Why pain hurts
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We have made great strides in understanding how the human brain constructs the multidimensional experience of pain – both acute and chronic – over the past few decades. Pain wears many guises, but at its core, it hurts. How is this core component of pain represented in the brain, and how can we target it for relief?

The quest to find the hurt of pain

“Will it hurt”? This common question beles our longstanding fear of pain. Oscar Wilde purportedly said: ‘I don’t mind pain, so long as it doesn’t hurt.’ Brilliant in its simplicity. Riven with the essence of the problem. If only we could take the hurt away. But from where? Therein lies the problem and the challenge.

Pain is one of our fundamental emotional and sensory perceptions. It is your body’s alarm system and vital for survival. We consider pain as belonging to two major classes: acute pain – your everyday pain – that acts as a warning system of tissue damage or impending harm, and chronic pain. The latter is defined as pain that persists or recurs for more than 3 months and it produces untold suffering to patients, carers, and families; it also has a substantial financial cost to society. There are three main types of chronic pain: inflammatory, neuropathic, and dysfunctional (Figure 1). An estimated 20% of adults fulfill the criteria for chronic pain, and pain and pain-related diseases are the leading cause of disability and disease burden globally. Comorbid anxiety, depression, insomnia, cognitive dysfunction, and sometimes addiction or substance abuse occur, adding to patient suffering and the clinical challenge. The latest International Classification of Diseases (ICD-11) now describes pain as both a health condition (chronic primary pain) and a symptom that is secondary to an underlying disease (chronic secondary pain) – an important development for the field that reflects the science. Sadly, however, chronic pain remains a major unmet medical need, and patients continue to suffer in large part because of the overwhelming hurt or unpleasantness of the experience [1].

However, there is hope. In recent decades, our understanding of the neurobiology of acute and chronic pain has advanced rapidly – witness the Nobel Prize for Medicine and Physiology in 2021 awarded to two giants of the field, Ardem Patapoutian and David Julius, for their ground-breaking discoveries of receptors for temperature (noxious and non-noxious) and touch. Other fundamental discoveries related to chronic pain mechanisms have also occurred – the therapeutic opportunity is significant [2].

Twenty-five years ago, I began my post-doctoral research career in pain. It was an exciting time as neuroimaging tools became available to the neuroscience community allowing us to relate brain activity to people’s experiences and perceptions. We quickly recognized the value in having tools to explore private and subjective experiences that had been so challenging to understand, especially in nonverbal subjects. Pain imaging studies took off. However, soon we realised the enormity of the challenge, as we navigated our way mapping this multidimensional sensory, emotional, and cognitive experience onto brain networks. In my opinion, the quest for finding the hurt of pain, however it is represented in the human brain, remains. Finding it has basic and clinical neuroscientific value.

Current landscape of pain research

Hippocrates proposed that pain, like grief, probably arose from the brain, and Descartes’ famous boy with his foot in the fire emphasised the brain’s involvement in decoding peripheral noxious signals – though his model assumed, wrongly, a simple, linear, and one-to-one relationship between nociception and pain (Figure 1). Neuroimaging studies have proven how, for example, your mood, cognitive state, or expectations can all shape the pain you experience, explaining the commonly observed nonlinearity between injury and perception.

Early lesion and surgical studies were focused on the (wrong) concept that there must be a primary pain cortex – akin to vision and touch – so that lesioning it would remove pain. Spinal cord pathways and the thalamus were early targets – it did not work. Then the anterior cingulate cortex was targeted with some reports suggesting the affective component of pain was removed and that patients cared less about their pain – but the data are inconsistent. Studies continue, but now stimulate rather than lesion brain regions/networks as potential targets for relief that are informed by neuroimaging data and our improved understanding of endogenous modulatory pain-relieving systems [3].

Melzack coined the phrase ‘the body self neuromatrix’ to describe the widespread network of activity that was flexibly and variably activated as neurosignatures during acute and chronic pain experiences [4]. Neuroimagers quickly adopted the phrase, pain matrix, for better or worse. Key components of pain (e.g. sensory-discriminatory, attentional, anticipatory and fear, decision-making, movement, memory and learning, etc.) – are features not unique to pain but do form an important part of the overall perception – and these are encoded in these neurosignatures. Many of us developed psychological and pharmacological paradigms to dissect the experience into dissociable brain networks to better understand the underpinning activity as it relates to these components. Wise interpretation of what it meant to activate apparently similar brain regions...
in other contexts (e.g., social exclusion or empathy) was required but did not always occur, leading to frustration within the field. Multivariate pattern analyses and machine learning approaches were used to disambiguate different neuronal patterns of activity within a ‘blob’ of activity that might appear the same for, say, vicarious and nociceptive driven pain. Similar approaches combined the growing number of data sets available to classify neurosignatures for different types of pain (and nonpain) experiences. From all these combined efforts, the field started to build confidence in what brain regions and networks seemed necessary for eliciting pain, as reported by adults [5]. However, it is still not crystal clear, at least to me, how the quintessential component of pain, the hurt, arises.

As new approaches are tested for their ability to bring relief to patients, it is clear we still have much to learn about the basic neuroanatomy of the central pain system in humans, and equally important is a better understanding of how electrical brain oscillations encode the hurt of pain [6]. More studies that combine the fields of electrophysiology with neuroimaging could prove fruitful.

Of course, chronic pain is not acute pain and so targets and mechanisms will often differ. Progress to understand such differences has been made by laboratories around the world. We are even daring ourselves to think that we might have some credible neuroimaging biomarkers for chronic pain mechanisms related to predisposing susceptibility, as well as its maintenance and exacerbation [7]. However, the basic neuroscience question of why pain hurts, whether acute or chronic, remains a target for relief.

Future opportunities
Identifying nociceptive-related activity in babies’ brains provides another opportunity to examine what networks activate at an early stage of brain development, and explore how early life experiences shape pain expression and network activity. Colleagues and I hypothesised that a simplified network of activity might occur – but results to date reveal brain activity surprisingly similar to that of adults reporting pain [8]. Of course, we do not know what the babies are feeling, and the same holds

Figure 1. Modernised illustration of Descartes’ drawing. Figure describing the purpose of acute pain and the three main types of chronic pain, with examples, and the core networks underpinning the multidimensional experience that is pain. We now know that Descartes’ drawing was an oversimplification and pain perception rarely has a linear relationship to injury, but is influenced by many factors like mood, cognition, and expectations. There is not a simple one-to-one mapping between nociception and perception. Through neuroimaging and electrophysiological studies in humans, we now have a better understanding of how the brain constructs the experience of pain. However, work is still needed before we understand how the core element of pain, the hurt, is encoded.
for studies in patients undergoing general anaesthesia or sedation. Pain and consciousness go hand in hand, and I encourage more pain researchers to consider using anaesthesia as a tool to determine how the brain dismantles and constructs perceptual experiences, including pain. All these studies are technologically highly challenging, but the data is rich [9].

As pain is one of our oldest sensory and emotional experiences, perhaps a comparative neuroanatomical, cross-species assessment of what commonly activates in response to noxious inputs might yield insight into the shared neural architecture that encodes the hurt of pain. This will require multidisciplinary methodological and analytical approaches, and more extensive collaboration between different laboratories.

Studies in nonverbal animals are challenged by not knowing how brain activity maps to the subjective experience – does it hurt? We look to clever and novel behavioural paradigms and observations (in addition to conventional assessments of a change in physiology) to help us; for example, behavioural measures in nonhuman animals that reflect a change in motivation, choice, and decision-making that from ethological studies we believe are influenced by pain. I believe that some of the most exciting research to understand brain processing as it relates to the hurt of pain is currently coming from innovative animal studies embracing new molecular tools and cellular imaging techniques alongside these newer behavioural paradigms [10–12]. The ability to learn from the human imaging studies and then reverse-translate in a directed and more causally interpretive way to animals is fantastically exciting. These studies are already yielding results that might, just might, bring us closer to understanding the mercurial hurt of pain. More forward and reverse translational collaborations between human and animal pain researchers is to be welcomed. Good luck colleagues.

Additional Note
Due to limitation in references the reader is encouraged to also read the references cited by papers selected in the reference list.

Declaration of interests
No interests are declared.

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