Finding the Hurt in Pain

By Irene Tracey, Ph.D.

Editor's Note: Pain is unique to every person, and difficult to quantify and treat. Whether it is delivered as a jolt or a persistent, dull ache, pain is guaranteed to affect one's quality of life. Our author examines how brain imaging is opening our eyes to the richness and complexity of the pain experience, giving us extraordinary insight into the neurochemistry, network activity, wiring, and structures relevant to producing and modulating painful experiences in all their various guises.

A wise man, purported to be Oscar Wilde, once said: *"I don't mind pain, so long as it doesn't hurt."* Packed into that flippant comment may be insight beyond his intent.

The ability to experience pain is shared across species. Acute pain is the body's alarm and warning system and, as such, a good thing. It is key to survival, and is evolutionarily old. All living things have the ability to detect factors in the environment that might 'hurt' and cause injury, harm, and, ultimately, perhaps death. These factors are lumped into thermal, chemical, and mechanical categories. Without pain you simply don't survive. We know this, sadly, because a rare genetic condition, congenital insensitivity to pain, produces a phenotype in people such that they don't get the 'good' warning pain after damaging themselves; historically, they didn't survive to adulthood due to the consequences of unfelt injury.

Why does congenital insensitivity to pain cause death and why does experiencing pain aid survival? One reason is that pain motivates decisions to act. Think about an everyday painful experience: One picks up something hotter than expected. One's options are drop it and make a mess or grin and bear it until a solution is found. In an instant one has detected it's hot (thermal), it's on the hand (location), it's painful (intensity), one doesn't like it (unpleasant), attention is now fully directed toward it (cognition), and one is unhappy about it (emotional). But what is one going to do?

Based upon learned responses, past experiences, and competing other interests (being told off for dropping it) we make a decision and act. Recruiting extraordinary brain-based networks, we're able to block the pain and get the hot item safely to a place where we can set it down. Then we act again to nurse our injury—perhaps running our hand under cold water. For the person who cannot feel pain, there is no warning sign and the injury, perhaps considerably more than the one described, might produce an undetected infection and subsequently death. So, pain is essential for survival.

The nature of pain, however, is hard to understand and pin down, and is, in a word, complex. Pain, by definition, is a subjective and private multidimensional experience. Further, it's highly malleable, depending upon the context and the cognitive and/or emotional state in which we experience the

injury. In short, subjective pain is not linearly or simply related to the tissue damaging signal input. The classic soldier on the battlefield or sportsperson not experiencing pain during an injurious tackle on a rugby pitch are the exemplars illustrating how evolution has fined-tuned our nervous system to be capable of changing the pain experience we have. Why? Because this means we'll make the right decision about how to act in response to that pain. For the interested reader, there are several excellent books that discuss pain and its importance to life and influence on history and society that I recommend.[1-5]

Understanding Signals

Confronted by a lion, we can make the decision to scream in agony after he or she has bitten our arm off or block the pain from this injury so that we are better able to run away. Similarly, if we can modulate the incoming signals from the damaged tissue (nociception) along its journey to the brain, from which the conscious experience of pain emerges, then perhaps we can generate a pain-like experience without a nociceptive input using brain-based networks when perceiving a threat of pain. Historically, if people reported pain in the absence of identifiable tissue injury, it was called 'psychogenic' pain. Back in the day, this was a pejorative term because there was little understanding of the mechanisms that underpin nociceptive processing and pain generation by the peripheral and central nervous system. The same was true for patients having undergone a placebo test to 'catch them out.'

Now we know better and such terms are respected. Indeed, the very definition of pain by the International Association for the Study of Pain (IASP) allows for pain occurring with and without tissue damage: *"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."* The IASP goes on to say that an inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Individuals learn the application of the word 'pain' through experiences related to injury in early life. As such, we must always trust what they say about *their* pain, irrespective of what looks like a similar injury because this will be felt and experienced differently for these and other reasons, such as genetic and epigenetic influences. Pain is not a unitary thing and no two pains are the same, even in the same individual.

Despite this complexity, can we do better in understanding why someone's pain is the way it is? What about the demented elderly, comatose individuals, anaesthetised patients, or nonverbal infants who don't have speaking skills or options to describe their pain? Brain imaging has been one such tool that has opened our eyes to the richness and complexity of the pain experience, giving us extraordinary insight into the neurochemistry, network activity, wiring, and structures relevant to producing and modulating painful experiences in all their various guises. Techniques such as functional, diffusion, and structural magnetic resonance imaging; positron emission tomography; and electro- and magneto-encephalography are now widely used to understand acute and chronic pain.[6-8]

The High Costs of Chronic Pain

Chronic pain is defined as pain that persists beyond normal tissue healing time. It is estimated that one in four adults has a persistent pain state that, on average, lasts approximately seven years (20 percent for more than 20 years). As such, it brings considerable suffering to patients and their families, alongside significant costs to society (estimated at 200 billion Euros annually in Europe and $630 billion annually in the US). Co-morbid problems like depression, anxiety, and sleeplessness are inherent in chronic pain.[9]

Sadly, current treatment options don't provide adequate relief to the majority of patients. As such, it's one of the largest medical health problems worldwide. But scientific research at a preclinical and clinical level using an array of techniques—from molecular and cellular biology to advanced neuroimaging—is giving us unprecedented insights into chronic-pain states. A paradigm shift in our thinking has occurred, one that is slowly unraveling throughout the medical and scientific communities.

We've stopped thinking about chronic pain as a continuation of what caused the initial, perhaps acute, pain. Chronic pain is a whole new state, with its own underpinning mechanisms that can be shared across many different types of chronic pain despite completely different initiating causes (e.g., symptoms are similar whether it is painful diabetic neuropathy and neuropathic pain states caused by traumatic nerve injury or having chemotherapy—and this means that the underpinning mechanisms must be similar, too)—almost considering chronic pain now as a disease in its own

right. This new way of thinking has given us insight into a new biology with new mechanisms to target, making the future very bright for chronic-pain sufferers.[10]

Getting to the Roots of Pain

Now, back to the basic neuroscience question of where the 'hurt' is of pain. In short, we still don't know, but we're closer. What we have learned after 20 years of neuroimaging is that the brain is key to experiencing pain—not impressive when you consider that Hippocrates suggested this was the case thousands of years before we were certain that the brain was the organ for perception and sensation.

We know that the brain responds to 'painful' or nociceptive events in a host of brain regions spanning sensory, discriminatory, affective, emotional, cognitive, brainstem modulatory, motor, and decision-making circuits in a flexibly accessible manner. Not all regions within this expansive network activate every time, even to the same nociceptive input or injury, and certainly not to the same extent. This ability to activate a varying set of brain regions in a highly flexible manner provides for the endless possibilities of varying painful experiences people need if they are to have 'the pain that is appropriate for the situation they are in,' such that they mount the right decision and action as to what to do about it.[11]

Imaging reveals that many of these brain regions are not pain-specific but nonetheless relevant for providing that rich multidimensional experience that is pain (e.g., threat, fear, attention networks). My group and others have used novel methods and paradigms to help dissect neuroanatomically this complex network in order to disambiguate which brain regions subserve the different features of a painful experience.[12]

Using psychological paradigms, pharmacological agents, novel imaging methods, and various injury models of peripheral and central 'sensitisation' or amplification, we've been able to relate neurophysiologic measures from advanced brain imaging to perceptual or nonperceptual changes in pain experiences induced by these methods. Noninvasive identification of where functional and structural plasticity, sensitization, and other amplification or attenuation processes occur along the pain neuraxis for an individual, and relating these neural mechanisms to specific pain experiences (measures of pain relief, persistence of pain states, degree of injury, and the subject's underlying

genetics), has neuroscientific and potential diagnostic relevance. As such, advanced neuroimaging methods can powerfully aid in explaining a person's multidimensional pain experience, analgesia, and even what makes them vulnerable to developing chronic pain.[13]

Let me illustrate with examples. People report that when they feel sad, their pain is worse. Does sadness influence the physiological processing to change the experience? Understanding this has relevance to our understanding and treatment of depression in pain as a significant factor, as well as changing attitudes/biases/myths toward pain.

In a test performed by my laboratory to explore how mood and pain interact, we played healthy students Prokofiev's *Russia under the Mongolian Yoke* at half-speed as they read negative statements ("I have no friends," "My life is a failure," and so forth) and were given painful stimuli. Perhaps unsurprisingly, compared to the control mood condition (listening to Dvořák and reading neutral statements), the subjects rated the same stimulus in the two mood conditions as more painful when they were sad. Subtracting brain activity produced to the stimulus during the neutral mood from that produced during the sad-mood condition confirmed that more activity in various brain regions (sensory and affective) occurred and accounted for the heightened pain reported during sad music. In short, normal emotion regulatory circuitry was disrupted in the sad condition, and this influenced how pain was processed within the brain to increase its activity levels in various regions (e.g., amygdala, insulae, inferior frontal gyrus, anterior cingulate).[14]

Therefore, sadness produces a physiological amplification—akin to a volume button on a hi-fi—by brain-based mechanisms. Related experiments simulating going to the dentist and being anxious, terrified, and threatened have also been done by my group and others. Again, the story is clear. Manipulating a healthy subject's emotional state negatively (i.e., make them anxious or threatened) changes how they perceive the very same painful stimulus toward being more painful. The 'anxiety volume' button, if you like, appears to be centered on the hippocampus/entorhinal complex with interactions to the anterior insula and mid anterior cingulate.[15,16]

Understanding Clinical Pain

These basic findings have proved useful to interpret and understand clinical pain. Knowing that such regions are involved in a patient's painful experience highlights the relevance of treating these co-morbid factors just as seriously as the inciting nociceptive input. The medical model likes to see tissue damage in order to believe a person's pain. But now we know that factors such as sadness, anxiety, and threat can amplify nociceptive inputs via such neural processing circuits and make the pain worse. This helps us to understand why there is often a mismatch between what is observed in terms of injury and what the patient or person reports is their pain.

Also to be considered is that sometimes pain isn't so severe as it appears. Remember that circus trick involving lying on a bed of nails or walking across hot coals? People can be distracted from their pain by, say, listening to music or watching a gripping film. Experiments have shown that when you are distracted from pain, an evolutionarily old system centered in the brainstem and driven by subcortical and frontal cortical regions, and which is shared across species and unique to the pain system, is recruited to drive descending inhibition and block nociceptive inputs arriving into the spinal cord from the injured body part.

Consequently, there is less input to the brain, so less pain. This system, called the Descending Pain Modulatory System, has unfortunately an opposite and facilitatory action that makes pain worse. Current work suggests that an imbalance between this inhibitory and facilitatory action is important in chronic pain. This is why soldiers on the battlefield don't feel pain when their attention is diverted.[16,17,18]

Naturally, the question then asked is whether placebo analgesia uses the same brainstem mechanism or is something different. Placebos have a checkered history born from ignorance. The word describes the Latin chants sung at funerals by hired mourners, and because of this history its use invokes feelings of fakery, deception, and lies. To get a placebo effect requires conditioning or having someone learn to expect a certain outcome from a particular ritual that might be a treatment in a medical setting. It was once assumed that if the person had a placebo effect then he or she were faking it or lying, and placebo tests were used for such detection purposes. But as far back as Hippocrates' and Galen's time, it was known that physicians caring for patients could produce remarkable healing without any pharmacological aids. We now have proof that these effects are

actual physiological changes in the body that can be recruited and activated by the mere expectation of an outcome.[19]

The Role Placebos Play

Neuroimaging helped prove the mechanism behind placebo analgesia. It has shown that, for the most part, it is simply expectation driving the descending pain (inhibitory) modulatory pathway from the brainstem to the spinal cord, such that as less nociception (the nervous system's response to certain harmful or potentially harmful stimuli) arrives to the brain, less pain results. Of course, nocebo effects can be produced where pain is made worse, and imaging has also proved useful in identifying its neural basis.[20,21]

Why is this important? Well, to know that the brain has a powerful system for modulating the physical experience that a patient has—in this instance his or her pain condition for better or worse—again helps us understand the nature of a patient's pain. A patient may even set and manage his or her own pain expectations based on what he or she has Googled. Knowing and managing what their expectations may be can contribute to actual treatment outcome.

We simulated this precise scenario in an experiment where healthy subjects were given a powerful intravenous opioid (painkiller) during a brain-imaging study throughout which we gave them painful stimuli. We manipulated their expectation of having this analgesic drug by simply not telling them when we started the infusion (hidden injection), then telling them we were starting it (driving positive expectation—even though they were already now on the drug), and pretending we stopped it when we didn't (driving negative expectation or nocebo). The results were striking. There was a small analgesic effect to the painful stimuli when the drug was given by hidden injection; we doubled that analgesic effect by driving positive expectation (even though nothing changed in terms of the drug dose being delivered), and then overrode and killed all the analgesic effect of the opioid when we pretended we stopped the infusion (which we didn't—so subjects were still on the drug but thought they were not), returning their pain ratings to preinfusion levels of the drug.[22]

The imaging revealed how these effects were produced and confirmed that the descending pain modulatory system was recruited during positive expectation and the network by which anxiety

makes pain worse (the hippocampal neural 'amplifier' of pain discussed above) was recruited during the nocebo part when they thought the infusion had been stopped and their pain ratings returned to preinfusion levels! This experiment speaks to the value of physicians and patients having time to discuss their condition and treatment options, so that expectations can be reliably managed and not unduly influence treatment outcomes.

Hedonic Flipping—Making Pain Pleasant

Is it possible to not just block pain, but actually make pain pleasant? English philosopher Jeremy Bentham once suggested that we seek pleasure and avoid pain. But that's a relative judgment. Sometimes pain might be the lesser of another evil, in which case its subjective value can be pleasurable or thought of in such terms. There are everyday examples where reappraising pain as something pleasurable or rewarding is done—and not by the sadomasochist. After a vigorous run, for example, runners may not perceive their tired body or aching muscles as unpleasant pain. Rather, they may perceive what they feel as pleasant pain, indicating health, exercise, and achieving their goals.

Imaging by our group has explored the neural basis of 'making pain pleasant' and how that might be harnessed in a clinical setting. Changing the hedonic value of pain is achieved by the reward system and the descending modulatory pain system working in concert to reduce the intensity of the painful inputs and make their value appear rewarding.[23,24]

The Pros and Cons of Brain Reading

Finally, a new area of imaging is emerging that has the potential to impact other spheres of society beyond the laboratory and clinic: brain reading. For pain, such an approach might be useful in situations where pain cannot be communicated through speech or behavior (i.e., an infant, a demented elderly person, or a comatose or anaesthetized patient). The approach is to use neuroimaging alongside algorithms that are trained to classify patterns of brain activity, or 'brain reading,' based upon what we know the person thought or felt during that pattern generation. Then, classifier algorithms predict what experience the person had by putting his or her brain data during that experience into a classification computer program or multivariate pattern analysis.

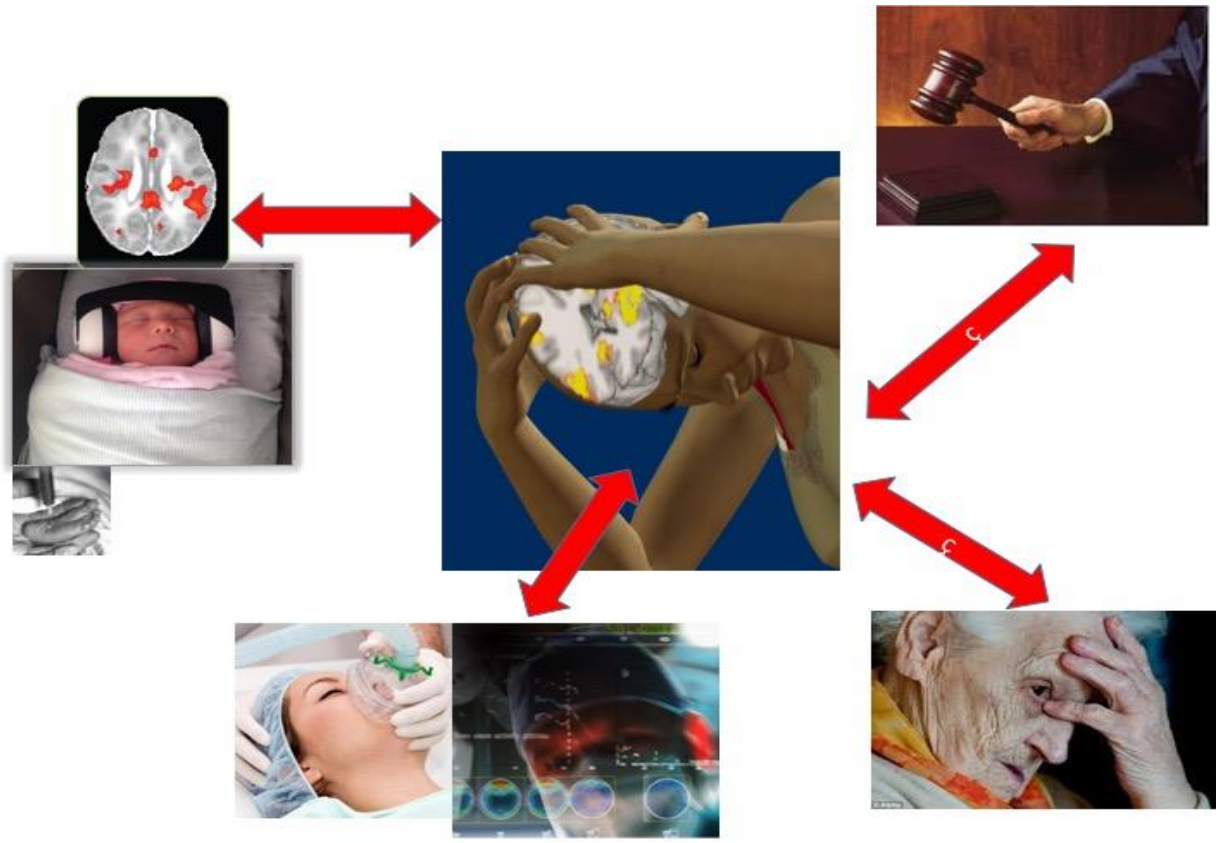

Illustration of various situations where a neuroimaging-based 'brain reading' approach might be useful.

The accuracy has proved reliable and the approach popular with companies selling the technology to insurance companies, courts of law, and situations where there is a desire to have presumed independent and objective readouts. But the practice is controversial. Complex interpretative issues need to be resolved before brain reading is used as a guide in determining an individual's pain.[25,26]

What the next decade brings about in perceptions of pain will hopefully generate benefits to patients and society at large, as well as enrich our neuroscientific knowledge regarding this most complex of subjective experiences.

Bio

Irene Tracey, Ph.D., holds the Nuffield Chair of Anaesthetic Science and is head of the Nuffield Department of Clinical Neurosciences at the University of Oxford. Tracey did her undergraduate and graduate studies at the University of Oxford and then held a postdoctoral fellowship at Harvard Medical School. She helped to co-found and for ten years was director of the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain at the university. She was an elected councillor to the International Association for the Study of Pain and chair of their Scientific Program Committee, is a member of the Medical Research Council, and is on the Brain Prize selection committee. In 2008 she was awarded the Patrick Wall Medal from the Royal College of Anaesthetists and in 2009 was made a Fellow of the Royal College of Anaesthetists. In 2015 she was elected a Fellow of the Academy of Medical Sciences and in 2017 was awarded the Feldberg Prize. Tracey is married to Professor Myles Allen, a climate physicist, and they have three children.

References:

1. The Story of Pain: from prayer to painkillers. Joanna Bourke. Oxford University Press. 2014.

2. The Body in Pain: The making and unmaking of the world. Elaine Scarry. 1985 Oxford University Press.

3. The Challenge of Pain. Patrick Wall, Ronald Melzack. Penguin. 1996.

4: Pain: The Science of Suffering. Columbia University Press. 2000.

5. Regarding the Pain of Others. Susan Sontag. Penguin Books. 2004

6. Lee MC, Tracey I. Imaging pain: a potent means for investigating pain mechanisms in patients. Br J Anaesth. 2013 Jul;111(1):64-72.

7. Lee M, Tracey I. Neuro-genetics of persistent pain. Curr Opin Neurobiol. 2013 Feb;23(1):127-32. doi: 10.1016/j.conb.2012.11.007. Review. PubMed PMID: 23228429.

8. Tracey I. Can neuroimaging studies identify pain endophenotypes in humans? Nat Rev Neurol. 2011 Mar;7(3):173-81.

9. Institute of Medicine *Relieving Pain in America,2011; www.painineurope.com*

10. von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron. 2012 Feb 23;73(4):638-52.

11. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron. 2007 Aug 2;55(3):377-91. Review.

12. *Ploghaus, A., *Tracey, I., Gati, J.S., Clare, S., Menon, R.S., Matthews, P.M., Rawlins, J.N.P. Dissociating pain from its anticipation in the human brain (1999) Science, 284 (5422), pp. 1979-1981. **joint corresponding*

13. Denk F, McMahon SB, Tracey I. Pain vulnerability: a neurobiological perspective. Nat Neurosci. 2014 Feb;17(2):192-200.

14. Berna, C., Leknes, S., Holmes, E.A., Edwards, R.R., Goodwin, G.M., Tracey, I. Induction of Depressed Mood Disrupts Emotion Regulation Neurocircuitry and Enhances Pain Unpleasantness (2010) Biological Psychiatry, 67 (11), pp. 1083-1090.

15. Wiech K, Tracey I. The influence of negative emotions on pain: behavioral effects and neural mechanisms. Neuroimage. 2009 Sep;47(3):987-94.

16. Wiech K, Ploner M, Tracey I. Neurocognitive aspects of pain perception. Trends Cogn Sci. 2008 Aug;12(8):306-13.

17. Bingel U, Tracey I. Imaging CNS modulation of pain in humans. Physiology (Bethesda). 2008 Dec;23:371-80.

18. Tracey I, Dickenson A. SnapShot: Pain perception. Cell. 2012 Mar 16;148(6):1308-1308.e2.

19: The Placebo Effect in Clinical Practice. Walter A Brown. Oxford University Press. 2013

20. Tracey I. Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. Nat Med. 2010 Nov;16(11):1277-83.

21. Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J, Büchel C. Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron. 2009 Aug 27;63(4):533-43.

22. Bingel, U., Wanigasekera, V., Wiech, K., Mhuircheartaigh, R.N., Lee, M.C., Ploner, M., Tracey, I. The effect of treatment expectation on drug efficacy: Imaging the analgesic benefit of the opioid remifentanil (2011) Science Translational Medicine, 3 (70), art. no. 70ra14.

23. Leknes S, Tracey I. A common neurobiology for pain and pleasure. Nat Rev Neurosci. 2008 Apr;9(4):314-20.

24. Leknes, S., Berna, C., Lee, M.C., Snyder, G.D., Biele, G., Tracey, I. The importance of context: When relative relief renders pain pleasant (2013) Pain, 154 (3), pp. 402-410.

25. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med. 2013 Apr 11;368(15):1388-97.

26. Duff EP, Vennart W, Wise RG, Howard MA, Harris RE, Lee M, Wartolowska K, Wanigasekera V, Wilson FJ, Whitlock M, Tracey I, Woolrich MW, Smith SM. Learning to identify CNS drug action and efficacy using multistudy fMRI data. (2015) Science Translational Medicine, 7(274):274ra16.