Cracking how our brain perceives pain could lead to treatments for even the most agonising conditions. **Clare Wilson** investigates

Pain be gone

OUCH! I have just been stabbed with a pin in the tender skin between my thumb and index finger. But instead of snatching my hand away, I lie still and carefully rate the experience, as instructed. Despite the initial shock, the discomfort is minimal and I score it a mere 1 out of 10.

I am lying on my back with a Darth Vader-like helmet immobilising my head. An MRI scanner is recording the blood flow in the different parts of my brain, while a team of researchers from the University of Oxford inflict pain on me.

What's their agenda? Most of us might assume that when we feel pain, its intensity is determined by the amount of injury to the body: how hard we were hit or how badly we were burned. But unconscious and conscious processing in the brain can also amplify or dampen the incoming pain signals, making an injury more or less painful. In the past decade or so, advances in brain scanning techniques have led to a wealth of new insights into these ways in which our mind shapes our suffering. The results of my scan will join this growing body of research.

This line of enquiry could lead to some novel forms of pain treatment. The most obvious application is to develop better pain-relieving drugs that directly target the brain regions involved. But the Oxford group and others around the world are also investigating more unusual approaches, to gain control of the neural processes that govern painful feelings. Ultimately, it may even be possible to train people to switch off their suffering at will.

Pain is seen as one of the banes of human existence. Yet its harsh lessons are essential for teaching us to safeguard our fragile flesh. The uncomfortable or agonising sensations warn us to leap back from danger and to rest and guard our injured body parts while they recover. Those with rare genetic conditions who feel no pain suffer repeated injuries and occasionally die young from infected wounds they hadn't noticed.

This evolutionary rationale is cold comfort to anyone actually experiencing pain, however, especially for those with long-term, or chronic, conditions like backache, arthritis or nerve damage. These disorders are surprisingly prevalent – according to several studies, between 10 and 20 per cent of adults in the west are in some kind of chronic pain. Backache is particularly difficult for doctors to treat, as in most cases a physical cause cannot be identified.

Current analgesics like paracetamol (acetaminophen), codeine and morphine offer some respite. These drugs act through a variety of mechanisms that block pain signals from being transmitted through the brain. Their value for certain complaints is questionable, though. "Nearly everything that's prescribed for chronic back pain is no better than placebo at the moment," says Vania Apkarian, a neuroscientist at Northwestern University in Chicago.

To make matters worse, these drugs often come with undesirable side effects. As a result, neuroscientists are always on the lookout for new ways to fight pain. Brain scans are proving to be a vital tool in this hunt, as they illuminate the various neurological and psychological processes that affect how much we suffer.

The idea that our minds control what we feel certainly fits with the anecdotal evidence. We have all heard tales of a soldier in the heat of battle only noticing their injury after reaching safety, for example. More commonly, we may be so absorbed in a good book we forget about a nagging toothache, say. Although these experiences are not the norm, they hint at the possibility of hijacking certain brain processes for pain relief.

That's partly what is motivating Irene ›

WAYNE MILLER/MAGNUM

Actual injury is just one of many factors shaping pain perception

"The team were considering rubbing my hand with capsaicin, the chemical that gives chilli peppers their heat. In the end, they settle on sticking pins into me"

Tracey, who heads the Oxford team. I first met her at a lecture held by the British Neuroscience Association in 2009, when she explained their approach was to stick people in MRI scanners and, essentially, torture them. "I have stuck pins into people, electrocuted them, burned their skin, and put balloons up their rectums and inflated them," she said. "We're always looking for volunteers."

Chatting to Tracey after her lecture, I rashly agreed to become one of her guinea pigs in exchange for a tour of her state-of-the-art MRI lab. When the appointed day arrives, I turn up feeling more than a little apprehensive. We have not discussed the method of pain infliction in advance, but I'd rather not have any balloons stuck up my rectum today, thanks all the same.

The pain matrix

The alternatives sound little better. I'm told that the team had been considering rubbing my hand with capsaicin, the chemical that gives chilli peppers their fiery heat. In the end, they settle on sticking pins into me, which apparently gives more consistent results.

The study is investigating how the brain's perception of a persistent pain changes over time, so each pinprick lasts for 5 minutes. Luckily for me, the worst pain I am subjected to is a mild 4 out of 10. Aside from the discomfort, my main impression is that an MRI scan is a lengthy and boring process, and a noisy one, too: at times it sounds like some road drilling is going on close by.

One day, my scan results will add to the literature identifying the different regions of the brain involved in processing pain signals. "Fifteen years ago we didn't have a clue," says Tracey. The initial hope was that a single discrete area of the brain controlling pain would be found, in the same way that vision is controlled by the primary visual cortex at the back of the brain, also known as V1. "We wanted to find P1 for pain," she says. "But it's just not like that." In fact so many different areas have been found to be involved that they are now known as the pain matrix.

What do all the different parts of the matrix do? Existing knowledge of brain anatomy gives some clues. The amygdalae, for example, which are twin almond-shaped structures buried deep in the brain, are known to be involved in the fear response and so probably have this role during pain too; perhaps they teach us to be wary of things that hurt us. The prefrontal cortex, at the front of the brain, is where executive-level thought goes on, so it is probably involved in our conscious response to pain.

Further insights have been gleaned by manipulating people's thoughts and feelings to see how this changes activity in their pain matrix and their perception of pain. "We can tweak one parameter and see which parts become more excited," says Tracey.

Take the fact that a good book can lessen a toothache. This highlights one of the key psychological modifiers of our pain experience: how much attention we are paying to it. Tracey's group has shown, for example, that when people are given a counting task in the scanner, they feel less pain, and several parts of the pain matrix show reduced activity (*Brain*, vol 125, p 310).

Mood and emotion have turned out to be equally important. Last year, Tracey's team showed that making people feel depressed in the scanner heightened the pain they felt from a hot probe, as well as boosting activity in several parts of the pain matrix (*Biological Psychiatry*, vol 67, p 1083). The researchers made their volunteers read demoralising statements like: "I am worthless" and played mournful music – Prokofiev's *Russia Under the Mongolian Yoke* at half its normal speed.

In a different approach, a group at McGill University in Montreal, Canada, tried to manipulate people's mood by puffing different smells under their noses (*The Journal of Neuroscience*, vol 29, p 705). Bad smells, like rotten fish, put people in a bad mood, and made them rate the pain as more unpleasant, while nice smells like violets or lemon meringue had the opposite effect.

Sniffing violets to reduce mild discomfort is all very well, but what relevance does this kind of research have to the 1 in 5 people who suffer from severe, long-term pain? Tracey hopes that doctors will one day be able to help people with backache, say, by scanning their brain. "We want to get an individual MRI map that I can interpret and say the reasons you're in pain are X, Y and Z," says Tracey. "Then we can target where we are going to treat it."

Suppose, for example, the scan shows that someone's pain is heightened by feelings of depression or anxiety. In that case antidepressants or psychotherapy might provide more pain relief than dosing up with ever stronger analgesics. Alternatively the scan could show excessive activity in the areas of the brain associated with our conscious attention. That would suggest the patient might benefit from cognitive behavioural therapy, a type of psychotherapy that in this case would be designed to distract people from pain and so reduce its impact on their lives.

"The hope is that with training people may learn how to switch off their pain, simply by making a conscious effort"

Unfortunately, although such measures help in treating chronic pain to some degree, trials have found that they rarely provide a complete cure, suggesting other factors come into play. Tracey suspects it may be down to some troubling, long-lasting changes to the brain. "When you get conversion from the acute warning pain to the pain that goes on for years, there are new mechanisms that go wrong inside the brain – mechanisms that sustain and amplify it," she says.

Apkarian agrees, having published several studies showing that people with bad backs have altered brains. They have less grey matter in several sites of the brain, for example, and more activity than normal in their medial prefrontal cortex when their pain flares up (*The Journal of Neuroscience*, vol 26, p 12165). "The brain is reorganising in these patients," he speculates. "It amplifies the pain signal."

There is a drug, cycloserine, that has been shown to damp down activity in this part of the brain, in rats at least. Apkarian hopes to begin trials of cycloserine in people with backache very soon. The compound is already licensed as an antibiotic for tuberculosis, so it shouldn't have unexpected side effects, particularly since the dose for treating TB is five times as high as that for relieving pain. "I'm very optimistic," says Apkarian.

As well as identifying specific targets for new pain-relieving drugs, brain imaging may improve the accuracy of clinical trials of such drugs. Currently, the only way to gauge someone's pain is to ask them to score it out of 10, giving a somewhat variable and subjective measure. This means that trials need large numbers of patients to generate a statistically significant result.

Tracey's group is trying to develop an objective measure based on people's brain activity in the scanner, which should allow trials to generate useful results with fewer patients. "The beauty of imaging is it's so sensitive," says Tracey.

Her team has tested this approach by comparing two known analgesics with placebo treatment. Although the results have not yet been published, last year they found that MRI scanning could clearly distinguish between the relative effectiveness of the drugs and placebo in a study of only 16 people. This was an important proof of principle that brain scanning can successfully quantify different levels of pain, says Tracey. "The next experiment would be to do it with a novel compound to decide whether to progress with it."

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Most pain-relieving drugs come with undesirable side effects

Drugs are not the only way to change brain activity, though, and mapping the pain matrix has suggested some promising alternative routes to pain reduction. One possibility is biofeedback, which involves giving someone a visual read-out of one of their physiological functions, like heart rate or brain waves, so they can try to influence it by pure force of will. The technique has a flaky reputation, since it has been marketed as a treatment for conditions ranging from asthma to autism, with little evidence to back it up.

Would it turn out to be more helpful when tackling pain? To find out, Sean Mackey, a pain specialist at Stanford University in California, set up a video screen inside an MRI scanner that showed an image of a flame. For some of the trials, the size of the flame varied according to activity in the subjects' rostral anterior cingulate cortex, an area thought to be involved in our conscious perception of pain. In the rest, the participants were given fake feedback. Each person was asked to make a conscious effort to reduce the size of the flame. The result? Those who saw and controlled their real brain activity significantly reduced their subjective feelings of pain compared with the subjects who saw sham feedback (*Proceedings of the National Academy of Sciences*, vol 102, p 18626).

The technique worked, both for people with various types of chronic pain and for healthy volunteers subjected to a hot probe on the palm. "The ability to see their pain in their own brain was a powerful tool to allow them to control it," says Mackey.

The hope is that further training might enable people to switch off their pain outside the scanner, simply by making a conscious effort. Ideally, Mackey would also like to replicate the effect with EEG-based biofeedback training, which would involve much cheaper and more widely available equipment.

Electrical control

If MRI scanning ever reveals the coordinates for an area or areas of the brain that can switch off pain, it raises the possibility of trying to control it electrically too. Techniques such as deep brain stimulation (DBS), where an electrode is inserted deep into the brain, and transcranial magnetic stimulation (TMS), which involves applying a magnetic field close to the head, have both been used experimentally on people with intractable pain. A few successes have been reported but both methods have severe limitations: DBS requires a risky operation, while TMS can only be performed in a lab. As a result, these approaches are generally considered a last resort.

A newer technique does exist, though, that uses simpler equipment and seems to be relatively safe. Direct cortical stimulation involves placing electrodes on the surface of the scalp and passing a current that stimulates or blocks electrical activity in the underlying brain areas. Tracey hopes to identify parts of the pain matrix that are close enough to the surface of the brain for such stimulation.

Still, it will be a long time before treatments like MRI-based biofeedback and direct cortical stimulation become mainstream, if at all. David Borsook, a psychiatrist at McLean Hospital in Belmont, Massachusetts, points out that the neuroimaging field is still so young it is hard to evaluate research papers from different groups. "We have different cut-off points or slightly different methods of setting up and acquiring data," he says. "We need standards of good imaging practice."

Evidently, there is a long way to go, though the start has been promising. "Imaging has transformed the way people think about chronic pain," says Borsook. "It is the future of pain treatment." ■

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