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Not just a headache: How migraine changes your brain

Migraine changes the way you experience the world all the time, not just during an attack. It's time for a new approach to treatment

Christina K

By **Helen Phillips**

“WELL a very, very heavy ah heavy duit burtation tonight. We had a very deres dereson. But let’s go ahead tarish tasen losh lobitt behend dupet.” News reporter Serene Branson’s unintelligible live TV commentary on the 53rd Grammy awards ceremony in 2011 made her an overnight internet sensation. As the paramedics attended, the worry was that she’d suffered a stroke live on air. Less-kind pundits blamed drugs, stage fright, or alcohol. In interviews shortly after, she revealed she’d been having a migraine.

I too have experienced this type of migraine “aura”, though thankfully rather less publicly. In mid-sentence, with absolutely no warning, I began talking drivel. I couldn’t find the right words, but I also couldn’t stop myself garbling nonsensical phrases with similar starting sounds or patterns to the words I sought. I was mortified. A few minutes

later I developed a steadily expanding blind spot edged with a semicircle of dancing black-and-white zigzags. Several days later came the most intense headache imaginable. I was 19.

Migraine is often thought of as an occasional severe headache, sometimes accompanied by strange visual effects and nausea. There's a feeling it isn't really serious because once the headache is over the person goes back to normal. But these bizarre and disturbing aura symptoms alone should tell us there's far more to migraine than meets the eye. Over the past decade, research has been building a picture of a condition which is much more serious than many give it credit for. It shows that migraine is caused by real structural and functional differences in the brain, and that people who experience migraines feel, see, touch, hear and respond to the world differently all the time, not just during an attack. Perhaps more worrying, the disorder, and the brain changes that accompany it, seem to be progressive, getting worse with each attack. "Migraine is a more serious condition than people have thought," says David Borsook of Harvard Medical School in Boston. "These repetitive strikes change brain networks, and we are just beginning to understand those."

More than 37 million people in the US alone experience migraine, although an estimated 50 per cent of sufferers, also known as migraineurs, go undiagnosed. Given these recent findings then, it's time to rethink how we tackle, diagnose and treat the condition. "We need to stop calling migraine a vascular disease or a pain condition," says migraine expert Peter Goadsby, who splits his time between King's College London and the University of California, San Francisco. "It is a neurological disorder."

The effects of migraine have been documented for centuries, but only now are brain imaging technologies allowing us to see the big picture. Most media attention so far has focused on reports that MRI brain scans of some people with migraine show tiny areas of damage, which show up as small bright spots on the image. In 2004, Mark Kruit from Leiden University Medical Center in the Netherlands and his colleagues scanned the brains of around 300 people with migraine and found that they were more likely to have such bright spots than carefully matched controls. Some of the spots, mostly in the cerebellum, related to changes in the deep white matter, which is the insulating sheath that allows nerve fibres to send electrical signals efficiently and is now also known to be important in learning and memory.

Worryingly, other spots closely resembled the kinds of damage you would expect to see in the brain of someone who'd had a stroke. The incidence of these so-called stroke-like lesions was not high, but it was statistically significant – they were apparent in around 8 per cent of cases of migraine with aura compared with 5 per cent of controls.

Stroke-like damage

As if the words "stroke-like lesions" weren't worrying enough, no one is quite sure what these spots of damage on the brain are, or what they mean. We already know that having migraines puts people at greater risk of stroke – especially those with aura and cardiovascular risk factors such as blood pressure problems, who smoke or are obese, and women taking certain oral contraceptives. "Because the blood flow to parts of the brain related to the aura first increases then decreases, it is possible that the changes are related to small strokes," says Richard Lipton of the Albert Einstein College of Medicine in New York, who recently published a detailed review of structural brain changes in migraine. But as both he and Kruit's team are quick to point out, the spots

don't appear to cause symptoms, or make migraine worse.

To find out what's really going on, these changes needed to be monitored. Do regular migraines cause more areas of stroke-like damage? And to what effect? Kruit and his team rescanned most of their volunteers nine years later. Interestingly they found the number of spots had slightly increased over time in women with migraine, but not in men, but they didn't correlate with migraine frequency, severity, or treatment. Neither did the spots seem to have any bearing on cognitive functions like memory or attention. Another long-term study in France found no link between migraines and cognitive decline, all the way to age 80.

That is good news given that even silent strokes – where damage to the brain can be seen on scans without there being any clinical symptoms – have been shown to be a risk factor for cognitive decline and dementia later on.

According to Kruit, the spots may relate to having the "disease" of migraine, rather than being caused by successive attacks. And it doesn't look like the brains of people with migraine age faster, says Lipton.

So the jury is still out on the significance of the stroke-like lesions in migraine. However, there are other, less-talked-about structural changes in the brain which may be much more important. These differences relate directly to the changing and increasing severity of migraine symptoms over time. Several groups have now described changes in the thickness or volume of various brain areas in people with migraine, and they seem to underlie the sensory, emotional and sex differences in people's experience of the condition.

In one study from 2007, Nouchine Hadjikhani and her team at Harvard Medical School found thickening of a region known as the somatosensory cortex, which maps our sense of touch in different parts of the body. They found the most significant changes in the region that relates to the head and face. "Migraine has always been considered as an episodic problem," says Hadjikhani. "But if you have a series of episodes of pain in the face area, it increases cortical thickness." If people have frequent migraines, they often develop a condition called allodynia, where even normal touch can feel painful. Estimates vary, but this condition is thought to affect at least a quarter of migraineurs. "It's an important finding," she says. "Migraine could have long-term consequences.

Her group has also identified thickening in the visual cortex, which makes sense when you consider how frequently migraine attacks are accompanied by visual disturbances. One of the physiological features of a migraine attack is a storm of neural activity called cortical spreading depression that passes in a wave across the brain's surface.

Hadjikhani's group was first to record this epilepsy-like activity in a brain scanner during migraine aura, in a visual region that responds to flickering motion. The study confirmed a long-suspected link between spreading depression and the aura that often precedes migraine pain. "People with migraine often have a history of motion sickness, sensitivity to stripes or certain visual stimuli," says Hadjikhani. "And we found increased cortical thickness in these visual areas."

She admits they don't yet know whether the changes cause the areas to produce these storm waves or are a result of them. Indeed other work suggests that spreading depression may occur all over the brain, often unnoticed, and may even happen in

healthy brains. So aura may be the result of a person's brain being more sensitive to spreading depression.

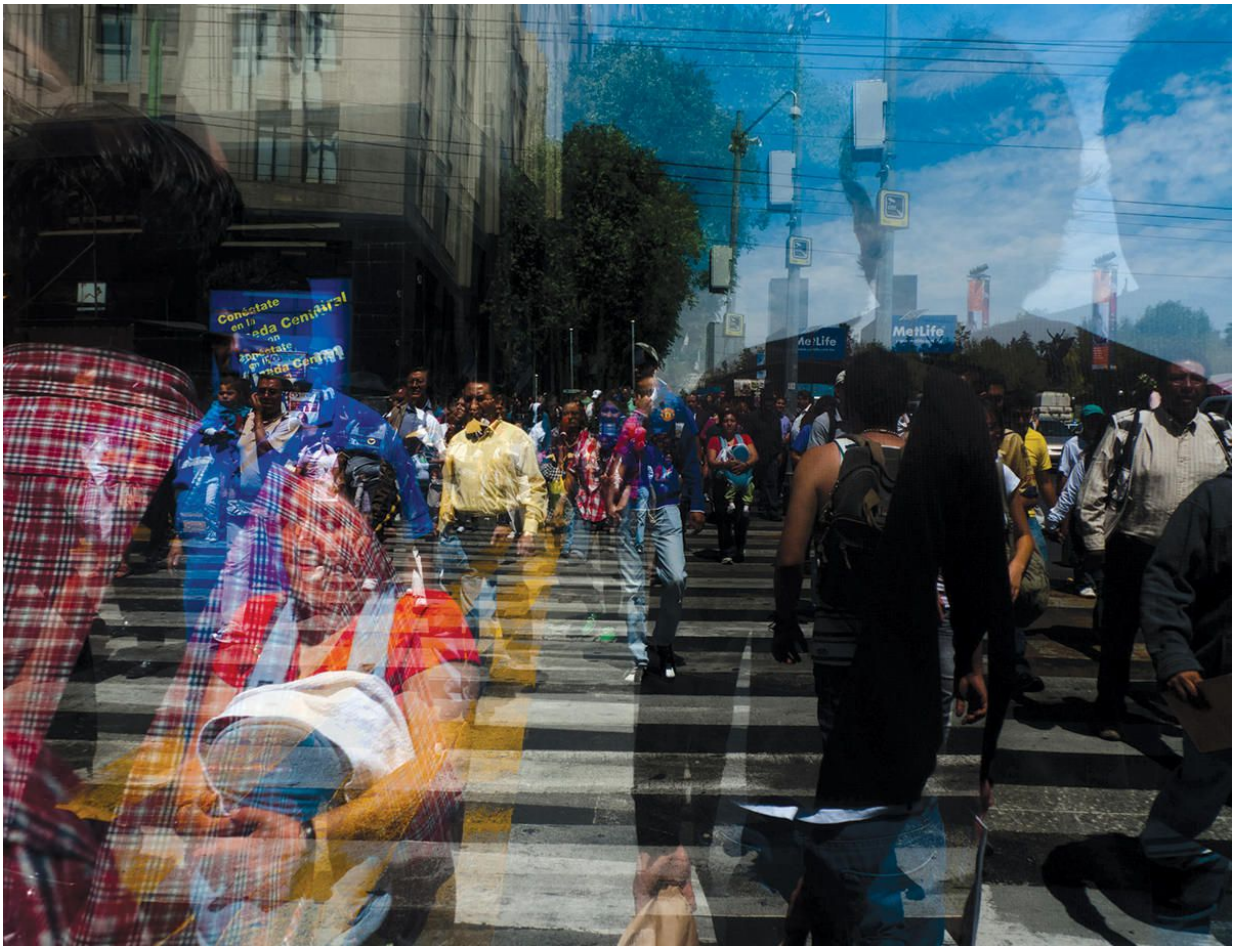
The list of structural changes, often in the form of thickening, has been growing in recent years, so that now there is barely a region of the migraine brain that has been found to be unchanged. This list includes sensory and emotion areas, and the hippocampus – which is involved in autobiographical memory and navigation – along with reward networks, frontal areas involved in planning, cognition and voluntary actions and, not surprisingly, regions that involve pain. "We have to look at [the possibility] that the whole brain is altered," says Borsook, with different structures being more or less involved. "The whole migraine brain is very excitable," he adds, "much more excitable than in healthy subjects." His suspicion is that repeated attacks make it that way. Indeed, Hadjikhani's team also found microscopic structural differences in the thalamus, an area that transmits sensory information to the cortex and controls its excitability. "It was as though small pathways had become highways to transmit the pain, says Hadjikhani. "Using the system repetitively makes it work more efficiently."

But it is perhaps functional changes in the hypothalamus that have caused most excitement in the medical world. The hypothalamus is vital for controlling internal body states – things such as sleep and waking cycles, metabolic balance, feeding behaviour, stress, and hormone cycles – all of which are linked to migraine attacks. Migraineurs will recognise many of the symptoms controlled by circuits around the hypothalamus: nausea and vomiting, nasal congestion, watering eyes, excessive urination, thirst and hunger, cravings, yawning and tiredness. "The idea that the hypothalamus is a critical centre in migraine is not new," says Borsook, "but we now know that there are functional differences in how the hypothalamus interacts with other brain areas in migraine."

Functional MRI scans enable researchers to look at how closely correlated the activity of different brain areas is. In people who get migraines, such scans revealed raised "functional connectivity" in the circuits between the hypothalamus and areas that control automatic regulation of our body states. These areas normally respond to all sorts of stressors including cold, hunger and exercise. This makes the circuits much more sensitive. Think of the level of sensitivity as a threshold. If you haven't slept well or eaten properly, your over-sensitivity to dysfunctional activation allows your brain to overreact, and go into a full-blown migraine attack. What's more, says Borsook, this sensitivity seems to increase during an attack, and with more severe or more frequent migraines.

A better grasp of these structural and functional changes may also be the key to understanding one of the most curious aspects of migraine – that it affects around three times as many women as men. Nasim Maleki, also at Harvard Medical School, and colleagues including Borsook, found that the biggest differences between male and female migraineurs were in two brain regions. One was the precuneus, an area that is likely involved in self-awareness, which fits with my own experience of migraine – I always describe the pain as coming from the part of my brain where I feel "I" am when I close my eyes.

The other is the insula, specifically the posterior insula, which is involved in sensory processing and control of our automatic body functions. The insula is an intriguing part



The brain attends to all sorts of things it should be ignoring
Alex Coghe/plainpicture

of the emotional brain, involved in several important functions including sensation, autonomic regulation, understanding our internal state (interoception), and "salience", in other words judging what is important right now. Both areas were thicker in women with migraine than in men with the condition.

When it comes to functional imaging of male and female brains, Maleki's team found that migraine in women seems to involve more activity in emotion circuits than in men. The pain may be a more emotional experience for women, and anecdotally many do report feeling intense mood swings before and after migraine strikes. There is also a strong association between depression and migraine. Female sex hormones may well underlie the differences, somehow making the circuits more sensitive to change with repeated attacks, but the mechanism is not clear.

Borsook is now studying how migraine progresses in children as they enter and pass through puberty, and has found stark differences between boys and girls. "There's no question that when boys go through puberty there's a good chance their headaches will resolve," he says, "and in girls, a good chance their headaches will get worse."

Work with children is adding weight to the idea that migraine is a progressive brain disease, which may appear in different ways at different stages of life, beginning with some kind of genetic susceptibility. One startling suggestion is that infant colic, the uncontrolled crying and fussiness often blamed on sensitive stomachs or reflux, may be an early form of migraine. Goadsby and colleagues have looked at the prevalence of migraine in mothers of babies with colic, and early indications are that it is more

prevalent in the family of colicky babies. In a study of 154 mothers whose babies were having a routine two-month check-up, the migraine sufferers were 2.6 times as likely to have a baby with colic. It is possible that a baby with a tendency to migraine may not cope well with the barrage of sensory information they experience as their nervous system starts to mature, says Goadsby, and the distress response could be what we call colic.

So what are we to make of all this research? The brain of a person with migraine is emerging as oversensitive, and increasingly so with successive attacks. Perhaps not surprisingly, researchers are finding corresponding differences in brain function, even between attacks. Marla Mickleborough, a vision specialist at the University of Saskatchewan in Saskatoon, Canada, found heightened sensitivity to visual stimuli in the supposedly "normal" period between attacks. People with migraine are less able to tolerate staring at a bare light bulb, for example.

Her findings draw on previous work showing that the brain's response doesn't "habituate" as it would normally do. Usually the brain comes to see something repeating over and over again as unimportant, but in people with migraine the response doesn't diminish over time. Suspecting that the problem was related to attention, Mickleborough recently tested visual attention in migraineurs. "They seem to be attending to things they should be ignoring," she says: "They find it hard to concentrate." It matches anecdotal reports and my own experience that especially in the day or two before an attack, I find myself easily distractable and unable to settle at my computer. I can't tolerate flickering adverts, or ignore TV screens and am much more distracted by music or talking.

Hard to ignore

Mickleborough also finds that migraineurs do not perform well in tests of negativity bias – a well-studied psychological phenomenon in which we pay more attention to stimuli we don't like, perhaps because they have a higher chance of being important and threatening. The fact that migraineurs don't do this could add to the general feeling of being distracted by numerous stimuli all at once and finding it harder to focus on the right thing.

The idea that our brains are different, and growing ever more so with every attack, is deeply worrying for those of us who experience migraine. It's a wake-up call for doctors to treat the condition more aggressively, and to find out more about each individual's particular triggers (see "Trigger trouble") so as to stop attacks from happening, rather than let people suffer through each one while it sensitises the brain.

But there is a silver lining. Despite talking about migraine as a progressive neurological disorder, these structural changes should not be likened to dementia, Alzheimer's disease or ageing, where brain tissue is lost or damaged irreparably. "That's the wrong way to look at it," says Borsook. In migraine, the brain is compensating, he says. "Even if there's a genetic predisposition, it is the disease itself that is driving networks to an altered state." That means that treatments that reduce the frequency or severity of migraine will probably reverse some of the structural changes too. Lipton agrees.

"Headache begets headache," he says. Treatment used to be about reducing the immediate pain, he says, but now it seems that finding good treatments for migraines may have much longer-term benefits.

Read more: "How to understand and deal with migraines"

Relief ahead

As we learn more about the underlying neural mechanisms of migraine, new treatments are emerging. Brain stimulation will be huge in the next five years, says Peter Goadsby of King's College London.

Transcranial magnetic stimulation (TMS) and other techniques that deliver small electrical currents through electrodes on the forehead are already proving effective in some cases of migraine, as well as for chronic pain conditions and depression.

These treatments seem to work by steadily altering and normalising oversensitive brain circuits, though at present it's not clear how. One big advantage is that they are well tolerated compared with other therapies, including drugs and botox – which is approved for migraine treatment by the US Food and Drug Administration.

TMS and the like also have scope to treat people who have become insensitive to migraine drugs, those who experience rebound symptoms (see "If you get them..."), and women who are pregnant or breastfeeding.

A huge change in drug treatment is on the horizon too. The first group of medicines to be developed specifically for treating migraine is just a few years from the pharmacy. These block a molecule called calcitonin gene-related peptide, or CGRP. Goadsby first found CGRP in the blood of people experiencing a migraine attack nearly 30 years ago.

Now, a handful of drugs that interrupt CGRP receptors are being tested for episodic migraine, and monoclonal antibodies, which bind to the receptors for longer, are being tested for people with chronic migraine. Several candidate drugs are in phase II trials. These could be ideal for tackling the long-term effects of migraine on the brain.

Types of migraine

Migraine with aura Warning signs before the migraine begins, such as visual distortions

Migraine without aura Migraine occurs without warning signs

Silent migraine Aura or other migraine symptoms are experienced, but no headache

Chronic migraine Experienced at least 15 days in every month

Episodic migraine Occurs occasionally

Abdominal migraine Usually occurs in children. Recurring attacks of abdominal pain

Menstrual migraine A specific condition where the attacks occur around menstruation and at no other time

Hemiplegic migraine Attacks include paralysis or weakness on one side of the body

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Helen Phillips is a consultant for *New Scientist* and author of *Emotion: Pleasure and pain in the brain* (OUP, 2014)

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