Taming migraine

Migraine and its causes have long been a major mystery. Finally, we are starting to get answers about this debilitating disorder, as **Jessica Hamzelou** reports

I WAS 15 years old and halfway through a family meal when the blow to my head came out of nowhere. It felt as if someone had clobbered me on the side of the skull with a mallet, the sudden pain making me drop my fork. Then came a second hit. And a third. I remember pleading with my sister to stop her noisy whingeing before running to hide under a duvet until the pain eventually subsided. I had experienced my first migraine.

Twenty years later, my migraine-coping technique remains largely unchanged, except that it is now my toddler whose whining becomes unbearable. Migraine treatments don't really work for me. They don't really work for a lot of people.

Despite migraine being among the most common neurological conditions, affecting around a billion people worldwide, we know incredibly little about what causes them, how to avoid them and how best to treat them.

That is partly because migraines are so complex. They impact people differently, can be unpredictable and affect many more women than men. Migraine research has been dismissed, derided and underfunded. But a handful of dedicated scientists have spent decades trying to make progress. For the first time, they have uncovered a mechanism behind migraines in the brain, and with this knowledge have developed treatments not only to relieve them when they strike, but possibly to stop them occurring. Finally, migraine science is having its moment.

For those lucky enough to be unfamiliar with migraines, they can seem far-fetched. Someone can be fine one minute, then suddenly unable to speak or see. The symptoms are varied, and can last from a few hours to days. "We talk about migraine collectively, but actually migraine comes in lots of different forms," says Debbie Hay at the University of Otago in New Zealand. While many people experience headaches – often severe – a migraine is much more than that and can involve other symptoms. "The famous saying is that migraine is just a headache, which is a little bit annoying because it isn't just a headache – it's a brain disorder," says Parisa Gazerani at Aalborg University in Denmark. "Headache is just one of the features of migraine."

Premonitions and auras

Migraine attacks can begin with what is known as a premonitory phase, or prodrome, which can involve a range of symptoms, such as mood changes, neck stiffness and yawning. My prodrome is marked by a vague feeling that something bad is going to happen.

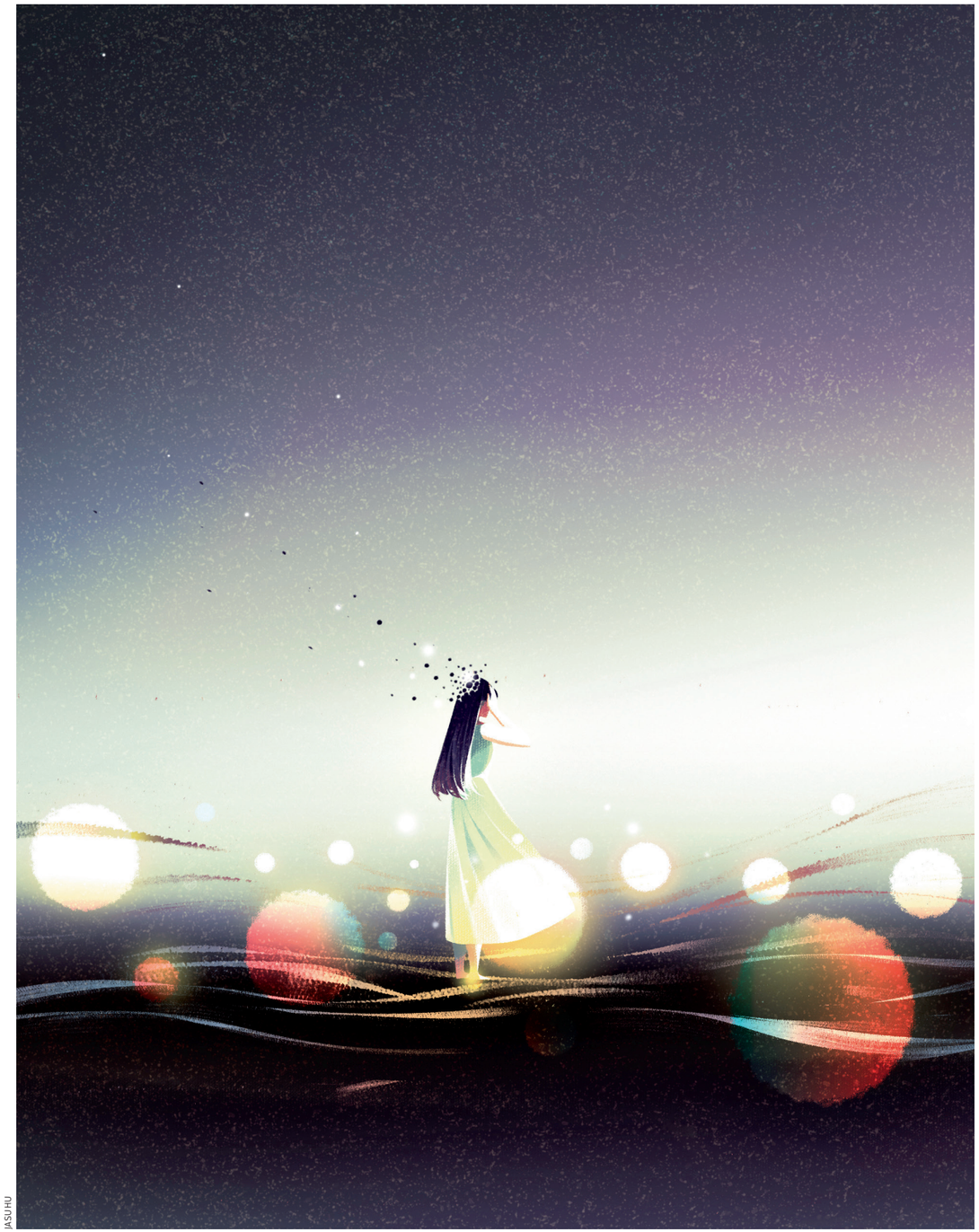
The prodrome is usually followed by the migraine attack itself, which is often associated with pain. The pain can be debilitating and might be preceded by an aura. Aura symptoms – sensory disturbances that might affect a person's vision, speech or movement – can range from mild to unbearable. This can occur independently of any headache. However, the headache tends to be the most debilitating symptom, lasting for minutes, hours or days, depending on the attack and the effectiveness of treatment.

Finally, there is the migraine "hangover", or postdrome, in which some people can continue to feel tired or unwell for days.

Migraine is the third most prevalent disorder in the world and the third-highest cause of disability. The annual indirect cost of migraine due to missed work and reduced productivity is thought to be around $19.3 billion in the US alone – and that doesn't include the substantial cost of treatment.

Despite all this, headache research received less than 0.05 per cent of the US National Institutes of Health budget in 2007. Funding for research on other common chronic conditions, such as asthma and diabetes, received, on average, $153.90 per person experiencing them. The figure for migraine, on the other hand, was a mere 36 cents. People with migraine can be let down at the clinical level, too. Only around 40 per cent of them get a diagnosis, for a start. In the UK, a quarter of those with a diagnosis say they had been having attacks for over two years beforehand, according to a recent survey conducted by the Migraine Trust charity. Most of those who responded were never referred to a headache specialist, and many struggled to get a prescription for migraine treatments.

At a science conference, I once heard a pain ›



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specialist dismiss pain in those who experience migraines as "psychological". "I don't believe this is a one-off experience," says Hay. "The neurologists I speak to in my department are fighting against this all the time."

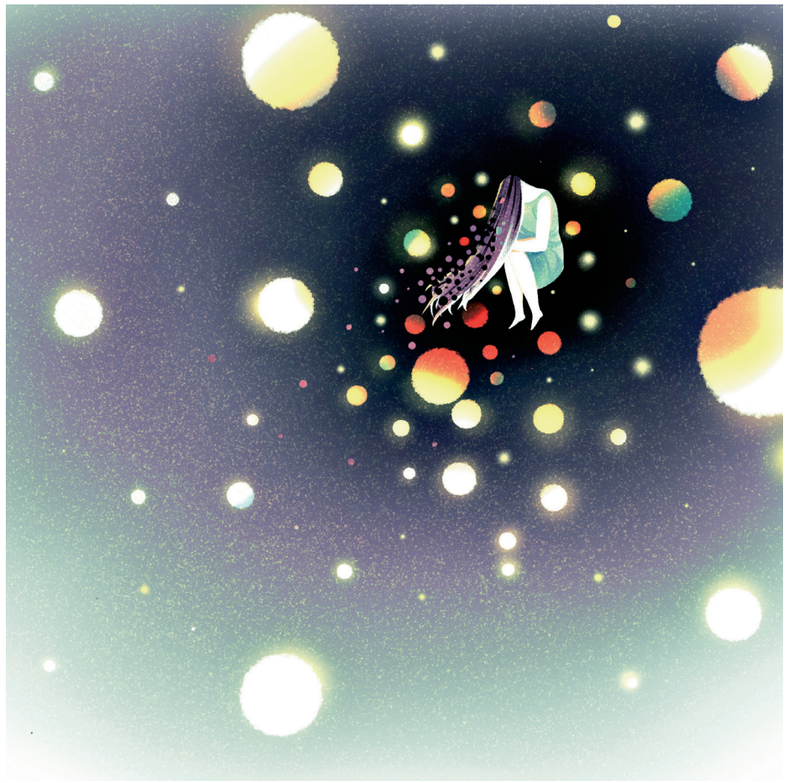
Some of this prejudice can be attributed to the fact that pain is such a subjective experience, and so hard to unravel, and because migraine causes such varied symptoms. Added to which, migraine has been derided as an affliction of hysterical women, says Peter Goadsby at King's College London. "The peak prevalence is at age 40, three women experience it for every male and it manifests around periods," says Goadsby. "It's a prejudice born in prejudice heaven."

Finally, migraine doesn't result in the severe damage to the brain that is seen in degenerative conditions such as Alzheimer's and Parkinson's disease, and in stroke, all of which also affect life expectancy, so understandably attract more funding.

"Migraines affect three women for every man. It's prejudice heaven"

This is something that Lars Edvinsson at Lund University in Sweden experienced first-hand. He found it almost impossible to get funding for his migraine research in the 1980s and 1990s. In the end, he secured funding to study stroke, which "kept me going in science", he says. His migraine research became something of a side project. But he persevered with it and this paid off. Last year it won him, along with three other migraine researchers including Goadsby, the Brain Prize – a prestigious award of 10 million Danish krone (around £1.1 million) in recognition of pioneering work in neuroscience. One revolutionary discovery that led to the win was that neurons, as well as blood vessels, play a vital role in migraines.

The idea that blood vessel dilation causes migraine was originally based on the fact that people who have migraines usually experience a throbbing headache, says Gazerani. This hypothesis was supported by research that involved injecting volunteers with drugs to dilate their blood vessels, which tends to cause headaches and can trigger migraines. The success of triptan drugs in treating migraine threw more weight behind the idea. These drugs, introduced in the 1990s, were the first designed specifically to treat migraine – and seemed to work by constricting blood vessels.



But cracks in the dilation theory had been starting to appear well before then, when neuroscientists developed tools to better measure blood flow in the brain. They saw that people experiencing a migraine didn't appear to have dilated vessels as expected. Even where there was dilation, it didn't seem to trigger the headache, with studies finding it started afterwards and outlasted the pain.

Then, 40 years ago, came the discovery of a chemical called calcitonin gene-related peptide (CGRP) that seemed to influence the function of neurons in the nervous system and the brain, and could also dilate blood vessels. Around the same time, Michael Moskowitz at Harvard Medical School, another of the four 2021 Brain Prize winners, identified the trigeminal nerve – which connects the brain to the face – and its associated blood vessels as playing a key role in migraine pain.

In 1988, Edvinsson teamed up with Goadsby to learn more about what CGRP might be doing. By the mid-1990s, the pair and their colleagues had discovered that CGRP was released from the trigeminal nerve during a migraine attack, pinpointing for the first time a brain chemical that could be triggering migraines. The fourth 2021 prizewinner, Jes Olesen at the University of Copenhagen in Denmark, was part of a team that confirmed this by showing that giving CGRP to people who are prone to migraines caused an attack, and that natural CGRP release could be prevented with sumatriptan, the most often-prescribed triptan drug. Finally, the group had discovered a mechanism for migraine and a possible way to treat it, other than the one type of drug available.

That was desperately needed because triptans come with their own issues. Because they act to constrict blood vessels as well as restrict CGRP, you can't take them if you have a history of stroke, for example. And there are side effects, including nausea, fatigue and neck, jaw and chest tightness. What's more, they don't work for everyone: studies show triptans to be effective in stopping pain within 2 hours in 42 to 76 per cent of people, and even then, they act only on the pain, not the aura.

With CGRP as a target for new treatments, research has now led to new types of drugs for migraine. These block the action of CGRP, but, unlike triptans, don't constrict blood vessels, so can be taken by more people. Some of these are monoclonal antibodies, which are injected every few months to help prevent migraines. Erenumab – one such drug that was found to halve the number of migraine days experienced by volunteers in a clinical trial – was approved by the US Food and Drug Administration (FDA) in 2018, becoming the first new migraine drug since the 1990s. Others have followed, and still more are under review.

"What this tells us, for the first time, is that we can treat migraine acutely and preventatively via the same mechanism," says Hay. "It was always thought it has to be different… This suggests we are targeting a key part of the migraine pathway."

Goadsby and his colleagues have also been developing new CGRP-targeting drugs, called gepants, that don't have to be injected. Two have been approved for use by the FDA for treatment of acute migraine, and there is evidence that one might also be useful for preventing the onset of attacks.

Getting real

The discovery of the CGRP mechanism and the development of new migraine-specific drugs have gone a long way to highlight the status of migraine as a real neurological condition, too. "Now we have mechanisms, and we have specific drugs, and that makes a difference," says Edvinsson. "You can't argue with biology," says Goadsby.

Despite these breakthroughs, we are still some way from understanding exactly what causes an attack in the first place – in other words, what fires up the trigeminal nerve. The aura that many people experience offers some clues to the pain side. Brain-imaging studies have shown that, during an aura, there is a wave of changes in brain activity, starting from the occipital lobe at the back of the head. Neurons first switch on, then off again, and this pattern spreads across the brain. This helps to explain some of the common symptoms of aura – flashing lights are thought to result from the switching on of neurons in the visual cortex, while blind spots are likely to occur when nerves switch off, says Goadsby.

Research now suggests that something about this wave of activity irritates pain-sensing neurons in the membranes that surround the brain, or that it triggers the trigeminal nerve to release CGRP.

Goadsby, however, thinks that aura and pain are two separate phenomena that both happen to be triggered by something that occurs in the prodrome. "It's not that aura causes pain, it's that something else causes both," he says.

Other mysteries remain, too. One elephant in the room is the fact that migraine affects so many more women than men. People tend to experience their first migraines around puberty, and the incidence rises throughout adulthood, before declining after menopause. Some people find that their migraines disappear during pregnancy or become ›

HOW DOES A MIGRAINE START?

Migraines are thought to begin in the hypothalamus, a cone-shaped structure at the base of the brain. That is because many of the early symptoms align with known functions of the hypothalamus. Yawning, tiredness and mood changes – common features of migraine onset – are all controlled by the hypothalamus.

The exact role it plays in triggering migraines is unclear, but some kind of signal seems to cause a wave of disrupted brain activity. Studying people with migraines in brain scanners has revealed that the wave starts at the back of the brain, in the occipital lobe. This is where the visual cortex is located, and the fact that the wave begins here helps to explain why so many people have visual symptoms as part of the migraine aura that often precedes the headache.

The wave of disruption seems to spread from the back of the brain to the front. The path of disruption can vary, and this might explain why people who have migraine with aura experience such a wide range of symptoms. A path through the left hemisphere might leave some people struggling with language. Disruption that reaches the motor areas at the front of the brain might cause the sensation that your arms are made of lead.

The cause of migraine headaches is less clear, but plenty of research suggests that the trigeminal nerve, which affects the head and face, releases chemical signals that cause pain (see main story). Most researchers believe that blood vessels also play a role.

HENRIK SORENSEN/GETTY IMAGES

A higher prevalence among women suggests that certain hormones may be involved in migraines

more frequent during perimenopause, which precedes the menopause.

All this implicates certain hormones. "We have found that trigeminal neurons contain receptors for oestrogen and oxytocin," says Edvinsson. So the hormones might influence the perception of pain in migraine, he says. Both hormones are known to fluctuate with menstrual cycles and are more stable in men.

At Leiden University in the Netherlands, Gisela Terwindt is part of a team trying to unpack the link through a study looking at levels of several sex hormones in blood samples from female volunteers who experience migraine to see if they fit with the timing or symptoms of migraine attacks. The team is also giving volunteers contraceptive pills containing synthetic oestrogen to see whether this helps with migraine, a commonly touted treatment despite a lack of evidence. "It's not without side effects, so we need clear proof," says Terwindt.

Another lingering question is why there is so much variation in symptoms between people who have migraines. My auras usually start with flashing lights. A friend of mine sees light in zigzags during her migraines, and some people develop blind spots or tingling sensations.

"It might be that we're classifying it too broadly, and actually there are multiple individual diseases here that we haven't quite got a handle on diagnosing," says Hay. "It could be an individual combination of different genes in a person that's creating their unique experience."

Terwindt has spent much of her career trying to understand the genetic factors. She was part of the team that identified the first gene linked to familial hemiplegic migraine – a subtype that is thought to have an especially strong genetic component – in the 1990s.

Heritable headaches

Since then, Terwindt has been looking for genetic factors that might explain more common types of migraine. After all, if one or both of a person's parents experience migraine, there is a 50 to 75 per cent chance that person will experience attacks too. "We recently published that there are more than 123 places on the genome which may be implicated in migraine," she says. "It's quite complex."

On top of all that, we still haven't answered perhaps the biggest questions: why and how migraines start in the first place.

People who experience migraines often have a list of things that seem to trigger them, and are usually advised to keep a migraine diary, so they can keep track of any changes in their routines, diets or anything else that seems to reliably occur before a migraine.

But how might things like stress, a lack of sleep or a cheese-laden snack lead to an attack? Some researchers believe that the brains of people who get migraines have a lower threshold for responding to stimulation, and that certain stimuli can essentially tip them over the edge, switching on neural activity that leads to the attack. Given the common early signs, such as yawning and tiredness, it might also be that some sort of change in the brain's hypothalamus, which is linked to things like this, is triggering the attack (see "How does a migraine start?", page 41). And some apparent triggers, such as food cravings or bright lights, might simply be a result of the attack already being under way. "If you think chocolate gives you headache, but actually the craving starts during the premonitory phase, then avoiding chocolate doesn't make [any] difference," says Goadsby. "Punishing yourself for things doesn't make any sense."

What is clear is that, given the huge variation in migraine, what works for one person won't necessarily work for another. Some trials in which people take a high daily dose of vitamin B2 have found that some, but not all, of them experience fewer migraines. One man made headlines in November for seemingly curing his migraines with a diet rich in leafy green vegetables. That doesn't mean that others should start swapping triptans for kale.

It is also clear that more treatments are desperately needed. No single drug so far works for everyone. And many of those who do benefit still experience migraine attacks, even if they are reduced in number or severity. "That tells us we haven't quite figured out that system properly, or that there are more factors involved," says Hay.

Until we discover what those factors are, there are things that doctors, employers and all of us can do to make life better for people who get migraines. One step is to improve knowledge among doctors. "The amount of training healthcare professionals receive is abysmally small," says Hay. She is also a proponent of changing the language used for migraines, to bring it in line with the way we describe other neurological conditions. "You don't have a migraine, you live with migraine, and sometimes you have an attack," she says.

I'm one of the lucky ones – my migraines have decreased in frequency and severity since I entered my 30s, perhaps due to the hormonal changes of pregnancy. Given the propensity for migraine to run in families, I hope that the new buzz around migraine research will mean my whingeing toddler won't have to hide under her own duvet a decade or so from now. ▮

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