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# Lifting the fog

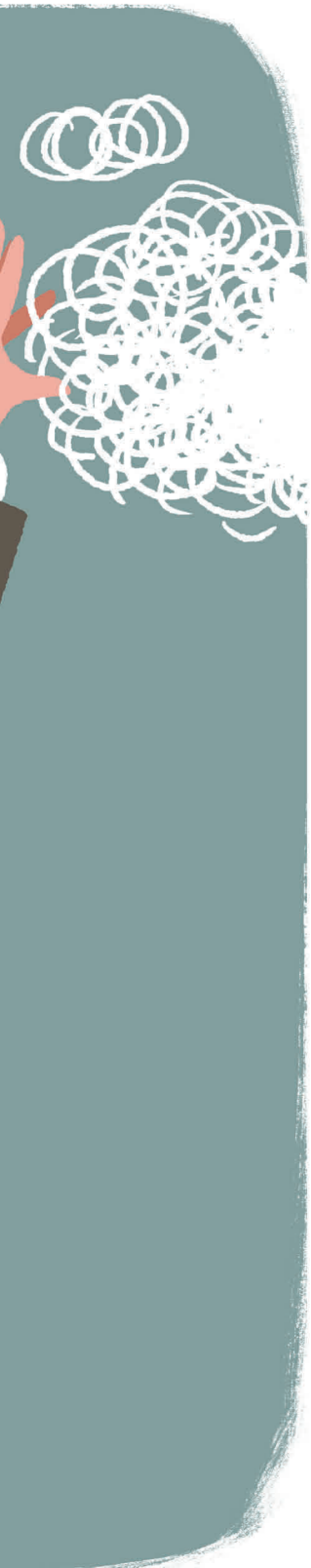
Brain fog is a nebulous concept that eluded scientific scrutiny – until covid-19 thrust it into the spotlight. **Kayt Sukel** reports

**C**OURNEY SHUKIS was looking forward to lunch: she had just recovered from covid-19 and was glad to be meeting her friends again. Before leaving her home in Plano, Texas, she checked the calendar, making a mental note of the restaurant and when to meet. “But instead of going there, I got in my car and drove to a completely different place,” she recalls. “I sat at the table for half an hour, looking at my phone, wondering where everyone was. My brain fog was really bad.”

That wasn't a one-off. After having covid-19, Shukis had frequent episodes of memory loss. She would forget to make dinner, had trouble finding the words to describe things and got confused about school pick-up times. “I had never had any difficulties with these kinds of things before. It just felt like my brain wasn't working right.”

Shukis is one of millions of people worldwide reporting a severe dent in cognitive functioning following a covid-19 infection, and as a result, the issue of brain fog has been thrust into the limelight. For many, this is long overdue. “It's something that patients with a wide variety of different medical problems have said has interfered with their ability to function for a long time,” says Sabina Brennan, a neuroscientist at Trinity College Dublin, Ireland, and author of *Beating Brain Fog*. The hope is that this interest could improve care for those experiencing it. “If there's anything positive to come out of the covid-19 pandemic,





it's that the spotlight is now on brain fog and the scientific community is paying much more attention to it," says Brennan.

The concept of brain fog goes back to the early 1800s, when German physician Georg Greiner first used the words "fogging of the light of reason" or "clouding of consciousness" to describe the cognitive deficits accompanying delirium. Brain fog, as a term, has been used intermittently since then as a way to characterise sluggish cognition, but it became popular again in the 1990s, to describe the experience of living with chronic fatigue syndrome and some autoimmune conditions.

Brain fog isn't a medical condition in its own right, however, and there are no diagnostic criteria. Rather, it is an umbrella term that covers a wide range of cognitive

## **“For many, brain fog lasts weeks, months or even years”**

symptoms, including a lack of mental clarity, memory problems and an inability to focus. "It's a way to describe that one's thinking, memory or concentration are just not as good as they once were," says Andrew Budson at the Veterans Affairs Boston Healthcare System in Massachusetts.

Today, there are dozens of conditions that are associated with brain fog, including allergies, menopause, attention deficit hyperactivity disorder (ADHD) and kidney failure, as well as mental health conditions such as anxiety and depression. "People have been using brain fog to describe a host of cognitive symptoms that come with a wide variety of different medical issues for a very long time," says Anna Nordvig, a neurologist at Weill Cornell Medicine in New York. Because of this, it is hard to pin down statistics on how prevalent brain fog is, but she believes it is more common than many clinicians think.

What we can say is that brain fog is more than just a passing feeling. Most of us have probably experienced dull or laboured thinking at some point, perhaps after an infection, taking medication or even a night of heavy drinking. Generally, that foginess

soon dissipates. But for many, brain fog lasts for weeks, months or even years, according to Suzanne Gilberg-Lenz at Cedars-Sinai Medical Center in Beverly Hills, California. "If you find you are having trouble with brain fog on a regular basis – your memory or your attention isn't working the way it once did and it's disrupting your life – that's when it's a problem and you need to do something about it," says Gilberg-Lenz.

Added to the subjective nature of brain fog is the fact that two people might not experience it in the same way, making it a particularly "squishy" term, says Julie Dumas, a neuroscientist who studies menopause and cognition at the University of Vermont. "Some people have problems with memory, others with attention. Other people are just really tired," she says. All this also makes it hard to measure, which means it hasn't had as much attention as it might have done in the past, she says. When people experiencing brain fog undergo standard tests of cognition, they tend to fall within the normal range of function, "even if they feel like their brains are really failing them", says Dumas.

And like some other neurological issues, such as migraine, brain fog disproportionately affects women, and, as a result, has historically been downplayed by clinicians, according to Brennan. "It's not always been taken seriously by doctors because they've thought that women might be exaggerating or catastrophising what was happening to them," she says.

In the wake of the pandemic, it has become harder to dismiss brain fog. Approximately 10 to 25 per cent of those infected with the SARS-CoV-2 coronavirus develop long covid, a condition characterised by new, returning or ongoing health issues related to the infection. While many people report fatigue, muscle pain and digestive problems, among the top three most commonly reported issues is brain fog. Last year, a survey of nearly 1000 adults in the US with long covid found that almost half reported lasting brain fog, forgetfulness and concentration problems.

### **No clear pattern**

As is the case with brain fog related to other conditions, in people recovering from covid-19, it can be varied. Emma Ladds at the University of Oxford and her colleagues interviewed hundreds of long-covid patients about their neurocognitive problems. They learned that people's lived experiences with these cognitive

issues were broad. “You can definitely see some overlapping problems like with memory or word-finding problems, but there was really no particular pattern to the dysfunction,” says Ladds. “The one common thing between all patients is they described these cognitive problems as being some of the most functionally difficult to live with after covid.”

Muzaffer Kaser, a psychiatrist at the University of Cambridge, and his colleagues have been attempting to quantify the effects of brain fog after covid-19 through the COVID and Cognition (COVCOG) study. They collected subjective reports from 181 people who had previously had covid-19, as well as 185 individuals who hadn’t. They also gave participants a series of standard tests that assess memory, attention and executive functioning – a suite of mental abilities including working memory – to better understand what they were dealing with.

With mild cognitive impairment, a type of memory problem that is a risk factor for going on to develop Alzheimer’s disease, people tend to see around one “standard deviation” from the average score on these cognitive tests. Kaser’s team found that for post-covid brain fog, it was about half this – 0.5 standard deviations. “It may not look like a lot on paper – in fact, it may read as normal to someone who doesn’t have a baseline test to compare it to – but 2 pints of beer will give you a 0.5 standard deviation decline in your cognitive function,” says Kaser. “It’s enough that it can really interfere with your ability to perform day to day.”

## Inflamed brain

So what might be happening in someone’s head to result in such cognitive dysfunction? To perform at our best, different regions of the brain – and the neurons within them – need to be able to communicate efficiently with one another to process and respond to the world around us.

Studies looking at other organs have shown that much of the covid-19-related damage is due to an overactive immune response. That has led many researchers to suggest that inflammation in the brain, caused by that same heightened immune reaction, gums up the neural works, leading to the kind of cell damage and death that makes it harder for brain cells to send signals to one another.

The idea is plausible. The COVCOG study found that the more severe the illness, the greater the cognitive problems. And when



PLAINPICTURE/JESSICA PRAUTZSCH

**Brain fog is one of the most difficult symptoms of long covid to live with**

## “Cell damage might make it harder for brain cells to send signals to one another”

Gwenaëlle Douaud at the University of Oxford and her colleagues compared existing medical records of 401 individuals before covid-19 and then after they recovered, including brain scans, they not only saw greater cognitive decline on cognitive assessments but also tissue damage in certain areas. These included the hippocampus, the brain’s memory hub. Even so, says Douaud, it isn’t possible to say whether these tissue changes are related to brain fog. “We have no way of knowing if any of the infected participants suffered from brain fog,” she says. “But the greater cognitive decline was seen in processing speed and particularly in executive function for infected participants. They had a harder time performing complex tasks.”

Nordvig, however, believes that the “nuts and bolts mechanisms” of covid-19-related brain fog are more complicated than inflammation alone. For instance, we know that SARS-CoV-2 infection can affect the

circulatory system, and it is possible that subsequent blood vessel changes affect the blood-brain barrier, which separates and protects the brain from what is going on in the rest of the body.

Nordvig’s own research suggests that covid-19 may not always result in damage to areas of the brain, but may rather lead to “tissue at risk”. For a host of reasons – ranging from inflammation to compromised blood vessels – there may be brain areas where cells are no longer able to get the nutrients or blood flow they require to work at their best. “There have been a number of studies now that talk about the decreased ability of the brain to pick up nutrients,” she says. “It’s quite patchy, with different small areas affected.” This could explain why there is such a variety in dysfunction between individuals, she says, and why the severity of brain fog often seems to fluctuate. “It’s also actually good news: this tissue is still there and still is functioning, albeit not as well as it could. That means it’s recoverable and there’s the potential for people to get better.”

It is also likely that, in many people, covid-19 is worsening pre-existing conditions that could be related to brain fog. These might include sleep problems, such as sleep apnoea, which we know can affect cognition, as well as migraine and ADHD. Depression and anxiety are also linked to brain fog-like symptoms, and can occur or worsen after a bout of covid-19, especially a severe one.



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“In our clinic, we see a lot of comorbidities,” says Nordvig. “These conditions, as much as covid itself, may be contributing to that overall cognitive dysfunction.”

Studies are also showing commonalities between the brain issues seen following covid-19 and in other conditions associated with brain fog. That increased inflammation, for example, can also be seen in the menopause as well as in depression, anxiety and most autoimmune disease. This makes it all the more difficult to treat.

“We are learning that brain fog is really complicated. There’s not just one thing that you can measure and then fix,” says Nordvig. “There are likely dozens of different factors, beyond inflammation, that are affecting a lot of different bodily systems that ultimately lead to this cognitive dysfunction.”

Even so, the consensus is that the problem is reversible. “We’ve learned that brain fog really is more of a cognitive dysfunction than a cognitive impairment,” says Kaser. “Impairment has the connotation that something is lost and you aren’t likely to get it back.”

While there are no exact statistics, most studies suggest that, provided any underlying medical condition related to brain fog is being managed, people will see improvement within three months. That is why, says Dumas, it is so important to communicate with your doctor not only about your brain fog, but what other symptoms you may be experiencing. One of the best things you can do, she argues, is “treat everything that can be treated”.

That is what happened to Shukis, even if her doctor didn’t have much to offer her in the way of relief. “They basically said it should resolve on



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### Feeling forgetful? A good diet might assist

from the brain, removing molecular debris that hampers neural signalling. A healthy diet, such as the Mediterranean diet, ensures your brain is getting the nutrients it needs for optimal functioning. “What you put into your mouth affects what comes out of your brain,” says Brennan. “Adopting a healthy diet is the best way to get the nutrients your brain needs to work its best.”

As for exercise, it stimulates the production of a chemical called brain-derived neurotrophic factor, sometimes referred to as “brain fertiliser”, because it helps promote repair and enhances the performance of connections between brain cells. And exercise pumps more blood up to the brain. “When you start exercising, the blood flowing to your brain carries extra oxygen and nutrients to your neurons, which optimises signalling,” says Brennan. “With regular physical exercise, people will see improvements in memory, attention and the speed in which you can process information.” Cognitive behavioural therapy can also help people to deal with some of the impacts of brain fog, for instance reduced ability to work and exercise.

Occupational therapy has been shown to help some people with brain fog learn new strategies to mitigate attention or memory issues. And appropriate therapy to help cope with depression and anxiety can also help.

Brain fog remains complex and mysterious, but studies into it are continuing. Ladds and her colleagues are looking at changes in small molecules involved with cell metabolism, known as metabolites, to see if they might help to predict who is at greatest risk of developing brain fog after infection with the coronavirus. And Nordvig and her team are looking for biological molecules involved with brain fog symptoms with the goal of understanding what is happening in the brain and identifying potential targets for treatment.

“The fact that we see so many overlaps with other conditions means we may be in a better position to pinpoint certain molecules, antibodies or other immune molecules that get triggered when you have covid-19 or some of these other health issues,” says Nordvig. “It’s possible we will find some small molecule that can one day become a treatment for brain fog. But it’s going to take time.” ■

its own – and about three months later, it did.”

Despite a dearth of treatments, lifestyle changes can often help, says Brennan. Sleep is a good place to start, because sleep deprivation contributes to those slow and fuzzy feelings associated with brain fog. Making improvements to your diet and exercise regimen can also help.

“We’ve known for a long time what’s good for the heart is good for the brain,” says Brennan. “That includes anti-inflammatory diets like the Mediterranean diet and physical exercise. Physical activity really is one of the best things you can do for your brain to keep it sharp. Even if you just start with a short walk and then build up gradually, it’s a big help.”

Sleep, diet and exercise are all known to help reduce inflammation in the body and brain – and certainly that is of benefit. But there are other explanations, too. Sleep is now believed to promote waste clearance

### Exercise can help lift brain fog in some cases



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