude levers of control. Can we find more precise, targeted ways of producing similar effects? This would give us the means to predict and explain (in a causal sense of the word) why our subjective experiences have their particular content and character (or 'phenomenology').

The 'virtual body swap', originally developed by Henrik Ehrsson, is one example of the 'real problem' programme. It allows us to look for levers of control over a specific kind