Why does it hurt? An overview of pain mechanisms

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Understanding the underlying anatomical and neurochemical mechanisms of pain is critical in optimising clinical outcomes, prevention of chronic pain and associated suffering, and novel analgesic development.

In the year 2020, for the first time since 1979, the International Association for the Study of Pain revised the definition of pain as "an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage". This was further expanded upon by the following six keynotes:

1. Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.

2. Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.

3. Through their life experiences, individuals learn the concept of pain.

4. A person's report of an experience as pain should be respected.

5. Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.

6. Verbal description is only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

Pain is generally considered to be body's protective response or alarm system which facilitates avoidance from injury or protection of an injured body part during the healing process. **Acute pain** typically follows traumatic tissue injuries, is well characterised, limited in duration, while improving with time and tissue healing. However, sometimes the body's alarm function is lost and chronic pain may develop, which can linger on and often presents a significant level of distress. **Chronic pain** may have a gradual or distinct onset, often persists beyond three to six months of expected healing/resolution, serves no protective response and can be refractory to treatments. The temporal distinction between acute and chronic pain has arbitrarily been defined as a period of greater than three months, however it is increasingly recognised that the transition from acute to chronic pain can take place over the course of a few weeks to a few months, essentially depending on the expected trajectory of recovery. Some authors have suggested the category of **subacute pain** as pain lasting over six weeks but under three months.

One of the earliest scientific models for explaining pain was provided by Renee Descartes (**Cartesian dualism theory**) which suggested pain to be a mutually exclusive entity caused by either physical or psychological injury. Over time, especially through the work of Joseph Bonica and John D Loeser, the understanding of pain is better explained as a biopsychosocial phenomenon (**Biopsychosocial model**) wherein one's overall, usually complex, pain experience is the result of an interplay between **nociception**, (the neural process of encoding noxious stimuli), with their psychological factors (thoughts and behaviours), and their social circumstances and past experiences. It is commonly seen that people who tend to catastrophise, have a fear avoidance attitude towards rehabilitation, lack social support or healthy lifestyles are likely to experience greater pain and poorer recovery, for example, after a knee replacement surgery, than people for whom these psychosocial factors do not apply.

Pain pathways, unlike other sensory pathways, are not modality-specific, hard-wired systems, but are dynamic such that the output (response) to the input (stimulus) is variable, accounting for the theoretical systems which explain the clinical and neurophysiological observations, in acute and chronic pain. **Nociceptors** are receptors including free nerve endings which respond to thermal and mechanical stimuli and are distributed throughout the body including skin, viscera, joints, muscles and meninges. Some of these nociceptors (silent nociceptors), while providing continuous information about the tissue environment tend to be refractory to mechanical and electrical stimuli. However, in the presence of chemical mediators of inflammation they become active, converting the signals into electrical impulses (**transduction**) and facilitate **transmission** of the signals.

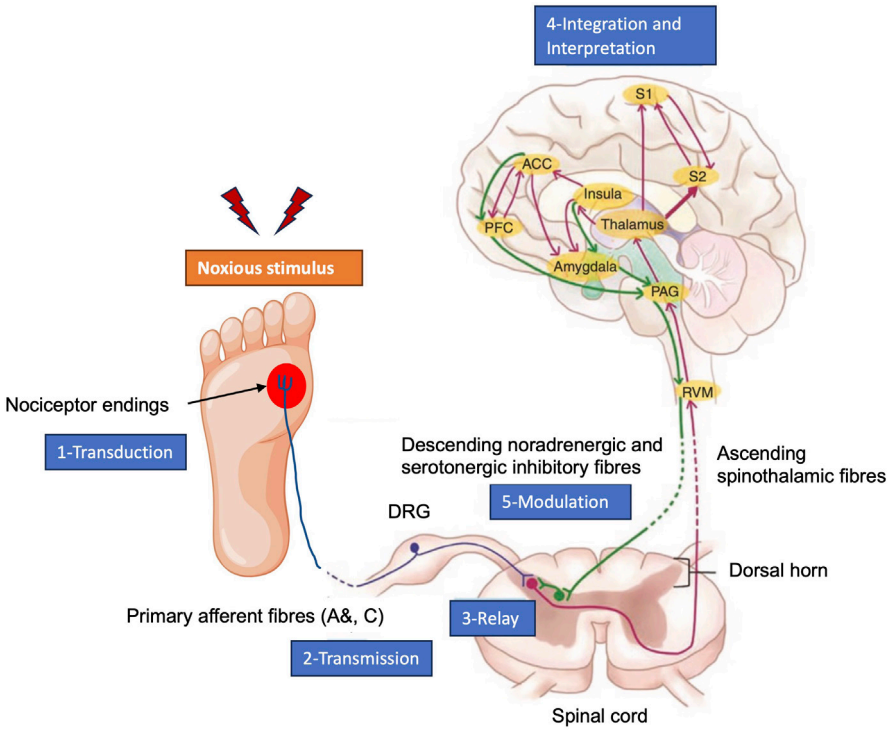

Figure adapted from Chen Y. and Abdi, S. 2022. Basic Science: Pain Mechanisms and Pathways. *In:* Banik, R. K. (ed.) *Anesthesiology In-Training Exam Review: Regional Anesthesia and Chronic Pain.* Cham: Springer International Publishing.

This transmission occurs through the primary afferent fibres, A-delta and C, which differ in terms of their microscopic structure and velocity of conduction of electrical impulses. A-beta fibres, being highly myelinated and large in diameter facilitate rapid signal conduction in response to touch and non-noxious stimuli. A-delta fibres, being lightly myelinated and smaller in diameter, conduct slower than A-beta and respond to mechanical and thermal stimuli, typically causing the initial pain response to acute pain. C fibres, being un-myelinated and smallest in diameter are the slowest conductors, and respond to a wide range of chemical, mechanical and thermal stimuli, typically leading to slow burning type pain. These fibres travel through the sensory nerves and synapse with the second-order neurons in the dorsal horn of the spinal cord.

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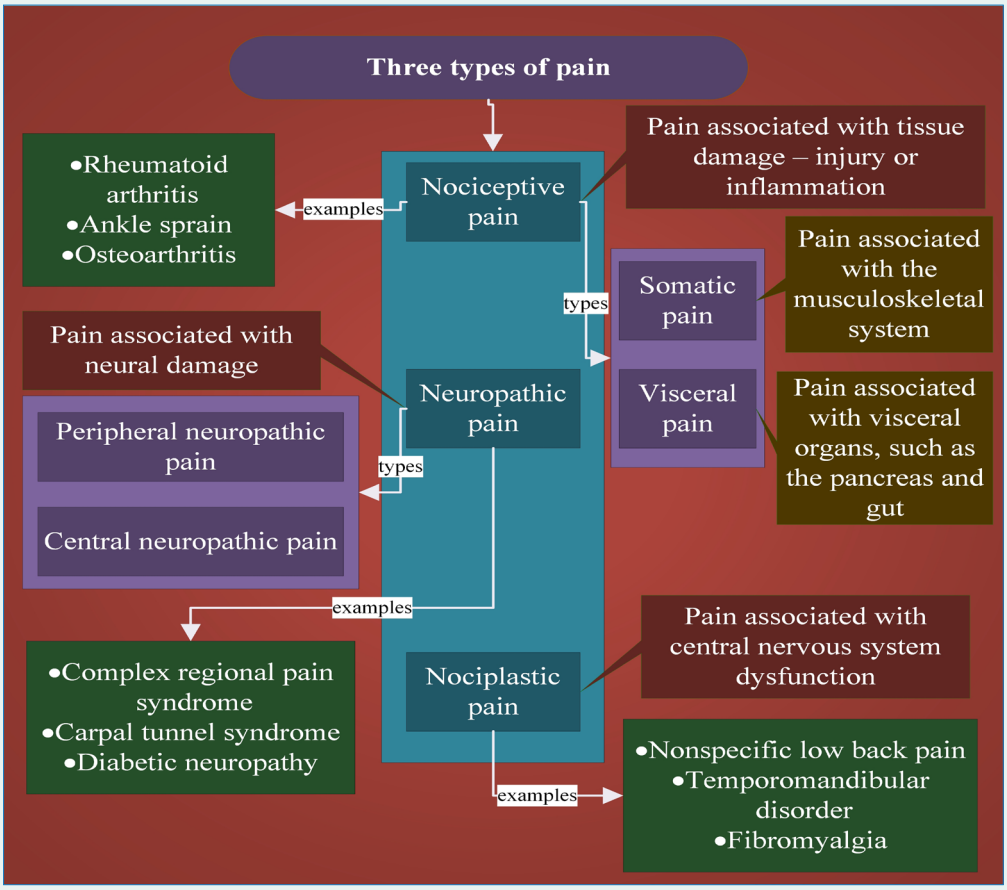
Once in the dorsal horn these fibres transmit their information to the brain, through the spinothalamic (predominant) and spinoreticular pathways. Within the spinothalamic tract, these second-order neurons crossover to the other side within a few segments, ascend as the contralateral spinothalamic tract to the thalamic nuclei, and largely contribute to pain localisation. Some fibres project to the periaqueductal grey (PAG) matter, which is involved in pain modulation. The fibres within the spinoreticular tracts also crossover to reach the brainstem reticular formation and from there on to the thalamus and hypothalamus. With the multiple cortical projections these fibres are generally involved in the emotional aspect of pain. Key brain areas involved in pain processing have been identified particularly through functional neuroimaging tools like functional MRI and PET scans. This so-called **pain matrix** includes the primary and secondary somatosensory (S1 and S2), insular, anterior cingulate cortex and prefrontal cortex, and the thalamus.

The overall output of the fibres in the spinothalamic tract depends on the net balance between the facilitatory and inhibitory signals at the dorsal horn. **Gate-control theory**, proposed by Melzack and Wall, implies that both non-painful stimuli from the periphery, transmitted by A-beta fibres and descending inhibitory cortical pathways would block the nociceptive pathway at the dorsal horn. This theory helps explain our reflex response of 'rubbing away pain' wherein rubbing stimulates the A-beta fibres to stop pain signals propagating. Clinical application of this occurs in a range of non-pharmacological techniques such as TENS (transcutaneous electrical stimulation), massage, acupuncture, or even invasive options such as spinal cord stimulation. Descending pathways, especially from the PAG and rostroventral medulla (RVM) project serotonergic and noradrenergic signals to the spinal cord inhibitory interneurons (**diffuse noxious inhibitory control**). This supraspinal pain modulation can either amplify or inhibit transmission of pain related signals. Increased activation of the 'ON' cells in the RVM facilitate increased pain transmission to the brain, while 'OFF' cells inhibit transmission. Indeed, this mechanism is exploited in pharmacological neuro-modulation through opioidergic, serotonergic and noradrenergic drugs, and non-pharmacological neuro-modulation like meditation, or cognitive-behavioural therapy. >>



The pain pathways described are activated in conditions producing acute pain, which are expected to settle once symptoms resolve over time. Often prolonged nociception outlasts its usefulness, resulting in changes within the different limbs of this pathway and the pathogenesis of chronic pain.

Sensitisation may occur peripherally (at the level of the nociceptors; **peripheral sensitisation**) and centrally (at the level of the dorsal horn; **central sensitisation**) contributing to the development of chronic pain. Increased responsiveness and reduced sensitivity of peripheral nociceptors primarily due to persistent inflammatory stimulation through chemicals including H+, K+, bradykinin, serotonin, prostaglandins and neurokinins results in the development of **primary hyperalgesia** (increased pain response to a stimulus that normally provokes pain, tested clinically through pinprick and compared with adjacent or contralateral areas). Such peripheral sensitisation can also affect A- beta fibre functioning to inhibit pain transmission. Strong activation of nociceptive afferents, particularly C-fibre nociceptors may lead to sensitisation of dorsal horn neurons (**windup phenomenon**). This involves a combination of mechanisms such as an increased receptive field size, lower neuronal firing thresholds, increased magnitude of action potential discharges and increased spontaneous impulse activity; akin to turning up a sound system amplifier. These pathophysiological changes result in clinically observed features of **secondary hyperalgesia** (increased pain sensitivity to adjacent un-injured area); **allodynia** (painful response to non-noxious stimuli); and spontaneous pain. Patients reporting painful sensations when clothes rub against their skin, or shaving the area, gentle touching or pressing on the area or even contact with mildly warm or cold objects, are all clinical manifestations of allodynia. Further long-term potentiation occurs due to repetitive activation of high-threshold C fibres which result in increased strength of their synaptic connections with dorsal horn neurons. NMDA subtype of glutamate receptors and the substance P receptors (NK1) play a key part in such long-term potentiation.

Supraspinal mechanisms also contribute to the development of central sensitisation. Reduction in central inhibitory outflow causes spinal hyper-excitability through reductions in efficacy of GABAergic and glycinergic transmission. In addition, activation of astrocytes and microglia occurs through neuronal signals including substance P, glutamate and fractalkine which promotes central sensitisation, directly through release of pro-inflammatory cytokines and indirectly through reducing efficacy of GABAergic inhibition. As stated previously, this forms a key target for modulation through both pharmacological and non-pharmacological tools.

Based on the pathophysiology described, chronic pain may be classified in the following three categories:

1. **Nociceptive** (or inflammatory),
2. **Neuropathic** or
3. A newly defined class of **Nociplastic pain**. While considered distinct classes, it is acknowledged that a combination of these may co-exist within a single individual.

Nociceptive pain, particularly if somatic, follows a typical dermatomal pattern, often proportionate to degree of inflammation, and reflects activity related to the nociceptors. Examples include trauma, surgery, infection and arthritis. Nociceptive pain arising from the internal organs (**visceral pain**) occurs due to smooth muscle distension, or contraction, stretching of the capsule around an organ, ischaemia, necrosis and/or chemical inflammatory process. Visceral pain tends to be diffuse, poorly localised and often described as deep, dull and dragging. Such pain is often associated with a strong autonomic response (nausea, vomiting, heart rate and blood pressure changes). Pain may be referred to distant sources due to convergence of different afferents on the same dorsal horn neurones (for example, shoulder pain following laparoscopic surgery due to diaphragmatic stretching). **Neuropathic pain** occurs due to a lesion or disease of the somatosensory system, for example, post-surgical, trigeminal neuralgia, post-herpetic neuralgia, diabetes, HIV, chemotherapy associated pain or nerve entrapment. Central causes include conditions such as multiple sclerosis, spinal cord injury and stroke. The typical characteristics of neuropathic pain are those of secondary hyperalgesia and allodynia. It is now understood that pain may arise from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain. This has been classified as **Nociplastic pain** and applies to conditions such as fibromyalgia, complex regional pain syndrome, irritable bowel syndrome and mechanical back pain.

There still remain a lot of un-answered questions, such as why individuals differ in their pain experience, how acute pain transitions to chronic pain, and why individuals differ in their susceptibility to analgesics. However, the progress in our understanding of pain mechanisms has helped pain specialists apply multimodal tools including analgesics and non-pharmacological therapies ranging from simple interventions to the more invasive ones such as spinal cord or deep-brain stimulation while exploring pre-emptive opportunities to prevent sensitisation/chronicity. ■