

Breaking the pain cycle is going to take more than drugs, says Jessica Hamzelou

Hitting where it hurts

EMMA PAYNE'S day starts at 6 am, when the pain from her joints wakes her. She takes prescription painkillers and stays in bed until late morning, when they finally kick in, giving her a few hours of respite before the pain returns. "By 3 pm, all my joints hurt, whatever I've done," she says. The rest of the day passes in a cycle of ever-stronger painkillers, rounded off with sleeping pills. Payne has lived this way for the past two years, not only struggling with the pain but grieving for the active life she had before.

An estimated 10 million people in the UK and a fifth of the world's population has chronic pain, lasting 12 weeks or more. For many of them, treatments provide little relief. Even the strongest drugs often don't eliminate discomfort, and come with serious side effects. Not to mention they are addictive, make pain worse long-term and are all too easy to accidentally overdose on.

Now, though, researchers are starting to tackle the problem by rethinking the root causes of chronic pain. Rather than seeing it as a lingering version of the acute form, they have begun to recognise it as a complex disorder of the nervous system that changes the brain's structure, chemistry and activity. Such thinking could help dispel the myth that there is nothing wrong with those with chronic pain, and could lead to a new wave of treatments.

Part of the problem has been that most research into pain hasn't been asking the right questions. The majority of what we know so far is based on research into acute pain, says Marco Loggia at Harvard University.

When we experience an injury, the nervous system sends a pain signal to the spinal cord and the brain. The spinal cord provides the rapid reaction that makes you recoil from the

source of the injury – a hot surface, for example. Your brain tells you you're in pain, and enlists a complex set of structures, including emotion and memory networks, to help you remember that pain for future reference.

In chronic pain, says Loggia, this system goes awry. The pain signal doesn't switch off, and the brain networks involved in pain start to change their activity, telling you you're at risk of injury when you're not. "Acute pain is mostly helpful, but chronic pain is not," says Loggia. While acute pain is like an alarm state, as it becomes chronic, the patterns of brain activity begin to change, he says.

Neuroimaging is starting to reveal physical differences between the brains of people with and without chronic pain. This suggests doctors should be looking at people's brains when there is no obvious physical explanation for their pain. "If doctors examine a patient and see nothing, they don't understand why the person is feeling pain," says Marwan Baliki at Northwestern University in Chicago. "But they are looking at the wrong region – they are looking at the back or stomach, for example, when they should be looking at the brain."

In a recent study, Baliki and his colleagues scanned the brains of people with back pain, and re-scanned them several times over the

In the US, **259 million** opioid prescriptions were dished out in 2012 – more than one for every adult

SOURCE: ASAM.ORG/DOCS/DEFAULT-SOURCE/ADVOCACY/OPIOID-ADDICTION-DISEASE-FACTS-FIGURES.PDF

12 per cent of adults in the UK take prescription painkillers

following three years. They found that two brain structures in particular – the hippocampus, which is the brain's memory hub, and the amygdala, which processes emotion – were 10 to 15 per cent smaller in people who went on to develop chronic pain. "The brain was the strongest predictor of whether a person's pain became chronic or not," says Baliki.

What's more, those who went on to develop chronic pain lost grey matter unusually quickly in the years that followed. "Patients with persistent chronic pain experience about 8 to 10 per cent greater grey matter loss than those without pain," says Baliki. Each year lived in chronic pain causes as much brain shrinkage as 10 to 20 years of healthy ageing, he adds.

His team are studying mice to investigate why some people might have smaller hippocampi and amygdalae to begin with, and how this might affect their chance of developing chronic pain.

As for the cause of grey matter loss, there's evidence that the immune system might be involved. Researchers started entertaining the idea in the 1970s, after they noted that people in chronic pain display "sickness behaviour", becoming lethargic, anxious and sometimes depressed. This is a well known side effect of the immune system's inflammatory response, which is thought to have evolved to encourage us to rest when ill or injured.

In the brain, the inflammatory response is linked to glia – brain cells that outnumber

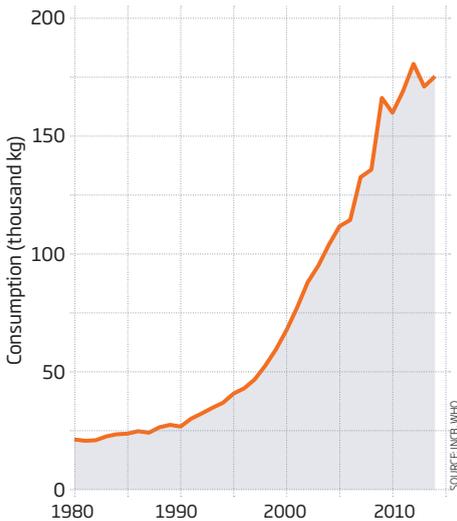


MARTIN LEON BARRETO

Four out of every five new heroin users in the US started out on prescription opioids

On the up

Opioid drug use has rocketed over the past few decades, but there is no evidence they work long term



neurons and fulfil a structural and maintenance role in the brain. Some forms of glia stimulate inflammation, while others filter harmful substances, repair injuries or clear debris. Using a chemical that binds to active cells, Loggia's team were able to track their activity in people who had had chronic back pain for two years or more and people without chronic pain.

Pain in the brain

Sure enough, they found striking differences between the groups, with those experiencing pain having significantly higher glial activity than the pain-free participants. The difference was most pronounced in sensory areas corresponding to the site of their back pain and in the thalamus, a region that acts as a gateway from the senses, including the sensation of pain. "You could just look at an individual's scan and tell by eye whether they had chronic pain or not," says Loggia.

They have since used the approach to look at the brains of people with fibromyalgia, a mysterious syndrome that causes pain all over the body. Volunteers with fibromyalgia also had more active glial cells in their brains, although this time in the cerebellar cortex and the medulla – regions that are linked to movement and automatic functions like breathing and digestion. Why they might also have a hand in pain is not yet clear.

Nevertheless, the findings suggest that

different types of chronic pain could be described as different brain immune disorders, each with a particular pattern of glial cell activity, says Loggia, who presented the work at the World Congress on Pain in Yokohama, Japan, in September.

Whatever triggers the immune system in the first place, its involvement makes sense because we know it can affect pain directly. Research in animals has shown that the chemicals produced by glial cells can act to sensitise the nerve pathways that deliver pain signals, lowering their trigger threshold. "They essentially turn up the pain volume," says Peter Grace at the University of Texas MD Anderson Cancer Center.

They might also be responsible for the brain shrinkage seen in chronic pain. In healthy brains, glia help shape the connections between brain cells to optimise the communication between them. Over-active glial cells might prune too many connections.

If confirmed, these findings could have huge implications for people living in chronic pain, many of whom feel they are not believed by their doctors, employers or even friends and family, and are accused of being lazy or making things up. "A lot of people see fibromyalgia patients as a bunch of malingerers – that there's nothing wrong with them," says Loggia. "If we can show that there is inflammation in the brain, we can provide more evidence that the disorder is real."

The research could also point to new treatments for chronic pain. Drugs that dampen down the activity of glial cells might be one option, and several candidates are in clinical trials. The hope is that such treatments could be given to people before their brains become sensitised and their pain becomes chronic. "If we could shut down glial cells, we could shut down the pain sensation," says Grace.

Even if these kinds of treatments work, they are unlikely to be enough on their own. Chronic pain is a complex beast. As the disorder develops, it implicates more brain regions, such as those involved in emotion and memory, changing their activity, too.

Recent research has shown that emotion-linked pain has a separate pattern of activity that is distinct from pain processed from a site of injury. While both networks are active in response to an injury, the emotion-linked pain signature is what neuroscientists commonly see in the brains of people with chronic pain whose physical symptoms of injury have healed. This suggests that the signals from psychological pain networks may take over

when the problem becomes chronic.

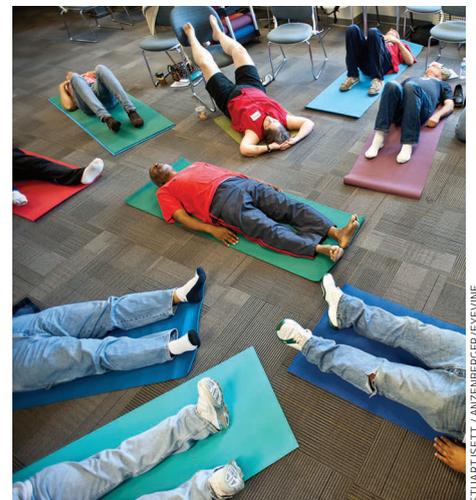
This raises the possibility that psychological interventions might be effective. A 2010 review of 30 studies concluded that, for people with chronic lower back pain, cognitive behavioural therapy and other coping techniques are more effective than standard treatments.

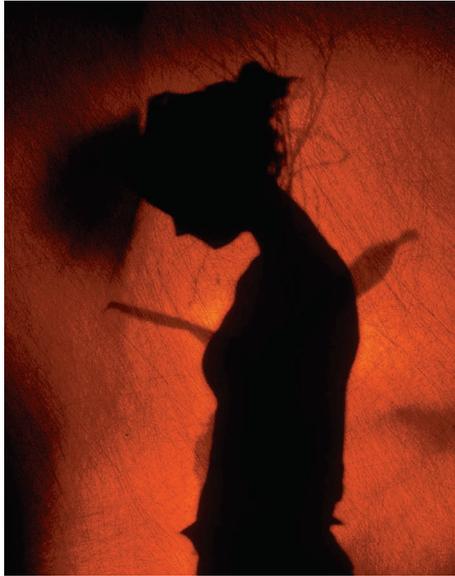
People can even be trained to more directly influence their own brain activity and, potentially, turn down the pain signal. In neurofeedback, electrodes placed on participants' scalps are linked to a real-time display of their brain's electrical activity. With training, people can learn to alter their brain activity to dial down their pain. Preliminary studies suggest that neurofeedback might be useful for people with fibromyalgia, as well as those with chronic pain resulting from spinal cord injuries and cancer.

Mindfulness meditation is a lower-tech way to achieve something similar. The goal is to achieve a state of "detached observation", which can help people cope with pain. Studies so far suggest that it improves various types of chronic pain, including fibromyalgia and lower back pain. What's more, a study of 17 people who practised mindfulness-based stress reduction found that, over time, meditators experienced increases in grey matter in regions of their brains involved in learning, memory and emotion – all of which influence pain perception. It's also cheap, and can be done anywhere with a little training.

Exercise is helpful, too, although if the pain starts with an injury, it can prove both physically and mentally challenging. If a person learns that a movement is painful,

Learning to cope with pain through exercise may be more effective than drugs





Many of those with chronic pain feel that people don't believe them

or a limb is delicate, the information can become crystallised in the brain, almost like a phobia. In these cases, it can be worth re-learning to move the body. Evidence suggests that exercise can improve the symptoms of lower back pain and chronic fatigue syndrome, which also causes pain.

Advocating these non-pharmacological approaches might sound controversial – surely no one wants to be told they just have to think positive or move more. But people with chronic pain are desperate, and most will try anything. “If you’d have told me to stand on my head and bark like a dog, I would have done it if it might help my pain,” says Payne.

What is most important is that we all recognise chronic pain for what it is – a neurological disorder in dire need of effective treatment. “These aren’t weak people – they have a physical disease in their brain and spinal cord,” says Grace.

For her part, Payne has taken matters into her own hands, seeking out talking therapies and alternative remedies to help manage her brain’s response to her pain. And while we wait for better treatments to become available to all, she advises others to read as much as they can about their condition. “One of the first things I did was educate myself about pain,” she says. “That education has brought me a certain peace of mind that I’m not going mad.” ■

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What is itch for, and what does it have to do with pain? Stephani Sutherland investigates

When pain feels good

AS WE improve our understanding of chronic pain, there is a related problem that has researchers scratching their heads.

The sensation of itch, which shares many nervous pathways with pain, has long been a mystery. One reason is that it can be conjured up entirely by the brain. Just thinking about something tickly, or even watching someone else scratch, can set us off. Efforts to find out why this is, and why only scratching makes it stop, have led researchers to study how itch is processed in the skin, spinal cord

165,000 people in the US died from prescription opioid overdoses between 1999 and 2014

SOURCE: CDC.GOV/DRUGOVERDOSE/DATA/OVERDOSE.HTML

and brain. In recent years they have begun piecing together a more complete story of what itch is for – and what to do when an itch can no longer be scratched.

Itch, like chronic pain, is a surprisingly common problem. It comes as a side-effect of opioid painkillers, the use of which has rocketed in recent years (see graph,

p 36). It also comes with skin conditions such as eczema as well as nerve damage, kidney disease and allergies. An estimated one in five of us will experience chronic itch at some point, and current remedies are providing little relief.

The most common treatments are antihistamines, which block the part of the immune reaction that causes itching when we are bitten by a bug, for example. Not all itches are immune-related, however, and antihistamines have proven to be ineffective for most forms of chronic itch. Neuropathic itch, which stems from damage to sensory nerves in the skin, has no effective treatment.

In recent years, researchers have discovered new kinds of receptor in the skin and spinal cord that play a role in the sensation of itch. They are working to figure out what naturally activates these receptors in the hope of designing drugs that can deactivate them.

For now, though, the single most effective way to get rid of an itch is what we do instinctively: to scratch. But why do we rake our nails across our skin, when it causes pain and, potentially, tissue damage?

The answer lies in the way that the spinal cord is wired, says Sarah Ross, a neurobiologist at the University of Pittsburgh. Neurons that transmit long-distance messages between the body and the brain are bridged by smaller ▶