- Brain / Mind and body

Features Cover story



JOEY GUIDONE

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Clear your mind

As we start to understand the effects of chronic inflammation on the brain – from depression to dementia – we are unlocking new treatments, says **Manuela Callari**

GOLAM KHANDAKER's mother has had arthritis for as long as he can remember. She also lives with depression, and it always struck Khandaker how precisely her arthritis flare-ups coincide with her most severe episodes of low mood.

Perhaps it isn't surprising that these bouts of painful inflammation might cause her to feel low. But as Khandaker, then studying for a PhD at the University of Cambridge, investigated more closely, it became clear there was more going on.

In fact, research is revealing the profound effect persistent low-level inflammation has on the brain – which was once thought largely impervious to the fires burning elsewhere in the body – and what this means not only for depression, but for anxiety, schizophrenia, Alzheimer's disease and more. By unpicking the mechanisms driving these connections, researchers are coming up with new ways to protect people's brains and mental health, on top of the many day-to-day ways we can help ourselves.

Our immune defences are vital for survival. When the body detects an infection or injury, it activates an immune response, characterised by a cascade of inflammatory proteins called cytokines, to eliminate the pathogen and promote tissue repair. "Sickness behaviour" can also be triggered – a constellation of symptoms such as fatigue, social withdrawal and loss of appetite that is strikingly similar to major depression. In the acute phase of an illness, this behaviour is beneficial and signals the need to rest and recover during times of physical injury or infection.

Sometimes, however, the acute immune response doesn't fade, and cytokines linger long after the initial battle is won, resulting in chronic low-grade inflammation. This is one of the scourges of the modern world, contributing to heart disease, type 2 diabetes, kidney disease and more. Now, the toll this takes on our brains is also becoming evident.

High levels of inflammatory markers are often found in people with acute mental health conditions. One 2020 study of more than 5000 people with depression, for instance, found they had elevated levels of inflammatory molecules in their blood compared with a control population, leading the study's authors to conclude that "depression is... a pro-inflammatory state".

The fire within

Elevated cytokine levels have also been found in people with schizophrenia and bipolar disorder, and in June, the link between chronic inflammation and mental health conditions was confirmed on a massive scale. An analysis of 1.5 million people from the UK's Our Future Health cohort found that people with conditions associated with chronic inflammation – such as multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease – have almost double the risk of experiencing anxiety and depression, even after adjusting for factors like chronic pain and income.

"The surprising part was that the risk for all the different mental health conditions was pretty much identical [regardless of which inflammatory condition they had]," says Arish Mudra Rakshasa-Loots at the University of Edinburgh, UK, who led the study. "This indicates there is something more going on there beyond just the experience of chronic pain or social isolation." The consistent link across different conditions strengthens the case that a shared biological mechanism – inflammation – is at play.

But teasing apart cause and effect is tricky: does the inflammation cause the illness, or is it a consequence of it?

One of the first researchers to begin to untangle this question was Andrew Miller at Emory University in Atlanta, Georgia, based on observations in the early 2000s that people receiving interferon-alpha (IFN-alpha), an inflammatory cytokine used as a cancer therapy, were developing severe depression. "We knew there was a relationship between increased inflammatory markers and depression, but we didn't know which was the chicken and which was the egg," says Miller.

To find out, Miller and his colleagues carried out a randomised controlled trial, in which people were randomly assigned to receive either the treatment or a placebo. They found that pre-treatment antidepressants decreased the incidence of depression associated with IFN-alpha treatment in people with melanoma, and this causal link has since been replicated with at least two other inflammatory stimuli – endotoxin and typhoid vaccination.

Another way to tease apart causality is to ›

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analyse long-term monitoring studies to test whether pre-existing inflammation increases the risk of subsequent mental health conditions. For instance, Khandaker – now a psychiatrist at the University of Bristol, UK – and his colleagues used data from the Avon Longitudinal Study of Parents and Children in the UK, which measured levels of the inflammatory protein IL-6 in about 4500 children when they were 9 years old. They found that higher levels of this inflammatory marker in childhood were associated with 50 per cent higher odds of depression and a nearly two-fold increased risk of psychosis at age 18. "That clearly suggested that inflammation can precede mental illness," says Khandaker.

The team then used a genetic technique called Mendelian randomisation, which tests whether the association between two things is likely to be a causal relationship or due to some third factor that influences the likelihood of both, such as lifestyle or another illness. In a study published earlier this year, the researchers sifted through 735 immune-related proteins and found strong evidence that specific inflammatory pathways have a causal role in depression, schizophrenia and Alzheimer's disease. Of course, other factors are likely to be at play, too. "We know depression is a psychologically stressful condition, so the associated stress could itself cause inflammation," says Khandaker.

Still, for Miller, the evidence is compelling enough that he expresses frustration with the persistence of the idea that inflammation isn't a cause of depression, but merely a secondary symptom resulting from the lifestyle habits that often accompany it, such as smoking, poor diet and inactivity. "But [research] has shown that inflammation can cause depression," he says.

So, if chronic exposure to systemic inflammation affects our brain and mental health, the question is: how?

When Khandaker attended medical school in the 1990s, the brain was considered an immune-privileged fortress. "It was shielded from the rest of the body by the blood-brain barrier, our professors told us," he recalls.

This barrier – a tightly regulated perimeter of cells – is designed to allow essential nutrients, such as glucose and oxygen, to pass through, while blocking toxins, pathogens, inflammatory cells and proteins. But research is revealing that under conditions of chronic

"This relentless friendly fire ultimately leads to cognitive decline"

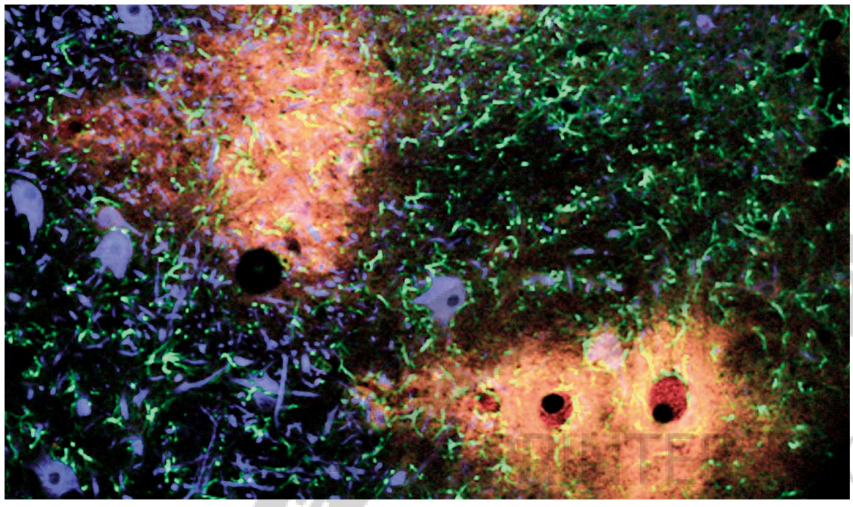
QUENCHING THE FIRE

Many lifestyle factors influence our levels of chronic inflammation. Here are some key findings:

SEDENTARY BEHAVIOUR
More time spent seated or reclining, whether watching TV, sitting in a car or working at a computer, is associated with higher levels of chronic inflammation. This effect is likely to be due to many factors, including reduced activity of an enzyme in load-bearing muscles in our legs and core, leading to abnormal metabolism of fats.

DIETARY FIBRE
Many studies show that a high fibre intake is associated with decreased inflammation. Fibre covers a broad range of different plant-derived compounds that feed our gut microbiome. This promotes gut bacteria to produce helpful substances called short-chain fatty acids, which help maintain the gut lining and have an anti-inflammatory effect on the body.

OBESITY
Obesity is a key risk factor for chronic inflammation, due to the pro-inflammatory effect of excess subcutaneous fat. This means that losing weight is one of the most effective lifestyle changes we can make. One study found that, for people with a form of chronic inflammatory arthritis, weight loss alone leads to significant improvement in symptoms, while also reducing the underlying inflammation.



When the blood-brain barrier breaks, leakage (orange) occurs from blood vessels (round black holes) into brain tissue

C.J.GUERIN, PHD, MRC TOXICOLOGY UNIT/SCIENCE PHOTO LIBRARY

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inflammation or stress, this protective wall can become leaky.

Caroline Ménard at Laval University in Quebec is investigating how this happens using an animal model of social stress – mice that can develop both high inflammation and behaviours akin to depression and anxiety. Using microscopy, Ménard's team saw that in healthy control mice, the barrier appears as a solid, continuous line, whereas in the stressed, inflamed mice, it looks as if it has been "ripped to shreds".

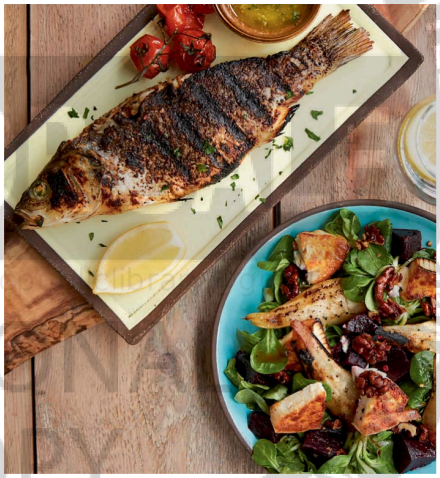
It is through these gaps that inflammatory molecules like cytokines are "sneaking" into the brain, where they can cause oxidative stress and disrupt neurotransmitter production, she says. In 2022, her team discovered similar structural damage in post-mortem brain samples from people who had depression.

The idea is that stress causes a large drop in levels of a protein called claudin-5, which holds the cells of the barrier together. With claudin-5 depleted, the barrier tears, letting inflammatory cytokines enter the brain. Once inside, they can disrupt key neurotransmitters such as dopamine and serotonin in certain areas, leading to reduced activity in brain circuits responsible for motivation. Inflammatory signals can also trigger the brain's own specialised immune cells, the microglia.

Under normal conditions, microglia act as vigilant housekeepers, cleaning up debris and protecting neurons. However, chronic exposure to inflammatory signals can cause these cells to flip from a protective state to a destructive, pro-inflammatory one, initiating a vicious cycle.

This neuroinflammatory state creates the conditions for the development and accumulation of amyloid-beta plaques, a hallmark of Alzheimer's disease. The presence of these plaques then further activates the microglia, which unleash a storm of inflammatory cytokines, such as IL-1beta, IL-6 and TNF-alpha, as well as oxidative molecules in response. This "inflammatory soup" not only causes direct harm to neurons through oxidative stress, but also recruits more microglia to the fight, amplifying the inflammation, says Ravinder Nagpal at Florida State University.

This mechanism also impairs the microglia's ability to perform their primary duty: clearing the very amyloid-beta plaques that are driving the problem, making the situation progressively worse, he says. "This relentless friendly fire ultimately leads to widespread neuronal death and cognitive decline."



GUERILLA/ALAMY

Eating a Mediterranean diet could reduce levels of inflammation

Another major pathway through which inflammation affects the mind originates in our gut. For starters, gut bacteria can produce many different neurotransmitters, which can influence the brain via the vagus nerve. So, when the gut microbiota is in an imbalanced state, known as dysbiosis, caused by a poor diet or antibiotics, this can affect the production of neurotransmitters, says Nagpal. As well as this, "bad" microbes can produce toxins, such as lipopolysaccharides, that damage the gut lining, allowing inflammatory molecules and bacteria to escape into the bloodstream and trigger systemic inflammation, which can, in turn, make the blood-brain barrier leaky.

In contrast, when the gut is in a healthy state, beneficial microbes produce anti-inflammatory compounds, such as short-chain fatty acids, that help maintain a strong intestinal barrier.

This has led some researchers to wonder whether transforming or replacing the gut microbiome could offer a new form of treatment for mental health conditions and neurodegenerative conditions. Emerging evidence, albeit from small-scale trials, suggests that a faecal microbial transplant can alleviate symptoms of anxiety and depression.

A less drastic way to tip our gut microbiome in a healthier direction is via our diet, and there is good evidence that anti-inflammatory eating patterns really do work. The most well-researched is the Mediterranean diet, which entails eating plenty of fruits, beans, nuts, whole grains and fish, with generous amounts of olive oil, while limiting red and processed meats. For instance, one study of nearly 15,000 people in Italy found that a closer adherence to this dietary pattern correlated with reduced levels of inflammatory markers.

The secret isn't a single superfood, but rather the combined effect of the entire dietary pattern, says Rosa María Casas Rodriguez at the University of Barcelona in Spain. "We think it is the combination of different foods that, with different synergies, increases the effects."

We don't yet know about the impacts on the brain, but some other studies show that adhering to a Mediterranean-style diet is associated with a reduced risk of depression, and further large-scale trials are under way.

The benefits of an anti-inflammatory diet may even extend to shielding the brain from dementia. A 2024 study of data from more than 84,000 older adults with pre-existing conditions such as heart disease or type 2 diabetes who participated in the UK Biobank study found that those eating the most anti-inflammatory diet had a 31 per cent lower risk of developing dementia.

To delve into the mechanisms of these effects, Nagpal and his colleagues conducted a small, randomised trial of older adults with mild cognitive impairment. They found that, compared with controls, following a Mediterranean diet that was also ketogenic (very low in carbs and high in fat) for six weeks increased the production of beneficial short-chain fatty acids, particularly butyrate, which is known to be neuroprotective and improve gut barrier health. These changes in the gut microbiome were associated with improvements in Alzheimer's disease biomarkers, such as amyloid plaques, in the participants' cerebrospinal fluid.

Of course, diet isn't the only lever we can pull. What about regular physical activity? ›

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Although higher-intensity exercise can cause a normal, temporary spike in inflammation for muscle repair, there is evidence that, in the long run, physical activity dampens chronic inflammation. It is also clear that a lack of exercise is linked to chronic inflammation. One study from earlier this year of nearly 16,000 people found that sedentary behaviour is correlated with chronic systemic inflammation – which the study's authors called a "sedentary disease". The less you move, the greater the risk.

Sedentary behaviour is also a risk factor for obesity, which has strong associations with chronic inflammation (see "Quenching the fire"). Age is another risk factor, as well as chronic stress, which has a direct impact on the body's inflammatory state by triggering the sustained release of the hormone cortisol. While cortisol normally acts as a potent brake on inflammation, prolonged exposure can lead to a condition where immune cells become less sensitive to anti-inflammatory signals, triggering a cascade of inflammatory cytokines that can disrupt neurotransmitter metabolism and exacerbate depression. To combat this stress response, there is evidence that mindfulness and meditation can help, but Nagpal's advice is to find an activity you genuinely enjoy, as "happiness is one of the key components that can directly reduce stress".

"Happiness is one of the key components that can directly reduce stress"

And then there are medications. In the past decade or so, Miller, Khandaker and others have tested anti-inflammatory drugs typically used for conditions such as rheumatoid arthritis to treat depression, and they have generally found a positive impact. However, perhaps unsurprisingly, these medications have by far the greatest impact on those for whom persistent, low-grade inflammation is driving their illness – perhaps up to 1 in 4 people with depression. "The most pressing question in our field right now is how to identify this group," says Khandaker. This isn't straightforward, because there isn't yet a standard biomarker to measure chronic inflammation, which is a complex process involving a range of different immune substances and cells.

Miller argues that a common blood test for C-reactive protein, a general marker of inflammation, is the "lowest-hanging fruit" for identifying people who might respond to anti-inflammatory treatments, and that this approach is already being trialled in clinics.

But perhaps the most talked-about new approach involves drugs that mimic the satiety hormone GLP-1, such as semaglutide (sold as Ozempic and Wegovy), best known for their dramatic effects on weight loss. While these drugs were originally used to treat diabetes and then obesity, their ability to combat inflammation has put them at the centre of research into cognitive decline and mental health conditions.

Several large observational studies link the use of these drugs to a reduced risk of dementia, depression and anxiety, though, so far, the findings from clinical trials are more of a mixed bag. But all eyes are on the results of two large-scale phase III trials, evoke and evoke+, which are investigating whether semaglutide can modify the course of early-stage Alzheimer's disease, with results expected later this year.

A key question is whether the anti-inflammatory effects of GLP-1 drugs are mainly due to weight loss and better blood glucose control, both of which dampen inflammation, or via a direct effect on the immune or nervous system. Studies presented at the Society for Neuroscience meeting in Chicago last October by the research company Neurofit in Strasbourg, France, show that in mouse models of Alzheimer's, GLP-1 drugs improve cognitive deficits even in healthy-weight animals. "This demonstrates that the beneficial effect occurs directly in the brain, rather than being a secondary consequence of weight loss," says Emile Andriambeloson at Neurofit.

All this highlights how there is still a way to go before we have a full understanding of how inflammation messes with our minds – but the research is already beginning to translate into tangible clinical progress. The other good news is that, for the majority of us who may be unknowingly experiencing long-term low-level inflammation, there are many lifestyle factors that can help simmer down the heat burning within. ▮



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Exercise is another way to dampen down inflammation



Manuela Callari is a freelance science writer