IMAGING

Show me where it hurts

Technology for peering into the brain is revealing a pattern of pain, and differences between the acute and chronic forms.

BY SIMON MAKIN

Researcher Tim Salomons examines brain scans as a person is subjected to laser stimulation in a scanner.

NATHAN CLARKE

David was lying in the brain scanner, showing no signs of reacting to an intense laser beam shining onto the back of his hand. Several minutes into the procedure, he said: "We should maybe stop this laser." When asked why, he replied: "It's starting to feel like when I used to burn my hand with a lighter."

Thanks to a rare genetic mutation, David cannot feel pain. "Most of us don't need to think: 'What does this feel like that I've experienced before?'," says Tim Salomons, a neuroscientist at the University of Reading, UK, who was part of the team running the study that David took part in. "It shows the role pain plays." Using a common brain-imaging technique called functional magnetic resonance imaging (fMRI) to measure brain activity, the team found that a painful stimulus activated the same regions in David's brain as it did in healthy controls[1].

Although this seems to cast doubt on the relationship between brain activity and pain, imaging studies in general have revealed much about how the brain processes pain. Some have found patterns that might offer a way to measure pain objectively, whereas others are exploring the differences between acute and chronic pain.

PATTERNS OF PAIN

In contrast with most other senses, conclusive evidence of a brain region dedicated to pain is lacking. Instead, pain is usually associated with activity in numerous areas — a 'pain matrix' of regions reliably activated by painful stimuli. These include the somatosensory cortices, which process sensory aspects of pain alongside sensations such as touch and temperature; and the anterior cingulate cortex and insula, which are thought to be important for emotional and motivational dimensions of pain (such as pulling your hand out of a fire). Other areas include the prefrontal cortex (the seat of higher cognitive processes) and the thalamus (a 'relay hub' for sensory and motor signals).

Pain-matrix regions are not specific to pain, they are also activated by attention-grabbing stimuli such as flashes of light and loud banging sounds. These stimuli trigger processes involved in detecting important events, directing attention and readying for a response. Because pain also grabs attention, Giandomenico Iannetti — a neuroscientist at University College London who worked with Salomons on the fMRI study — argues that pain-matrix activity may have more to do with the importance of painful events than with the pain itself.

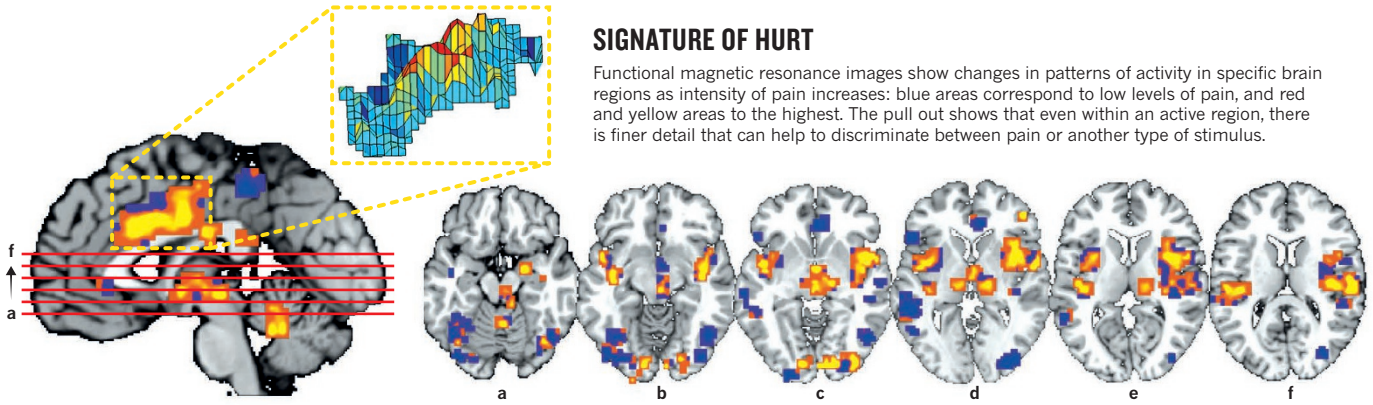
But others think that hidden within that general activity is something more specific. Tor Wager, a neuroscientist at the University of Colorado Boulder, used machine-learning techniques to classify patterns of activity over multiple brain regions — predominantly the pain matrix — to develop a 'neurological signature' of pain[2] (see 'Signature of hurt'). "We're showing very specific patterns within these regions that do encode pain," he says. "Other patterns encode other things, but we can separate them." For instance, among their other functions, pain-matrix regions are also activated by emotional experiences, such as social rejection and empathy for, or memory of, pain — leading some to say that those feelings also hurt, to some extent. But although rejection and physical pain share a dimension of emotional unpleasantness, heartache is clearly different from being stabbed in the chest — and this distinction can now be discerned in the fine detail of brain images. Wager's group used its system to distinguish painful heat from non-painful heat; actual pain from anticipation, or recall, of pain; and physical from emotional pain. The group's algorithm was able to correctly reject the non-pain experiences around 90% of the time, and determine actual pain with more than 90% accuracy — an impressive combination of specificity and sensitivity. Wager's system also predicted perceived pain levels and showed that administering a potent opioid drug significantly reduced activation.

"We're trying to develop measures that really track the pain that you feel, based on things that come up from the body," says Wager.

MIND OVER MISERY

Pain can also be influenced by factors such as expectation (which feeds into the placebo effect, see page S14), attention, emotion and even personality. Imaging is allowing researchers to investigate how these elements manifest in the human brain. The ability to exert control through willpower and imagination, known as self-regulation, can alter pain perception. But Wager's group found that self-regulation had no effect on the neurological signature[3]. It did, however, affect activity in other brain regions, most notably the nucleus accumbens, which operates through connections to the medial prefrontal cortex to form a circuit within the brain's reward network. The perception of pain, it seems, is not the result of one system. "The pain signature we developed is a really important component of pain," Wager says, "but it's not a complete description."

Imaging is already helping to determine those other components of pain. Researchers know from animal studies that attention and emotions can modulate pain through a descending system



SIGNATURE OF HURT

Functional magnetic resonance images show changes in patterns of activity in specific brain regions as intensity of pain increases: blue areas correspond to low levels of pain, and red and yellow areas to the highest. The pull out shows that even within an active region, there is finer detail that can help to discriminate between pain or another type of stimulus.

TOR WAGER; SOURCE: REF. 2

that connects parts of the brain's cortex and limbic system (the emotion centre) with various regions in the brainstem, which connects with the spinal cord (see page S2). This enables higher brain areas to enhance or inhibit pain signals. "What imaging has proven is when you're sad, anxious or distracted, it doesn't just change the way you express pain, it changes the physiological processing," says neuroscientist Irene Tracey. Her group at the University of Oxford, UK, has been using brain-imaging technologies to examine pain modulation in humans. One study[4] has already identified which brainstem regions reduce pain signals when a person is distracted, and they are now trying to identify risk factors and brain networks that might make someone more vulnerable to developing chronic pain. "We're using imaging to help explain why someone's painful experience is a particular way — and what mechanisms lock them into that state," says Tracey. "These provide exciting alternative targets for therapies." The hope is that a likely transition from acute to chronic pain can be prevented.

Chronic pain is a huge global burden, affecting around one in five people (see page S4). "We have no scientifically validated treatments for these patients," says physiologist Vania Apkarian at Northwestern University in Chicago, Illinois. "It's a massive health situation." Apkarian's group has found many functional and anatomical features that are unique to the brains of people with chronic pain, helping to establish that acute and chronic pain are fundamentally different. "By definition, that makes it a disease state," says Apkarian. Finding out whether such differences are the cause or consequence of chronic pain is trickier.

To tackle this question, Apkarian's group conducted the first longitudinal brain-imaging study of chronic pain[5]. The researchers followed 39 people with recent back pain for a year, periodically conducting brain scans. Over this period, those who developed chronic pain showed reductions in grey-matter density in the insula and nucleus accumbens. The researchers also found that measures of connectivity between the medial prefrontal cortex and nucleus accumbens taken at the start of the study predicted with around 80% accuracy who would develop chronic pain — stronger connections conferred higher risk. In a follow-up study, Apkarian's team tracked brain activity associated with perception of back pain and found that, as pain became chronic, activity shifted to brain regions associated with emotion and reward[6]. The extent of this shift was also related to the strength of the connectivity between the medial prefrontal cortex and the nucleus accumbens.

These findings reveal the circuitry that seems to trigger the transition from acute to chronic pain, together with the anatomical changes that are the consequences of it. "This disambiguates the chicken and egg of chronic pain," says Apkarian. His team has also shown that the main determinant of chronic pain is not the injury, but the properties of the person's brain, he adds. And, in rodents, the researchers have been able to block the transition from acute to chronic pain using drugs that inhibit neurons in the nucleus accumbens[7]; a trial is under way to see if this works in humans. "I'm confident we will quickly develop a whole series of new treatment options specific for different types of chronic pain," says Apkarian.

> ***"The use of the technology is getting ahead of itself."***

The brain regions that Apkarian identified are the same ones that Wager's group found to be involved in self-regulation. So, although this reward-learning and emotional circuitry is not part of the neurological signature for acute pain, it does seem to play a key part in chronic pain. "We're learning something about how different kinds of pain have different bases in the brain," says Wager. "What's driving your pain might not be the classic pain processes."

PAIN-O-METER

Could these developments bring us closer to being able to measure pain objectively? Such readings would be useful both for drug development and for people who can't express whether they are in pain, such as infants, people in a coma or those with dementia. Several companies in the United States are already offering a service that they say can detect a person's pain signature. And there has been at least one case in which brain scans have been accepted as evidence of chronic pain in US civil courts. But many researchers have grave concerns. Importantly, Wager's results don't apply to chronic pain. "The technologies Tor and others use involve recording how the brain responds to a stimulus," explains neuroscientist Karen Davis of the University of Toronto, Canada. "In chronic pain there's no stimulus, so we need a different approach."

Last December, the International Association for the Study of Pain, based in Washington DC, set up a task force, chaired by Davis, to study the use of brain imaging to identify pain. Over the next year it will produce guidelines on what the technology can and cannot do, whether it is accurate and reliable enough for legal settings, and what the ethical and social issues are. A key concern that Davis and many other researchers have is that fMRI might give misleading results. Certain drugs, for instance, can change vascular function and thus the fMRI signal without having changed brain activity. "Using a vascular-based technology has issues that people haven't been considering," says Davis. Getting this right will be crucial if brain imaging is going to play a part in evaluating pain. "The use of the technology is getting ahead of itself, and there are enormous legal and neuroethical implications," says Davis.

Put someone like David in the brain scanner and you get a false-positive result — he doesn't feel pain even though his pain matrix is active. Conversely, a lack of activity might seem to imply an absence of pain. But most researchers agree that such a conclusion would be unwarranted. "We can confirm pain of certain kinds," says Wager. "But you can never, even in principle, disconfirm pain — because a person's brain might just be unique." ■

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